CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-726

MEDICAL REVIEW(S)

JUN 2 1 1997

LABELING REVIEW No. 4: NDA-20726 Letrozole (*Femara™*)

NDA: 20726 / v.4 97 LABELING
Drug: Letrozole (*Femara™*)
Applicant: Novartis, Inc.
M.O.: G. Schechter, M.D.
Date: June 20, 1997

Comment:

In response to applicant's concerns about the wording in lines 356 to 383 of the Label revision dated June 4, 1997 the information about study discontinuations on AR/BC2 due to adverse events was reviewed again. Review indicated that on the letrozole 0.5 mg arm 11 patients (5.9%) discontinued study drug due to adverse events, on the letrozole 2.5 mg arm 11 (6.3%) patients discontinued study drug due to adverse reactions, and on the megestrol arm 26 patients (13.7%) discontinued study drug due to adverse reactions. Significantly fewer discontinuations occurred on the letrozole arms as compared to the megestrol arm ($p = 0.015$, two sided , Fisher's exact). When these study discontinuations were examined for relationship to study drug no significant difference in the number of patients who discontinued study due to adverse events definitely, probably, or possibly related to study drug could be detected (Fisher's exact, $p = 0.17$, two-sided). No significant difference in the number of study discontinuations due to adverse events was noted for any study arm on AR/BC3.

One death due to the study drug megestrol acetate was noted on AR/BC2 (Pat. fatal pulmonary emboli).An statistically significant increase in the number of thrombotic events was observed on the megestrol arm as compared to the letrozole arms (Fisher's exact, $p = 0.02$, two-sided). A statistically significant increase in the incidence of vaginal bleeding was reported on the megestrol arm as compared to the letrozole arms (Fisher's exact, $p = 0.03$, two-sided).

The applicant has tried use the significant difference in the number of study discontinuations on AR/BC2 due to adverse events as evidence that letrozole is than megestrol acetate without clarifying that no significant difference in the number of study discontinuations due to adverse events definitely, probably, or possibly caused by study drug therapy could be detected.

Action: The wording proposed by the FDA reviewer will be reinserted in this section with the numbers corrected to accurately reflect the number of adverse events which resulted in study drug discontinuation:

6-21-97

6/20/97

Genevieve A. Schechter, M.D.
Medical Reviewer - DOPD

John R Johnson, MD

John Johnson, M.D.
Team Leader - DOPD

6-21-97

Orig: NDA 20726
cc: Divisional File / HFD-150
c: wpfiles/letrozol/labrev#4

cc: ~~case~~ HFD-150 /G. Schechter
/D Spillman

MAY 16 1997

LABELING REVIEW No. 2: NDA 20726

NDA: 20726
DRUG: Letrozole (*Femara™*)
APPLICANT: Ciba-Geigy
M.O.: G. Schechter, M.D.
DATE: May 15, 1997
Revised May 16, 1997

This review is based on the revised label (copy attached) circulated after the labeling meeting of April 23, 1997 and a follow-up discussion of the labeling with Dr. Delap and Johnson on April 29, 1997.

I. Labeling Amendments:

CLINICAL PHARMACOLOGY

Pharmacokinetics

Hepatic Insufficiency

Biopharm to attach metric.

Lines 115 - 118: Delete.

Pharmacodynamics

Delete Lines 130 - 132.

Line 135: Delete the statement and insert

Line 151 - 153: Delete and insert the italicized words so that the sentence reads:

Clinical Studies

Line 169: Delete , add

Lines 172: Delete and add the italicized phrase after the

5-16-4

Line 173: Add the italicized word: '

Line 183: Delete

Line 183 - 201 are correct as written.

Delete line 205 - 229 and add the following paragraph:

Lines 236 - 248: Delete and insert:

INSERT

Delete Lines 249 - 299.

INDICATIONS AND USAGE

Line 302 -305: Change indication to read:

CONTRAINDICATIONS

Line 308: End sentence after excipients. Delete

ADVERSE REACTIONS

Lines 433 - 434: Delete sentence

Line 467: Insert the italicized word:

Line 470: Change sentence to read:

Line 473: Delete so sentence reads:

. Amend table to show only percentages but not number of patients with adverse events and include *Femara 0.5 mg* arm as shown in the revised table with penciled numbers attached to review.

Line 475: Instruct applicant to include a listing by Body System (i.e. *Body as a Whole, Cardiovascular, etc)* of any side effects which occurred between 2 and 5% of the time, whether related to drug therapy or not, which are not reported in the above table. Under each Body System the adverse events should be listed starting with the most common and decreasing to the least common. Continue with Line 476.

DOSAGE & ADMINISTRATION

Hepatic Impairment

II. Response to Letrozole with Regard to Response to Previous Antiestrogen Therapy:

Probability testing was performed for the subset of patients who had a response (CR, PR, SD) to therapeutic antiestrogens on AR/BC2. Response to antiestrogens did not influence the probability of response to letrozole therapy. Failure to have a response to therapeutic antiestrogens did not alter the probability of a response to letrozole therapy. (See attached review with tables and probability testing.)

ACTION:

Amend the label as noted in Part I. Obtain information from Applicant.

Genevieve A. Schechter, M.D. - M.O.

John R Johnson, MD 5-16-97
John Johnson, M.D. - Team Leader, DOPD

Orig: NDA 20267
cc: D. Spillman/HFD-150
cc: G. Schechter/HFD-150
c:/wpfiles/letrozol/labrev#2
cc: HFD-150/Div File

REVIEW: NDA20726

LETROZOLE (*FEMARA™*)

Medical Reviewer: G. Schechter, M.D.
Team Leader: J. Johnson. M.D.

Original: December 2, 1996
Revised: May 30, 1997
Revised: June 20, 1997

INDEX

Documents reviewed in this report include:

N 000	Submission Date:	July 24, 1996
N 000 BZ	Submission Date:	Sep. 09, 1996
N 000 BZ	Submission Date:	Oct. 25, 1996
N 000 BM	Submission Date:	Dec. 05, 1996
N 000 BM	Submission Date:	Dec. 09, 1996
N 000 SU	Submission Date:	Jan. 30, 1997

History of the Letrozole (CGS 20267) New Drug Application

The original phase I dose finding study (Protocol 01) for CGS 20267 in postmenopausal women with hormonally responsive breast cancer was submitted as a new IND, on July 29, 1991. In this study doses of up to and including letrozole 1.0 mg, 2.5 mg, and 5.0 mg were to be studied. The original review completed on August 27, 1991 states that thirty-six healthy men had been treated on three pharmacokinetic trials in Europe. The review mentions two clinical studies, one involving healthy postmenopausal women and one open label trial in patients with advanced breast cancer ongoing in Europe. The sponsor was advised that the study could proceed and was asked to submit information about pharmacokinetics and pharmacodynamics from the completed European trials as well as any safety information from completed or ongoing trials.

On March 11, 1994 Ciba-Geigy met with the Oncology Division to discuss strategies to gain drug approval in the US. Ciba -Geigy was advised that the two ongoing European trials, AR/BC 2 (letrozole 0.5 mg vs letrozole 2.5 mg vs megestrol 160 mg as second line therapy in postmenopausal woman) and AR/BC 3 (letrozole 0.5 mg vs letrozole 2.5 mg vs aminogluthemide 10 mg/d as second line therapy in postmenopausal women) would be adequate to gain approval provided letrozole proved superior to the comparitor with regard to efficacy and had an acceptable safety profile. The meeting minutes state that "Both trials must demonstrate the superiority of letrozole over the comparative agent (megestrol acetate and aminogluthemide) in terms of tumor response rate, or a dose response must seen in the two letrozole arms with the higher dose being at least equivalent in efficacy (based on tumor response data) to the comparator". The sponsor was assured that for trial purposes megestrol 160 mg daily was an acceptable comparator arm. Quality of life assessments were to be included in the trials.

In January, 1996 Ciba-Geigy requested a meeting to discuss NDA filing based on the analysis of the data from AR/BC 2 a three arm randomized blinded study (letrozole 0.5 mg, letrozole 2.5 mg, and megestrol 160 mg/day) involving 551 postmenopausal patients with advanced breast cancer. Ciba was advised that the NDA was filable based on results from AR/BC2 and the data from the phase II trials. Ciba-Geigy acknowledged during the pre-NDA discussion that AR/BC 3, the second trial in which the comparator arm is aminoglutethimide would be completed at the time of the NDA submission. Data analysis for AR/BC3 would not been completed until the last quarter of 1996. The one hundred thirty-one volume NDA was submitted on July 25, 1996 along with computerized data for the AR/BC 2 study core and update results. Demographic data from the letrozole 0.5 mg and letrozole 2.5 mg arms of AR/BC3 was included in the but no information about efficacy endpoints was included.

A third trial, Protocol 02, which compares letrozole 0.5 mg, letrozole 2.5 mg, and megestrol 40 mg qid to be conducted in the US has completed accrual as of October 31, 1996. Results of this study will be available in December, 1997. Ciba had proposed discontinuation of the letrozole 0.5 mg arm of this study since the comparison of the odds ratio for the response rates of letrozole 2.5 mg to letrozole 0.5 mg were statistically significant in favor of letrozole 2.5 mg on AR/BC2. The agency urged Ciba to continue the letrozole 0.5 mg arm pending analysis of AR/BC3.

HUMAN PHARMACOKINETICS

I. SUMMARY:

The T_{max} for letrozole is 1 - 2 hours with oral dosing. Concomitant intake of food has no effect on overall absorption but may slow the rate of absorption. Bioavailability is about 100%. Binding to plasma proteins is weak (~ 60%) with about 92% of the drug bound to albumin. RBC concentration of the drug is about 80% of the plasma concentration. The drug is extensively distributed in the tissues with the VD_{Dss} of ~ 1.87 L/kg. The terminal elimination phase ($T_{1/2\,B}$) is about 2 days with metabolic clearance. The major metabolite, 4,4' -methanolbisbenzonitrile (CPG 44645), is metabolically inactive and undergoes glucuronidation prior to urinary excretion. Fecal and renal excretion of unchanged letrozole and other metabolites play a minor role in metabolism.

Pharmacokinetics were dose proportional with single doses up to 10 mg/day or with repeated daily doses up to 1.0 mg/day. A more than proportional increase in AUC was observed with daily doses of letrozole at 2.5 mg and 5 mg. With 2.5 mg/day the AUC increased 3.8 fold rather than the expected 2.5 fold, while with 5 mg/day the AUC increased 12 fold rather than 10 fold.. These increases in the AUC are thought to be due to saturation of the metabolic processes. A daily dose of 0.5 mg or of 2.5 mg letrozole appears to suppress estrogen levels to a similar degree although the assay use to measure estrone and estradiol may not sensitive enough to detect dose related differences at or below the lower levels of detcction. Letrozole concentrations at a steady state could not be correlated with the severity of adverse events. Time to progression may be longer with the higher dose level (See AR/BC2 review).

Increase in age does not effect letrozole drug concentration. Renal impairment (Creatinine clearance $\geq$ 9 cc/minute) does not significantly alter letrozole pharmacokinetics, but moderate hepatic impairment led to a 37% increase in the AUC. In patients with abnormal hepatic function studies the AUC value was similar to the values near the upper limit of normal for patients without hepatic function studies. No difference in trough letrozole levels were observed in patients with hepatic impairment on AR/BC2 as compared to normal patients which suggests that that no dose adjustment is needed for patients with mild/ moderate hepatic dysfunction (Child's Class A or B) especially if due to underlying metastatic disease. No drug-drug interactions have been observed with cimetidine, warfarin, benzodiazepines, or omeprazole.

II. REVIEW: PHARMACOKINETIC STUDIES IN HUMANS

The objectives of following studies were to: 1) to estimate the tolerability and possible side effects of CGS 20267; 2) to obtain preliminary information on the magnitude and duration of the decrease in estrogen levels and on the possible effects on other hormones; and, 3) to estimate basis pharmacokinetics after single / multiple doses of oral doses of CGS 20267.

I. Study HPL 14/89: CGS 20267 (Aromatase Inhibitor): Open Pilot Phase I Study with Increasing Single Oral Doses to Assess Systemic Tolerability and Endocrine Effects in Healthy Male Volunteers

Study Population:	Eighteen healthy male subjects ages 20 - 60
Treatment Plan:	Single oral dose / three males per dose
Dose Levels:	0.02, 0.1, 0.25, 0.5, 1.0, 2.5, 5.0, 10, or 30 mg with placebo control
Results:	Estrone levels began to decreased at all doses levels within 2-4 hours after administration. Maximal estrone suppression to 70-85% of baseline was reach at 24-48 hours. At the 2.5 mg dose level estone levels in some patients were below the lower limit of detection. Estradiol levels decreased with all doses within 2 - 4 hours with maximal suppression after 10 - 24 hours with clear cut dose-dependency. Slow return to baseline (return to baseline greater than three days) was noted for both estrone levels and estradiol level with the 5, 10, or 30 mg dose levels; return to baseline levels more rapidly for estradiol than estrone. Dose related increases in testosterone, LH, and FSH levels were noted for 6 - 13 days after administration. No drug related changes in cortisol or aldosterone. No effect on blood pressure, heart rate, ECG, or body weight.
Pharmacokinetics:	Dose proportional from 0.1 - 10 mg, but the AUC was overproportional for the 30 mg dose due to an increase in terminal half-life of letrozole (See Table PK-1)
Adverse Experiences:	Four reported at 5 and 30 mg: orthostatic hypotension (0.5 mg dose); moderate headache day 1 and migraine day 3 with 5 mg dose; mild headache day 1 with 0.02 mg in two patients.

II. Study HPH 9003: CGS 20267 (Oral Non-Steroidal Aromatase Inhibitor): Endocrine and Tolerability Double-Blind, Randomized Single Dose Phase I Study of CGS 20267 in Healthy Male Volunteers

Study Population:	Twelve healthy males ages 20 - 50
Treatment Plan:	Single Dose double blind crossover study
Dose Levels:	Placebo and film-coated tablets, 0.01, 0.05, 0.25 mg

Results:	Estrone (E_1) levels decreased within two hours with maximal suppression at 24 hours post dose with a slow return to baseline within 7 - 14 days with a flat dose response curve; Estradiol (E_2) decreased within two hours of dosing with maximal suppression at 24 hours and a return to baseline within seven days without clear cut relationship of dose level to suppression of hormone. No effect on serum aldosterone and cortisol; increase in testostero+ne at 48 hours; increase in LH and FSH; no effect on TSH. No influence of test drug on blood pressure, heart rate, and ECG.
Pharmacokinetics:	Dose proportionality of letrozole plasma pharmacokinetics was observed at the investigated dose levels. (See Table PK-1)
Adverse Experiences:	Three subjects with five adverse experiences: Two patients had headache and / or migraine on **both** study days (placebo and control); one patient with headache on treatment only.

III. HPH 9026: CGS 20267 (Oral non-steroidal aromatase inhibitor): Endocrine and Tolerability Double Blind, Randomized, Single-Dose Phase I Trial of 0.1, 0.5, and 2.5 mg CGS 20267 in Healthy Male Volunteers

Study Population:	Six healthy male subjects ages 20 - 50
Treatment Plan:	Single dose
Dose Levels:	0.1 mg, 0.25 mg, and 2.5 mg with placebo (two tablets / subject)
Results:	Estrone (E_1) was decreased within two hours all dose levels to a minimum at 24 - 48 hours (70% of baseline at the 0.1 mg dose level; 80% at the 0.5 and 2.5 mg dose levels). Estradiol (E_2) was decreased within two hours ate all dose levels with maximal suppression to 67% from baseline (0.1 mg) at 10 hours and to 80 % of baseline at 24 hours (0.5 mg and 2.5 mg). No effects on serum aldosterone and cortisol; a trend toward an increase in testosterone, androstenedione, and 17*a* - hydroxyprogesterone at 48 hours (not significant). Significant increase above baseline at 24 hours for LH and FSH; no effect on TSH. No influence of test drug on blood pressure, heart rate, and EKG.
Pharmacokinetics:	See table PK-1
Adverse Experiences:	No adverse events related to drug were reported.

IV. AR/HW1: CGS 20267- Non steroidal aromatase inhibitor: Double-blind Randomized Single Dose Phase I Trial in Healthy Postmenopausal Women

Study Population:	Twelve healthy postmenopausal women
Treatment Plan:	Single dose
Dose Levels:	Placebo, 0.1 mg, 0.5 mg, 2.5 mg
Results:	Estrone (E_1) decreased within two hours at each dose level with

	statistically significant maximal suppression at 48 - 72 hours to 75% of baseline for 0.1 and 0.5 mg doses and to 78% of baseline for 2.5 mg dose with trend toward recovery during fourteen day follow-up. Estradiol (E_2) decreased within 4 - 8 hours after each of three doses with maximal suppression of 75-78% of baseline at 72 hours for the 0.1 and 0.5 mg dose and 48 hours for the 2.5 mg dose. A trend to recovery was noted during 14 days of follow-up. No effect on other hormones (cortisol, aldosterone, 17-hydroxyprogesterone, testosterone, androstenedione, LH, FSH, or TSH). No deviations were noted in the biochemistry and hematology related to study drug.
Pharmacokinetics:	Pharmacokinetics were comparable to those reported in healthy men (See Table PK-1)
Adverse Experiences:	Well tolerated with headache reported eleven times in seven subjects including three following placebo making drug related causality remote.

V. AR/BC1 Core: CGS 20267: Non-steroidal Oral Aromatase Inhibitor. Open Phase I Trial in Postmenopausal Patients with Advanced Breast Cancer

Study Population:	Twenty-one compliant postmenopausal women under the age of 80 years with loco-regional recurrence or progression of metastatic breast cancer not responding to conventional treatment
Treatment Plan: Dose Level:	Seven patients at the 0.1 mg dose level; seven patients at the 0.5 mg dose level, and seven patients at the 2.5 mg dose level to be treated for twenty-eight days with continuation if treatment showed benefit during first twelve weeks of study.
Result:	Estrone (E_1) suppression was evident 24 hours after administration of first dose at 61% of baseline with maximal suppression at 78% of baseline on day 28 for 0.1 mg dose level; for the 0.5 mg dose level suppression was $\pm$ 78% on day seven with maximal suppression of 83% on day 28; for the 2.5 mg dose maximal suppression was $\pm$ 80% on day 7. Estradiol (E_2) suppression was 80% seen on day 7 with 0.1 and 2.5 mg and 77% for 0.5 mg on day 14. No statistically significant changes were seen in cortisol, aldosterone, androstenedione, 17-hydroxyprogesterone, FSH, LH, and TSH.
Pharmacokinetics:	Plasma kinetics were similar to the single dose kinetics in healthy volunteers; a slight dose overproportional increase in systemic exposure (AUC) was observed with the 2.5 mg dose (See Table PK-1)
Adverse Experiences:	No patients died or discontinued treatment within the 28 day study period. Six patients reported 21 adverse events on the 0.1 mg dose

level, seven patients reported sixteen adverse events on the 0.5 mg dose level, and six patients reported twelve adverse events on the 2.5 mg dose level. One mild adverse event, headache, was felt to be related to study drug with the other adverse events of mild or moderate severity more likely related to disease process. Most common adverse events include: headache - 6 patients; constipation - 3 patients; back pain - 3 patients; nausea - 2 patients; leukorrhea - two patients; musculoskeletal pain - two patients; pneumonitis - 2 patients; and, dyspnea - two patients.

VI. P01 Core: Open-label Dose Range Finding Trial of CGS 20267 in Postmenopausal Women with Metastatic Cancer

Study Population:	Postmenopausal women ($\geq$ age 18) with evaluable progressive metastatic breast cancer ER + or unknown, nonresponsive to conventional therapy with a life expectancy of $\geq$ 16 weeks and ECOG $\leq$ 2. Normal or specified renal, hepatic, and hematologic profiles; Twenty-three patients evaluable for safety, twenty-one for tumor response, and 14 patients continued on to the extension trial until disease progression or discontinuation for other reasons
Treatment Plan: Dose Levels:	In the Core Trial treatment with two ascending doses of letrozole occurred over the twelve week trial: Sequence I - letrozole 0.1 mg / 0.25 mg (8 pts.); Sequence II letrozole 0.5 mg / 1.0 mg (7 pts.) ; and, Sequence III - 2.5 mg / 5.0 mg (8 pts).
Results:	In the Core Trial serum estrone (E_1) and estradiol levels (E_2) were suppressed by $\geq$ 63% within 24 hours of the first dose of 0.1 mg, 0.5 mg, and 2.5 mg with estrogen suppression 85 - 94% after six weeks of treatment. Slight incremental increases in percent estrogen suppression occurred during the first six weeks of therapy. Serum estrone levels were significantly suppressed to $\pm$ 95% for all visits as were urinary estrone and estradiol (at least 80% suppressed). No further suppression of estrogen levels was noted during the extension trial. One confirmed partial response and six stable disease responses were observed in the core trial and one further confirmed partial response was noted in the extension trial. No clinically relevant changes were reported in vital signs, chest x-rays, or ECGs. Serum and urinary cortisol, serum androgen levels, cortisol and aldosterone response to ACTH challenge remained within normal limits. No changes were seen in plasma renin levels, serum or urinary electrolytes, or thyroid function.
Pharmacokinetics:	AUC values increased with dose proportionally in the dose range of 0.25 to 1.0 mg/day, increased slightly more than proportionally

	at 2.5 mg/day, and increased dose over-proportionally after 5 mg/day.
Adverse Events:	Trial related adverse events which were mild to moderate in severity included: nausea (5 patients); hot flushes (5 patients); hair thinning (2 patients); diarrhea (2 patients); dyspepsia (2 patients); increased sweating (2 patients). Most commonly reported adverse reactions in the core trial were bone pain, nausea, hot flushes, and vomiting. One patient's bone pain increased to grade 4 severity with treatment. In the extension trial one new case of nausea, of hot flushes, and of peripheral edema were reported. No patients discontinued trial due to adverse experiences.

VI. 2026701005: Comparative Bioavailability Study of Letrozole (CGS 20267) Under Fed and Fasting Conditions in Twelve Healthy Male Subjects after 2.5 mg Single Oral Administration

Study Population:	Twelve healthy male subjects ages 20 - 45
Treatment Plan:	One 2.5 mg tablet on an empty stomach (overnight fast) and one 2.5 mg tablet after a standardized breakfast rich in fat
Pharmacokinetics:	As compared with fasting conditions the administration of letrozole after food resulted in a lower C_{max} and prolonged T_{max}. These results indicate a decrease in the rate of drug absorption after food intake, but no overall effect on drug absorption.
Adverse Events:	Six of the twelve subjects reported nine adverse events: three upper respiratory infections, two cases of headache/migraine, one each of fungal infection of the feet, hay fever, and nausea.

VII. 2026701011: Absolute Bioavailability of Letrozole in Healthy Postmenopausal Women

Study Population:	Twelve postmenopausal women ages 52 - 61 years
Treatment Plan	Administration on an empty fasted stomach of a single dose of intravenous or oral letrozole 2.5 mg tablets
Pharmacokinetics:	Absolute systemic bioavailability of letrozole after p.o. administration was 99.9 $\pm$ 16.3% with slow, monoexpotential elimination of letrozole from the plasma. Total body clearance of letrozole from plasma after i.v. administration was low. Calculated volume of distribution at steady state suggests a rather high tissue distribution. Biotransformation of letrozole is the main elimination mechanism and renal excretion of conjugated CGP 44645 is the predominant metabolite (See Table PK-1).
Adverse Events:	Seven patients suffered from mild to severe headaches. No difference is noted in the tolerability between the oral and the intravenous dose.

VIII. 2026701018: Pharmacokinetics, Disposition, and Biotransformation of CGS 20267 (letrozole) in Healthy Postmenopausal Women after a Single Oral Dose of 2.5 mg ^{14}C Radiolabeled Preparation

Study Population:	Six healthy postmenopausal women ages 45 - 65
Treatment Plan:	After administration of the radiolabeled drug [^{14}C]GCS 20267 study subjects had serial blood/plasma sampling. Radioactivity was calculated for labeled letrozole, CGP 44645, and for conjugated CGP 44645 and of other metabolites.
Results:	Virtually complete absorption was observed with letrozole as the main radioactive component in the plasma. Slow elimination of letrozole and radioactivity from the plasma with a large inter individual variability in $T_{1/2}$. Low systemic exposure to metabolites with the primary metabolites including CGP 44645 (oxidation) and with glucuronic acid conjugation and urinary excretion. Excretion is predominantly renal and slow with 92% recovery after fourteen days. Enterohepatic recirculation of letrozole may occur to a small extent.
Adverse Events:	Three reports of headaches possibly related to drug in one patient and one report of faintness unlikely to be related to study drug. Transient leukopenia and neutropenia were reported in two subjects.

IX. 2026701003: A Study of Dose Overproportionality of the Pharmacokinetics of Letrozole (CGS 20267)

Study Population:	Twelve healthy postmenopausal women ages 30 - 75 with body weight within +20% or -15% of desired height and weight
Treatment Plan:	Six received a single 5 mg dose and six received a single 30 mg dose. Study subjects were followed for clinical symptomatology, laboratory abnormalities, and adverse events.
Results:	No effect on blood pressure, heart rate, or ECGs were noted. No clinically significant changes in laboratory parameters (hematology, chemistry, urinanalysis) were noted. The plasma $AUC_{(0-inf.)}$ after a 30 mg dose was overproportional by factor of 1.5 compared with $AUC_{(0-inf.)}$ after a 5 mg dose. Dose overproportionality was not observed for the C_{max} and $T_{1/2}$. Dose overproportionality was related to relatively less urinary excretion of the major metabolite, CGP 44645 consistent with saturation or autoinhibition of letrozole metabolism. Urinary excretion of CGP 44645 relative to letrozole and the rate of elimination of plasma letrozole appeared to increase with time or with decreasing plasma letrozole levels consistent with saturation or auto-inhibition of

	letrozole metabolism. CYP3A4 activity was no different in subjects who received 30 mg and those who received 5 mg.
Adverse Reactions:	No serious adverse reactions were reported. No listing of the types of adverse reactions is provided with most patients reporting mild adverse reactions and three patients reporting moderate adverse reactions.

X. 2026701006: Kinetics of Letrozole (CGS 20267) After a Single Oral Dose of 2.5 mg in Postmenopausal Women with Varying Degrees of Renal Insufficiency

Study Population:	Nineteen healthy postmenopausal women age 35 or older with varying degrees of renal impairment with body weight within ± 25% of normal body weight
Treatment Plan:	Single dose of letrozole 2.5 mg orally on an empty stomach with two week observation for clinical, laboratory, and pharmacokinetic parameters
Results:	Impaired renal function did not significantly alter AUC, C_{max}, $T_{1/2}$, or renal clearance of letrozole. Renal dysfunction did not influence renal excretion of either letrozole or its metabolite, CGP 44645. No abnormalities of vital signs or clinical laboratory parameters were reported.
Adverse Experiences:	Two patients had treatment related diarrhea of mild to moderate severity.

XI. 2026701007: Pharmacokinetics of Letrozole (CGS 20267) after a Single Oral Dose of 2.5 mg in Postmenopausal Women with Varying Degrees of Hepatic Insufficiency

Study Population:	Twelve postmenopausal women with varying degrees of abnormal liver function as measured by the Child-Pugh classification (normal, mild, or moderate hepatic impairment)
Treatment Plan:	Single 2.5 mg dose taken orally on an empty stomach (overnight fast) with two weeks of followup
Results:	No changes in laboratory parameters or in vital signs with treatment. Pharmacokinetics were consistent with a slower metabolism for letrozole in hepatically impaired patients, but no statistically significant differences in comparison of pharmacokinetic parameters between the two hepatically impaired groups was observed. Trends were observed which suggest that hepatic impairment has a minor effect on the pharmacokinetics of letrozole, but the pharmacokinetic changes are not significant enough to warrant a dose adjustment. Half-life prolongation was significantly correlated with increase in SGOT and SGPT.
Adverse Events:	Two cases of mild dyspepsia were reported. One patient with a

history of hypertension required hospitalization for angina, however the adverse experience was not considered related to ingestion of letrozole. No increase in number or severity of adverse reactions was noted with increased hepatic dysfunction.

XII. 2026701004: Pharmacokinetic Effect of Cimetidine on a Single 2.5 mg Dose of Letrozole in Healthy Subjects

Study Population:	Healthy male volunteers or postmenopausal women ages 18 -65 with body weight within ± 15% of normal body weight (Twenty-one were enrolled: two discontinued prior to receiving any drug, one discontinued for administrative reasons, and two discontinued due to adverse reactions after first dose of drug).
Treatment Plan:	Letrozole 2.5 mg orally as a reference agent and after one week of cimetidine 400 mg p.o. BID a second dose of letrozole 2.5 mg followed by cimetidine 400 mg po BID with two further weeks of followup
Results:	Cimetidine treatment had no effect on plasma letrozole pharmacokinetics associated with a single oral dose of letrozole 2.5 mg. No clinical or laboratory abnormalities which could be related to a cimetidine - letrozole interaction were observed.
Adverse Experiences:	No serious adverse experiences were reported. The adverse experiences which occurred during this study were not considered to be related to study drug.

XIII. 2026701017: Single Center, Multiple Dose, Open Randomized, Two-way Cross-over Study of Letrozole 2.5 mg (CGS 20267) and Single Dose Warfarin in 14 Healthy Male Subjects

Study Population:	Fourteen healthy males between the ages of 18 - 45 (One participant withdrew consent so thirteen men were studied.)
Treatment Plan:	Letrozole 2.5 mg orally for twenty days with a single 25 mg dose of warfarin on day 15 of letrozole treatment
Results:	A small (+ 4%) but significant increase was noted in the prothrombin time as measured under the prothrombin time / time curve during treatment with letrozole. An increase of 9% was noted in the prothrombin time over the control, but this increase was not considered to be large enough to warrant a change in the warfarin dose. (An increase of ≥ 25% in the prothrombin time would be the guideline used to recommend a reduction in the warfarin dose.) No difference in letrozole pharmacokinetics was observed. No effect on clinical laboratory variables, hormone levels, or sperm counts were observed.
Adverse Experiences:	No serious adverse experiences occurred. Most adverse

experiences were of mild severity. Two subjects had headache of moderate severity requiring paracetamol for relief. One subject had moderate sciatica not related to study drugs and bleeding gums and moderate migraine which were considered to be related to study drug. One participant had night sweats not related to study drug.

XIV: 2026701010: Bioequivalence Study of Three Formulations of 2.5 mg Letrozole after a Single Oral Administration to Healthy Male Volunteers

Study Population:	Twenty healthy male volunteers ages 18 - 45 with body weight ± 15% of normal (One study subject withdrew due to an adverse event and a second subject withdrew consent.)
Treatment Plan:	One of three formulations (Treatments A, B, and C) of letrozole 2.5 mg were given on an empty stomach after an overnight fast
Results:	No abnormalities in clinical parameters (vital signs, ECGs) or laboratory abnormalities were reported. The three formulations produced similar plasma concentration / time profiles. The AUC ratios and the corresponding confidence intervals [AUC for Trt C vs Trt A = 1.06; 90% CI: 1.00, 1.12; AUC for Trt C vs Trt B = 1.0; 90% CI: 0.97, 1.09] were well within the limits to establish bioequivalence (0.8, 1.25). The proportion of extrapolated AUC from the last time-point with a concentration different from zero to infinity was between 2.5 and 17.6% of $AUC_{0\text{-}inf}$.
Adverse Experiences:	No serious adverse experiences were reported. The majority of adverse experiences were mild in severity. One volunteer suffered moderate intermittent urticaria after receiving the first treatment considered to be treatment related and was withdrawn from the trial. A second study participant suffered moderate depression after initiation of study drug, but the depression was not considered related to study drug.

XV. 2026701008: Bioequivalence Study of Three Formulations of 0.5 mg Letrozole after a Single Oral Administration to Healthy Male Volunteers

Study Population:	Eighteen healthy male volunteers ages 18 - 45 (Nineteen volunteers were enrolled, but two withdrew consent.)
Treatment Plan:	Three single doses with a washout period of at least three weeks between the three different formulations of letrozole 0.5 mg (Final Market Image), 0.25 mg (European Formulation), and 0.5 mg (US Formulation).
Results:	No abnormalities of clinical or laboratory monitors were observed. The three formulations produced similar plasma concentrations / time profiles and the comparison of Treatment C to Treatment B

	($AUC_{0\text{-}inf}$ Trt C /$AUC_{0\text{-}inf}$ Trt B = 0.99 (CV = 16.0%) and for Treatment C to Treatment A ($AUC_{0\text{-}inf}$ Trt C/$AUC_{0\text{-}inf}$ Trt A = 1.00 (CV = 11.0%) demonstrated bioequivalence. Mean C_{max}, T_{max}, and $AUC_{0\text{-}168\ h}$ were similar after administration of the three formulations. The mean difference between the $AUC_{0\text{-}inf}$ was small (about 6% for each formulation).
Adverse Experiences:	One study participant had a moderate headache with the third study formulation and was treated with paracetamol. One participant had moderate flatulence and abdominal pain during the first treatment period. Both were considered unlikely to be related to study drug. Another volunteer developed mild lichenoid dermatitis on both hands which recurred after the second and third treatments. This dermatologic condition was considered to be related to study drug. One serious adverse reaction occurred. A volunteer was admitted to the hospital overnight for observation after complaining of severe right sided chest pain, which after evaluation to rule out pulmonary embolus, was found to be musculoskeletal in etiology.

XVI. AR/BC2 PK: Pharmacokinetic and Pharmacodynamic Evaluations in a Double Blind, Randomized, Multicenter, Comparative, Between-Patient Phase IIb/III Trial Comparing Daily Doses of 0.5 mg Letrozole versus 2.5 mg Letrozole versus 160 mg Megestrol Acetate as Second-Line Endocrine Therapy in Postmenopausal Patients with Advanced Breast Cancer

Study Population:	552 postmenopausal women with breast cancer which progress on adjuvant antiestrogens, within six months of discontinuation of adjuvant antiestrogens, or with therapeutic antiestrogens (See AR/BC2 Study Report)
Treatment Plan:	Daily oral therapy with letrozole 0.5 mg, letrozole 2.5 mg, or megestrol
Results:	Letrozole plasma trough concentrations increased more than proportionally for the 2.5 mg as compared to the 0.5 mg - eightfold increase rather then the expected fivefold increase. Age, body mass index, visit number, hepatic impairment, renal impairment, or comedications did not influence the letrozole plasma concentration. Mean estrone concentration was suppressed at least 80%, and mean estradiol concentration was suppressed at least 60 - 65% from baseline. Letrozole trough plasma concentrations were not a predictor for the degree of estrone or estradiol suppression. Higher letrozole plasma trough concentrations (> 300 nmol/L) were associated with a tendency to prolong TTP. Plasma trough concentrations did not correlate with the severity of AEs.

Table PK-1: Pharmacokinetic Parameters in Healthy Males and Healthy Postmenopausal Women

Study Number and Description	Dose (mg)	C_{max} (nmol/l)	T_{max} (hours)	$AUC_{0-infinity}$ (h x µmol/l)	$T_{1/2}$ (hours)
HPL 14/89: Single Dose in Healthy Males	0.1 0.25 0.5 1.0 2.5 5.0 10.0 30.0	3.82 ± 0.95 9.56 ± 2.21 22.7 ± 11.9 30.6 ± 4.0 103.0 ± 7.0 206.0 ± 56.0 330.0 ± 33.0 1236.0 ± 66.0	Median = 1	0.19 ± 0.11 0.46 ± 0.04 0.78 ± 0.45 1.54 ± 0.65 5.08 ± 0.49 7.63 ± 1.73 18.34 ± 0.7 263.0 ± 106.0	For 0.1 - 10.0 mg mean = 43 range: 236 (range:106-394)
HPH 9003: Single Dose in Healthy Males	0.01 0.05 0.25	0.86 ± 0.10 2.58 ± 0.75 9.75 ± 0.94	Median = 1.5	0.86 ± 0.10 2.58 ± 0.75 9.75 ± 0.94	41 (range:
HPH 9026: Single Dose in Healthy Males	0.01 0.50 2.50	4.05 ± 0.13 22.9 ± 1.8 99.6 ± 13.7	Median = 2	175.0 ± 16 996.0 ± 45 6020.0 ± 1370	44 (Range:
AR/HW1: Single Dose in Healthy Postmenopausal Women	0.1 0.5 2.5	4.47 ± 0.65 23.8 ± 2.05 130.0 ± 20	Median = 1	160.0 ± 60 1040.0 ± 220 6210.0 ± 2200	Median = 51 (Range:
2026701005: Bioavailability in Healthy Males	2.5 Fasting Fed	129.0 ± 20.3 98.7 ± 18.6	Median = 1 Median = 2	5920 ± 2470 5730 ± 2240	50.2 ± 21.8 49.7 ± 18.3
2026701011: Bioavailability in Healthy PM Women	2.5 (PO) 2.5 (IV)			4290 (2320, 7740) 4330 (2540, 7960)	42.0 45.4
2026701018: PK, Disposition, Biotransformation of Radiolabelled Drug in Healthy PM Women	2.5 mg	Median = 2	88.6 ± 10.8	4919 ± 1639	50.8 ± 19.2
2026701003: Overproportionality of Letrozole PK in PM F	5 mg 30 mg	248 ± 52 1332 ± 144		10.8 ± 2.4 97.0 ± 28.4	60.0 ± 18.8 74.5 ± 28.4

SUMMARY: PHARMACOLOGY / TOXICOLOGY

I. SUMMARY:

Acute toxicology studies were performed in mice, rats, and beagle dogs. The principal toxicities were reduced motor activity, hypotonia, recumbency, piloerection, irregular respirations, skin and mucosal hyperemia with complete recovery in surviving animals and no finding on necropsy. In the mouse the LD_{50} was > 2000 mg/m^2, in the rat > 12,000 mg/m^2, and in the beagle dog about 3000 mg/m^2. In the subacute studies (fourteen days to three months) in females of all species signs of estrogen deprivation including disturbed estrous cycle, increased body weight, increase in free testosterone, with ovarian follicular hemorrhage, cystic and atretic follicles, decreased uterine weights, and vaginal atrophy. In the salivary glands of females epithelial duct hypertrophy / hyperplasia were observed. As the dose of letrozole (CGS 20267) and the length of drug exposure increased the severity of the clinical signs increased. In male of all species signs of testosterone deprivation occurred including decrease in hemoglobin, hematocrit, red cell mass, a decrease in the relative and absolute testicular weight, seminiferous tubular atrophy, epididymal oligospermia, and testicular interstitial cell hyperplasia. In both sexes, although at a higher dose level, in the male liver enzyme changes and hepatocellular changes were noted.

With longer dosing periods (three months to one year) in the rat and in the dog additional changes were noted. In females ovarian interstitial cell hyperplasia, mammary duct gland hyperplasia with increased secretions, decreased bone density, adenopituitary hyperplasia, hypertrophy of thyroid follicular cells, thymic atrophy, increase in serum cholesterol, elevated liver enzymes (GGT)and hepatocellular hypertrophy were observed. In males prostatic atrophy, decreased mammary gland proliferation, and in decreased in bone diameter / weight both species and at higher doses in dogs evidence of hepatic and renal tubular damage. In males at higher doses and / or with prolonged exposure basophilic cells of the pituitary hypertrophied. In rats the changes were reversible at three months and partially reversible in the six/twelve month study group. In dogs treated for three months or more the hormone effects were not reversed by the end of the recovery period.

In the toxicology studies drug effects are hormonal in nature with direct effect on the reproductive organs of both sexes and indirect effects on other endocrine organs (adrenal, thyroid, hypopituitary), the organ weight / size of non-endocrine organs (thymus, kidneys), bone density, bone marrow cellularity, and on the epithelial lining of the salivary glands. Liver function abnormalities and hepatic changes are considered related to the drug induction of the hepatic drug metabolizing enzymes. Renal tubular changes appear to be due in part to hypercalcemia due to bone resorption in the dog. Epithelial, conjunctival, and dermal irritation testing were negative in rabbits. The changes due to estrogen depletion are not reversible after prolonged exposure with the dog the more sensitive species to letrozole.

Carcinogenicity studies conducted for one hundred four weeks in mice resulted in the appearance

of benign ovarian theca cell tumors at doses greater than 60 mg/kg (mg/m^2) with a decrease in the number of benign and malignant mammary gland tumors. In reproductive toxicology studies in rats maternal toxicity was reported at all doses, with embryo and fetotoxicity at doses $\geq$ 0.03 mg/kg (0.09 mg/m^2). In the rat teratogenicity and maternal toxicity were observed at doses of 0.03 (0.18) mg/kg (mg/m^2) and embryo- and fetotoxicity at doses greater that 0.003 (0.018) mg/kg (mg/m^2). Similar findings were observed in rabbits at doses $\geq$ 0.066 mg/m^2. Mutagenicity testing was negative.

Radiolabeling studies in mice, rats, and dogs showed the greatest accumulation of radiolabel in the liver and adrenal with renal and fecal excretion over three to seven days depending on the species and sex. Oral bioavailability studies indicated that 100% of the dose was absorbed. AUC and C_{max} increased proportional to increasing dose in mice and rats. With repeated dosing drug accumulation was observed in rats but not in mice. In rabbits at higher doses (66 mg/m^2) an over proportional increase in AUC was reported. In dogs with fourteen days of administration drug accumulation was observed. In long term studies in dogs the AUC was higher on days 182 and 364 than on day 1 at doses from 0.6 mg/m^2 to 60 mg/m^2 but the trough plasma concentrations were proportional to dose. Protein binding was between 50 -60% in all species tested which is comparable to binding in human serum.

Studies of the P450 system using human livers (females) indicated binding to the ferric form of the heme moiety with inhibition of CYP2A6 (K_i = 0.12 *u*M) and CYP2C19 (K_i = 9.0 *u*M). In male and female rats treated for three weeks induction of hepatic microsomal enzymes was noted along with hepatocellular hypertrophy and increased hepatic size. Studies *in vitro* indicated that CGS 20267 inhibit aromatase but its metabolite CGP 44645 does not. *In vitro* studies indicate that the drug is a much more potent aromatase inhibitor than either aminoglutethimide or anastrozole.

In studies with DMBA and NMU induced estrogen dependent mammary carcinomas letrozole caused tumor regression of established tumors and suppressed new tumor development. In a study of letrozole vs. anastrozole treatment of the above tumor types, letrozole demonstrated efficacy while minimal effect on tumor growth was demonstrated with a comparable doses of anastrozole.

With intravenous administration of high doses (36 - 360 mg/m^2) of letrozole to cats, cardiac arrhythmias which in some instances resulted in sudden death was observed. Higher doses (120 - 360 mg/m^2) caused decreased respiratory rates. Some of the cardiac effects could be attenuated with propranolol. No effects on blood sugar were observed in male rats. Neurotransmitter studies in rats and mice did not reveal any effect on neurotransmitters with oral dosing. Temperature elevations about two hours after dosing with rapid return to normal was the only abnormality reported.

II. REVIEW of PHARMACOLOGY STUDIES:

1. Acute Toxicology Studies:

A. Mice (Test No. 896022) Oral:

Dose Levels:	200 mg/kg (600 mg/m^2) and 2000 mg/kg (6000 mg/m^2)
Study Group:	One male/group or five/sex/group
Clin-Path Findings:	200 mg/kg- no findings 2000 mg/kg - reduced spontaneous motor activity with ataxia; hypotonia; irregular respirations; piloerection; skin hypothermia; inhibition of pain response; hyperemic skin and visible mucosa; Death in 1/15 females; resolution of clinical signs in three days. Decreased body weight gain initially which resolved. Necropsy unremarkable.
LD_{50}	> 2000 mg/kg (6000 mg/m^2)

B. Rats (Test No. 896023) Oral:

Dose Levels:	2000 mg/kg (12000 mg/m^2)
Study Group:	Five/sex/group
Clin-Path Findings:	Reduced spontaneous motor activity; ataxia; dyspnea; muscular hypotonia; venterocumbency; inhibition of pain response; ruffled coat; skin hypothermia; chromodacryorrhea; salivation; increased defecation; resolution of clinical signs in 5 days. Decreased body weight gain during observation period. Necropsy unremarkable
LD_{50}	> 2000 mg/kg (12,000 mg/m^2)

C. Rats (Test No. 896024) Intraperitoneal:

Dose Level:	50 mg/kg (300 mg/m^2); 500 mg/kg (3000 mg/m^2)
Study Group:	Five / group / sex
Clin-Path Findings:	50 mg/kg - reduced spontaneous motor activity and irregular respirations for twenty-four post dosing. 500 mg/kg - death in 3/5 females within twenty-four hours of dosing; death in 1/5 males within seven days of dosing; reduced spontaneous motor activity; irregular respirations; skin and mucosal hyperemia; skin hypothermia; ptosis; ataxia; ruffled fur; labored respirations followed by ventricumbency with relaxed head; muscular hypertonia; extended limbs, diarrhea; chromodacryorrhea; and arched backs; after four days - stereotypy; after six days - no clinical signs; no gross finding at necropsy
LD_{60}	500 mg/kg (3000 mg/m^2)

D. Beagle Dogs (Test No. 896025):

Dose Levels:	100 mg/kg (2000 mg/m^2); 200 mg/kg (4000 mg/m^2)
Study Group:	One male /group
Clin-Path Findings:	100 mg/kg (2000 mg/m^2)- increased startle for three days; hyperactivity, ataxia followed by tonic clonic convulsions for two days; labored respiration for two days; rowing motions of the limbs in laterocumbency for two days; muscular hypertonia for four days; reduced spontaneous locomotor activity for two days; tremor; increased salivation; chomping for two days; and increased urinary output for two days; transient diarrhea at day 11. Asymptomatic on day 12. 200 mg/kg (4000 mg/m^2)- Similar toxicities as in the 100 mg/m^2 group with greater severity causing death due to tonic-clonic convulsions with respiratory arrest and death; tachycardia and hyperthermia also noted prior to death; Macroscopic finding include: subcapsular splenic hemorrhages; hyperemic gastric mucosa; congestion / hemorrhage in the proximal small intestine
LD_{100}:	200 mg/kg (4000 mg/m^2)

2. Subacute Studies:

A. Thirteen Week Oral Toxicity Study in Mice (MIN 924133):

Dose Levels:	0.6 mg/kg (1.8 mg/m^2); 6 mg/kg (18 mg/m^2); 60 mg/kg (180 mg/m^2)
Study Group:	Ten / sex / group
Clin-Path Findings:	0.6 mg/kg - Males: increased absolute and relative renal weights; Females: ovaries partially or totally containing dark lesions with microscopic findings of absent corpora lutea, ovarian hemorrhage, vaginal epithelial atrophy; mandibular salivary gland epithelial duct hypertrophy. 6 mg/kg - Females: increased body weight; increase in absolute and relative kidney wt., hepatic, and salivary gland wts. with salivary duct epithelial hyperplasia; decreased absolute and relative uterine weights with uterine atrophy; atrophy of vaginal epithelium; ovaries completely or partially filled with darken lesions; microscopic loss of corpora lutea and hemorrhages w/in ovary. 60 mg/kg: decrease in RBC parameters; increased absolute and relative renal and hepatic weight; microscopic hepatic changes including hepatocellular atrophy; Females - decreased uterine wts.; darkened ovaries with absent corpora lutea, uterine atrophy, vaginal epithelial atrophy; Males - decrease in relative and absolute testicular weight with seminiferous tubule atrophy, epididymal oligospermia, and testicular interstitial cell hyperplasia.

B. Fourteen Day Intravenous Toxicity Study in Rats (Test No. 946092):

Dose Levels:	0.03 mg/kg, (0.18 mg/m^2); 0.3 mg/kg (1.8 mg/m^2); 3 mg/kg (18 mg/m^2)
Study Group:	5/sex/group
Clin-Path Findings:	≥ 0.03 mg/kg: decreased food consumption; Females - decreased cholinesterase activity; disturbed estrous cycle; increased ovarian wt.: cystic and / or atretic ovarian follicles; vaginal epithelial atrophy or hyperplasia with mucification and cellular debris. ≥ 0.3 mg/kg: Males - decreased body wt.; Females- increased body wt; decreased uterine wt.; uterine atrophy (micro); slight lobular hyperplasia of mammary glandular tissue. 3 mg/kg: one death (1/6 females in the satellite group); decreased activity, ventral recumbency; dyspnea; pallor; muscular hypotonia immediately postinjection; decreased total protein and albumin; decreased Hgb. and RBC indices; on necropsy decreased uterine size and increased number of hepatocellular mitotic figures

C. Twenty-eight Day Oral Dose Finding Study in Rats (Test No. 886120):

Dose Levels:	0.5 mg/kg (3.0 mg/m^2); 5 mg/kg (30 mg/m^2); 5 mg/m^2)
Study Group:	Five/sex/group
Clin-Path Findings:	≥ 0.5 mg/kg: Males - decreased body wt; Females - increased body wt.; constant diestrus from week 2/3; decreased plasma cholinesterase; increased free testosterone; increased leukocytes and lymphocytes; decreased uterine weights; microscopic-decreased ovarian corpora lutea with increase in partially atretic follicles and corpora luteal cysts; uterine atrophy; vaginal epithelial atrophy ≥ 5 mg/kg: as above and increased alk. phos.; increased ALAT; microscopic-increased fatty change in the liver; increased thyroid follicular epithelial height; splenic hemosiderosis 500 mg/kg: as above and in Females - stiff gait; arched back; sunken flanks; decreased body wt. associated with transient decrease in food consumption; increased AST with increased liver wt.; micro - pituitary cell hypertrophy; Males - increased liver wt.; decreased epididymal, seminal vesicle and prostate wt.; microscopic evidence of eosinophilia and centrilobular hepatic hypertrophy; adrenal cortical vacuolization

D. Three Month Oral Toxicity Study in Rats (Test No. 896056):

Dose Levels:	0.3 mg/kg (1.8 mg/m^2); 3 mg/kg (18 mg/m^2); 30 mg/kg (180 mg/m^2)
Study Groups:	15/sex/group
Clin-Path:	≥ 0.3 mg/kg: Females- increased body wt.; signs of continuous diestrus;

decreased adrenal, pituitary, and uterine wts.; increased ovarian wt.; on necropsy decreased uterine size; histological changes included absent corpora lutea; increased old corpora lutea; stromal edema with increase in Sertoli-like structures; tendency toward follicular atresia; uterine atrophy; vaginal epithelial atrophy; 0.3 mg/kg (1.8 mg/m^2); 3 mg/kg (18 mg/m^2); mammary gland proliferation with increased secretory activity; Males - prostatic atrophy; decreased mammary gland proliferation; Both- adenopituitary hypertrophy / hyperplasia.
$\geq$ 3.0 mg/kg: as above and in Females - increase in leukocytes / lymphocytes; Males - decreased epididymal, seminal vesicle, and prostate wt.; Both - centrilobular hepatocellular hypertrophy; mild vacuolization and fatty changes in some animals
30 mg/kg: Females - Nonspecific clinical signs with increased in liver and splenic wts.; Males - decreased body wts.; Both - increased thyroid follicular epithelial height; increased extramedullary hematopoiesis; increased reactive hyperplasia in axillary lymph nodes; All changes partially to completely reversed by end of recovery period

E. Six / Twelve Month Oral Toxicity Study in Rats (Test No. 916010):

Dose Levels:	0.3 mg/kg (1.8 mg/m^2); 3 mg/kg (18 mg/m^2); 30 mg/kg (180 mg/m^2)
Study Groups:	40 / sex / group
Clin-Path Findings:	$\geq$ 0.3 mg/kg: Males - decreased body wt. and food consumption; decreased seminal vesicle wt with (microscopic) atrophy of seminal vesicles ; Female - increased body wt.; increased LH, alk. phos. activity; deceased cholinesterase activity; decreased gamma globulins; cessation of estrous cycle; atrophy of uterus and vaginal epithelium with microscopic ovarian changes of absent corpus lutea, stromal hyperplasia, and sertoli cell hyperplasia; diffuse hypertrophy of the thyroid follicular cells; hypertrophy of ant. pituitary cells, and bone marrow hypercellular $\geq$ 3.0 mg/kg: as above and Females - increased cholesterol; increased lymphocytes and total leukocyte counts; increased incidence of fatty changes and centrilobular hepatic hypertrophy; Males - decreased bone diameter with decrease in bone weight 30 mg/kg: as above and Females - five sacrificed between eight - nine months due to bone fractures correlated with decrease in bone diameter and bone weight; increased liver weights; Clinical signs of decreased activity, muscular hypotonia; uterine atrophy; Males - increased in liver weights; bone marrow hypercellularity; diffuse pituitary hypertrophy; slight nodular Leydig cell hyperplasia. Changes were partially reversible.

F. Fourteen Day Intravenous Toxicity Study in Dogs (Test No. 946093)

Dose Levels:	0.02 mg/kg (0.4 mg/m^2), 0.2 mg/kg (4.0 mg/m^2); 2 mg/kg (40 mg/m^2)
Study Groups:	3 / sex / group
Clin-Path Findings:	In all groups injection site irritation due to vehicle > 0.02 mg/kg: increased ovarian wt. with minimal Leydig cell hyperplasia, corpus luteal and follicular cysts $\geq$ 0.2 mg/kg: enlarged ovaries with increase in size and number of corpora lutea; vaginal epithelial atrophy

G. Twenty-eight Day Oral Dose Range Finding Study in Dogs (Test No. 886121):

Dose Level:	5 mg/kg (100 mg/m^2)
Study Group:	Two/sex/group
Clin-Path Findings:	5 mg/kg -sporadic diarrhea, lacrimation, watery nasal discharge (M), reddened ears; increased plasma calcium, increased urea and free testosterone (M); increased ALAT, ASAT, triglycerides, total protein, albumin in (F); increased alpha-2 globulin. Decreased thymic weight with reduction of thymic lymphoid tissue on microscopic exam. Decreased uterine weight with uterine atrophy and regression to juvenile vaginal appearance. Increased ovarian weight with grossly visible ovarian cysts on necropsy with large and occasionally cystic corpora lutea. Adrenal cortical atrophy with reduced adrenal wts.. Microscopic evidence in both sexes of chronic tubular renal lesions. Increased hepatic weight with hepatocellular swelling (necrosis and slight focal inflammation in females only. Nondevelopment of mammary glandular tissue in females. In males hypertrophy / hyperplasia of Leydig cells with minimal disturbance of spermatogenesis.

H. Three Month Oral Toxicity Study in Dogs (Test No. 896026)

Dose Levels:	0.03 mg/kg (0.6 mg/m^2); 0.3 mg/kg (6.0 mg/m^2); 3 mg/kg (60 mg/m^2)
Study Group:	3 - 6 beagle dogs / sex / group
Clin-Path Findings:	0.03 mg/kg: Females only - increased body wt.; microscopic evidence of papillary hyperplasia of the uterus $\geq$ 0.03 mg/kg: Males - decreased serum cholesterol; marked hypertrophy of LH and FSH staining cells in the pituitary; Leydig cell hypertrophy; spermatogenic arrest; tubular atrophy in the testicles; decreased thymic wt. with thymic atrophy; Females - increased ovarian wts. with histopath changes including increase in number and size of corpora lutea; cystic degeneration of the follicles and corpora lutea; increased mammary gland proliferation and secretory activity; marked hypertrophy of the LH and

FSH positive cells in the pituitary
0.03 mg: Females - increased body wt.
≥ 0.3 mg/kg: Females - decreased plasma cholesterol; decreased red cell indices; enlarged or cystic ovaries grossly with increased number of follicles with luteinization; Males - decreased testicular weights with absence of spermatozoa in the epididymides
3 mg/kg: Both sexes: increased alpha-2 globulin; increased beta-1 globulin; Females - thymic atrophy.
Hormone effects were not reversed by the end of the recovery period.

I. Six / Twelve Month Oral Toxicity Study in Dogs:

Dose Levels:	0.03 mg/kg (0.6 mg/m^2); 0.3 mg/kg (6.0 mg/m^2); 3 mg/kg (60 mg/m^2)
Study Groups:	8 / sex / group
Clin-Path Findings:	≥ 0.03 mg/kg: Skin lesions in individual dogs; hypertrophy of the basophilic cells in the adenohypophysis; Females - fewer occurrences of estrus at lower doses; increased gamma-glutamyl transpeptidase activity; increased ovarian wt. with enlarged and / or cystic ovaries; microscopic lesions related to the inhibition of estrogen synthesis including hyperplasia of corpora lutea, atrophy of ovarian follicles , formation of luteal and / or follicular cysts; hyperplasia of the mammary glands; cytoplasmic hyaline droplets in the renal tubular epithelium; epidermal acanthosis, thymic atrophy; Males - tubular atrophy; Leydig cell hyperplasia; hypertrophy of the basophilic cells in the adenohypophysis; ≥ 0/3 mg/kg: Females - weight lost during the first six months with slight increase in body wt.; increased liver weight; decreased uterine wt. with uterine atrophy; centrilobular liver cell hypertrophy; Males - decreased epididymis and testicular weights. 3 mg/kg: Both - Increased liver weight; Females - no signs of estrus; decreased neutrophil counts; vaginal atrophy; epidermal acanthosis, thymic atrophy; Males - decreased testicular size
Comments:	Dose related increase in gamma-glutamyl transpeptidase activity considered to reflect induction of hepatic drug metabolizing enzymes. At end of recovery period testicular and uterine wts. comparable to controls and uterine and vaginal epithelial atrophy were reversed. No reversal or partial reversal of gamma-glutamyl peptidase levels, ovary, testicular, and liver weights, microscopic lesions in the testes, changes in the ovaries, mammary glands, skin, thymus, kidneys, and liver was noted at all doses. Daily oral dose of 0.03 mg/kg (0.6 mg/m^2) was considered no adverse effect level by the applicant.

3. Carcinogenicity Studies:

A. One Hundred Four Week (Gavage) Carcinogenicity Study in Mice:

Dose Level:	0.6 mg/kg (1.8 mg/m^2); 6 mg/kg (18 mg/m^2); 60 mg/kg (180 mg/m^2)
Study Group:	70/sex/group (for toxicokinetic sampling; 5 - 15/sex/group)
Clin-Path Findings:	≥ 0.6 mg/kg: Clinical signs of abrasion; blepharitis; lacrimation (M); ocular discharge and hair loss; increased body wt. and % body wt. gain; increased food consumption (M); benign ovarian stromal tumors. nephropathy, hepatocellular hypertrophy ≥ 6 mg/kg: scabbing of skin; swollen neck, swollen appendages ≥ 60 mg/kg: decreased survival due to dermal irritation; dry and weight perineal stains (F); lacrimation (F); Increased body wt. and % body wt. gain followed by reduced body weight and % body weight gain; hepatocellular hypertrophy (F);.Dose related increase in number of benign ovarian granulosa theca cell tumors, atrophy of the genital tracts of both sexes at all doses and progressive worsening of dermal irritation with death are considered to be due to the inhibition of estrogen synthesis / severe estrogen deficiency. Toxicokinetic analysis indicated dose-proportional, systemic exposure to study drug was similar for both sexes with no accumulation in the plasma after approximately seventy-eight weeks.

B. One Hundred Four Week (Gavage) Study in the Rat (MIN 924172):

Dose Level:	0.1 mg/kg (0.6 mg/m^2); 1.0 mg/kg (6.0 mg/m^2); 10 mg/kg (60 mg/m^2)
Study Group:	60 / sex / group
Clin-Path Findings:	Reduced incidence of benign and malignant mammary tumors and uterine polyps at all dose levels; Increased incidence of benign ovarian stromal tumors and urinary bladder papillomas ≥ 0.1 mg/kg: Males - decreased body wt., decreased body wt. gain, decreased food consumption; Females - increased incidence of enlarged ovaries with microscopic ovarian stromal hyperplasia; ascending urinary tract infections with visible urinary calculi and urinary bladder papilloma; vaginal inflammations; centilobular hepatocellular hypertrophy; parathyroid hyperplasia; pituitary vacuolation ≥ 1 mg/kg: increased incidence of hepatic enlargement with centrilobular hepatocellular hypertrophy and bile duct hyperplasia with hepatocellular necrosis in the females 10 mg/kg: microscopic alterations of hepatic vacuolation, bile duct hyperplasia; increased incidence of benign ovarian stromal tumors; increased incidence of chronic progressive nephropathy and fibrous osteodystrophy

Toxicokinetic analysis: dose related, but not dose proportional systemic exposure with increasing dose and slight compound accumulation at low doses

V. Reproductive Toxicology Studies:

A. Oral Dose-Range Finding Study for the Effects on Embryo and Fetal Development in Rats (MIN 954026)

Dose Levels:	0.005 mg/kg (0.06 mg/m^2); 0.03 mg/kg (0.18 mg/m^2); 0.3 mg/kg (1.8 mg/m^2); 1.0 mg/kg (6.0 mg/m^2) given on gestation days 6 - 17
Study Group:	8 females / group
Clin-Path Findings:	0.005 mg/kg: vaginal bleeding, decreased food consumption; enlarged placenta on necropsy 0.03 mg/kg: vaginal bleeding and staining; decreased food consumption; on necropsy enlarged placenta surrounded by blood, fluid filled uterus, with uterine lesions / eroded lining; increased in early, late, and total resorptions; increased postimplantation with decreased live fetuses and increase in mean fetal body weight 0.3 mg/kg: vaginal bleeding with decreased food consumption; on necropsy fluid filled rigid and ruptured uteri with conceptuses in the abdominal cavity; increased early, late, and total resorptions; increase mean and percent postimplantation loss, decreased live fetuses; increased mean fetal body weights; two fetuses in one liter with hind leg hyperextension and anogenital swelling 1.0 mg/kg: 2/8 deaths observed; vaginal bleeding; decreased food consumption; necropsy finding of fluid-filled, rigid, and ruptured uterus with conceptuses in abdominal cavity; increased early, late, and total resorptions; increase mean and percent postimplantation loss; decreased live fetuses; increased mean fetal body weights and single incidence in each of two litters of umbilical hernia, fluid-filled shoulder / foreleg, or fluid filled mass in the head
Conclusion:	Maternal toxicity at all doses; Embryotoxicity and fetotoxicity at doses $\geq$ 0.03 mg/kg.

B. Oral Study For Effects on Embryo and Fetal Development in Rats (MIN 924027)

Dose Levels:	0.003 mg/kg (0.018 mg/m^2); 0.01 mg/kg (0.06 mg/m^2); 0.03 mg/kg (0.18 mg/m^2) on days 6 - 17
Study Group:	26 females / group
Clin-Path Findings:	$\geq$ 0.003 mg/kg: vaginal bleeding, decrease in mean food consumption; decrease in mean body wt. gain on gestation days 18 -20; increase in mean early, late, and total resorptions; increase in the mean postimplantation

	loss and percent post implantation loss; decrease in the mean number of live fetuses; increase in mean fetal body wts.; fetal visceral observations of short renal papilla and dilated ureter ≥ 0.01 mg/kg: fetal skeleton - bipartate sternebrae 0.03 mg/kg: death in 1/26; on necropsy fluid-filled, rigid, eroded and/or ruptured uteri; increased mean number of dead fetuses; fetal malformations of domed head and fused centrum / vertebrae with edema / swelling
Conclusion:	Teratogenicity and maternal toxicity are observed at 0.03 mg/kg and embryotoxicity and fetotoxicity are observed at doses of ≥ 0.003 mg/kg

C. Oral Dose-Range Finding Study for Effects on Embryo and Fetal Development in Rabbits (MIN 954024)

Dose Levels:	0.006 mg/kg (0.066 mg/m^2); 0.06 mg/kg (0.66 mg/m^2); 0.6 mg/kg (6.6 m mg/m^2); 2.0 mg/kg (22 mg/m^2); 6 mg/kg (66 mg/m^2)
Study Group:	8 females / group
Clin-Path Findings:	0.006 mg/kg: no significant findings ≥ 0.06 mg/kg: probable vaginal bleeding as evidenced by blood in cage pan; on necropsy dark red / black corpora lutea indicative of regression with increase in mean early and total resorption; postimplantation loss and percent postimplantation loss with decrease in mean number of live fetuses 0.6 mg/kg: blood filled uterus ≥ 0.6 mg/kg: decrease in mean body wt; 6 mg/kg: decrease in mean food consumption
Conclusion:	No effect level = 0.006 mg/kg (0.066 mg/m^2) Since 100% resorption at doses ≥ 2 mg/kg no fetus examinations could be performed; No gross abnormalities observed at lower doses

4. Mutagenicity Testing:

A. Ames Test:

Using Salmonella typhimurium (T-100, TA-1537, TA-98 stains) and E. Coli (WP2uvrA) with and without metabolic activation using rat liver S9 microsomal fractions no mutagenicity was observed.

B. Chromosome Studies:

Studies of the genome of CHO cells (CCL 61; V79) with and without metabolic activation using rat liver S9 microsomal fractions show no evidence of a clastogenic effect. Examination of the femoral bone marrow in Sprague-Dawley rats after single doses of 40 mg/kg (240 mg/m^2), 80