CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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Clinical Pharmacology and Biopharmaceutics Review

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Type of Submission: NDA -- NME, 1S

*changed per discussion E.A. Rahman 5/12/97 ddspilman

Generic Name: Letrozole

Formulation: oral, tablet

Sponsor: Ciba-Geigy Corporation
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Summit, New Jersey 07901-1398

Reviewer: Gene M. Williams, Ph.D.
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1. Synopsis

1.1 Clinical pharmacology and *in vitro* metabolism

Letrozole is an inhibitor of the aromatase enzyme system. The putative mechanism of anti-tumor action is the inhibition of the biosynthesis of estrogens (estrone and estradiol), thereby eliminating the stimulatory effect of estrogens on the growth of estrogen-dependent tumor tissue. The sponsor seeks to have the drug approved for the treatment of advanced breast cancer, in women with natural or artificially induced postmenopausal status, following antiestrogen therapy.

assays were used to measure letrozole and it's metabolites in human blood, urine and feces. These assays were validated with samples prepared by adding known amounts of the compound of interest to the appropriate biological matrix (eg. plasma). Using these assays, the sponsor studied the pharmacokinetics and biopharmaceutics of letrozole in humans and provided individual study reports of their investigations. The results can be summarized as follows:

- Letrozole is only weakly bound to plasma proteins (60%), mainly to albumin (55%). The concentration in the erythrocyte fraction is about 80% of that in plasma.

- Letrozole is rapidly and extensively distributed into tissues. Its volume of distribution at steady state is about 2 L/kg.

- The disposition of letrozole is characterized by a dominant terminal elimination phase with a half-life of about 2 days. Letrozole is eliminated mainly via metabolism. Metabolic clearance is estimated to be about 95% of total plasma clearance. The major metabolite, which is inactive in inhibiting aromatase, is 4,4'-methanolbisbenzonitrile (CGP 44645). It is eliminated almost exclusively as its glucuronide into urine. Systemic exposure to metabolites is low. Exposure to unchanged compound represented about 82% of the exposure to total radioactivity after administration of ^{14}C-labeled letrozole.

- The pharmacokinetics of letrozole were dose proportional after single oral doses up to 10 mg and after daily doses up to 1.0 mg. After a 30 mg single oral dose there was a slightly dose over-proportional increase in AUC. With daily doses of 2.5 and 5 mg the AUCs increased about 3.8 and 12 fold instead of 2.5 and 5 fold, respectively, when compared to the 1.0 mg/day dose. The recommended dose of 2.5 mg/day may thus be a borderline dose at which an onset of over-proportionality becomes apparent, whereas at 5 mg/day the over-proportionality is more pronounced. Steady state levels were reached after 1 to 2 months at all dosage regimens tested (0.1 - 5.0 mg daily).

- Daily administrations of 0.5 and 2.5 mg letrozole were found to suppress serum estrogen levels to a similar degree. However, the assay for serum estrogens was insensitive to the extent that significant dose-related differences in estrogen suppresion might not be detectable. High steady state letrozole concentration (>300 mnol/L, dose: 2.5 mg/day) showed a tendency to be associated with a prolongation of the time to tumor progression.

- Letrozole concentration at steady state was not correlated to the severity of adverse experiences.

- Age had little or no effect on letrozole concentrations. Dose adjustment due to age is not necessary for adult patients.

- No influence of renal impairment (creatinine clearance ≥ 9 mL/min) on the pharmacokinetic parameters of letrozole was found. Dose adjustment for patients with renal insufficiency is not necessary.

- Volunteers with moderate hepatic impairment displayed a 37% increase in AUC when compared to healthy subjects. However, the values were still within the range observed in studies with healthy volunteers. In AR/BC2 breast cancer patients with changes in liver parameters showed no statistically significant alteration of their letrozole trough levels.

- No clinically significant drug-drug interactions have been observed with cimetidine or warfarin.

- In recombinant c-DNA expressed human microsome systems, CYP3A4 metabolized letrozole to CGP44645 while CYP2A6 formed both CGP 44645 and CGP 44646 (the ketone analogue to CGP 44645) from letrozole. In these systems letrozole inhibited the metabolism of both ketoconazole (CYP3A4) and coumarin (CYP2A6) in a concentration-dependent manner.

- In human and rat liver microsomes, formation of CGP 44645 was inhibited by ketoconazole and TAO, known inhibitors of CYP3A4. The Ki for the inhibition of CGP 44645 formation by ketoconazole was approximately 1.5 μmol/L. In contrast to the c-DNA expressed result, 50 μmol/L coumarin only slightly inhibited CGP44645 formation in human and rat liver microsomes. In human liver microsomes, letrozole appeared to competitively inhibit CYP2A6 (Ki for coumarin 7-hydroxylation = 0.12 μmol/L) and CYP2C19 (Ki for S-mephenytoin 4'-hydroxylation = 8.5 μmol/L)

1.2 Biopharmaceutics

- Letrozole is well (AUCp.o./AUCi.v. = 0.74 - 1.30, Tmax 1 - 2 hrs) absorbed when administered as coated tablets.

- Concomitant intake of food reduces the extent (13% decrease) and rate (23% decrease) of letrozole absorption. These changes are unlikely to result in a significant reduction in efficacy if the drug is taken with food.

- The Final Market Image formulation was found to be bioequivalent to the formulations used during clinical development.

- The Ciba Monograph dissolution test method uses USP apparatus 2 (paddle) at 100 rpm and 500 mL of dissolution medium (0.1 M HCl) at $37^0 \pm 0.5^0$C. Paddle speeds less than 100 rpm, regardless of dissolution medium, result in incomplete dissolution. This incomplete dissolution at speeds < 100 rpm appears to be a function of the hydrodynamics of the testing apparatus rather than inadequate performance of the drug product.

2. Recommendation

The submission has adequately addressed the Office of Clinical Pharmacology and Biopharmaceutics' requirements and/or guidelines. The Labeling Revisions and General Comments need to be conveyed to the sponsor.

FT

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cc:

NDA 20,726	original
HFD-150	division file
HFD-150	Spillman, Schechter, Johnson, Tolgyesi, DIETZE, ZHOU
HFD-205	FOI
HFD-340	Vishwanathan
HFD-850	Lesko, Millison
HFD-860	Malinowski, Mehta, Rahman
CDR	Barbara Murphy

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4. Introduction

In postmenopausal women, estrogens are mainly derived from the conversion of adrenal androgens to estrone (El) and estradiol (E2). The elimination of estrogen-mediated stimulatory effects is a means for tumor suppresion in cases where the growth of tumor tissue depends on the presence of estrogens. The suppression of estrogen biosynthesis can be achieved by inhibiting the aromatase enzyme which is responsible for the generation of estrone and estradiol from androgenic precursors.

Letrozole, (4,4'-[(IH-1,2,4-triazol-1-yl)-methylene]bisbenzonitrile), is a new non-steroidal inhibitor of the aromatase enzyme system. It appears to inhibit by binding to the heme of the cytochrome P450 enzyme complex. Serum estrogen suppression up to 95% from baseline has been observed and letrozole appears not to affect adrenal steroidogenesis. The sponsor seeks to have the drug approved for the treatment of advanced breast cancer, in women with natural or artificially induced postmenopausal status, following antiestrogen therapy.

The present report summarizes the studies in which the pharmacokinetics and biopharmaceutics of letrozole have been assessed. Unless otherwise indicated, concentration-related data are reported in molar units (nmol/L or μmol/L). The relative molecular mass of letrozole is 285.31. To convert from nmol/L to ng/mL or μg/L multiply by 0.28531.

5. Analytical methods

Two different analytical methods were used for the measurement of letrozole and CGP 44645 (the major metabolite of letrozole) plasma and urine concentrations: an
methods [1, 2, 3, 4, 5, 6, 7, 8, 9, Lit. 1]. The main characteristics of these methods are summarized below.

Characteristics of analytical methods used in pharmacokinetic studies

Method	Sample[a] preparation	Detection[b]	LOQ[c] (nmol/L)		Accuracy[d] %	Precision[d] %	Reference
			Letrozole	CGP 44645			
	native plasma		P: 0.7 U: -	-	81 - 106	3.0 - 17.7	1, Lit. 1
	l-l extraction		P: 0.2 U:-	-	80 - 120	5 - 14	2
	l-l extraction	UV	P: 28 U: 180	P: 34 U: 210	90 - 103	1.1 - 13	3,4 Lit. 1
	s-l; C8 columns	UV	P: 8.9 U: 89	P: - U: 109	92.1 - 106	1 - 13.4	5
	s-l; C8 columns	F	P: 1.4 U: 2.8	P: - U: 8.54	93.4 - 108	0.6 - 13.6	6
	l-l extraction	UV	P: 17.5	P: 21.3	91 - 105	0.5 - 8.8	7
	l-l extraction	F	U: 8.76	U: 10.7	91 - 107	3.2 - 17.0	8
	l-l extraction	F	P: 1.75	-	87 - 100	1.5 - 12.2	9

a) l-l: liquid-liquid extraction; s-l: solid-liquid extraction
b) UV: ultraviolet; F: fluorescence
c) LOQ: limit of quantification; P: plasma; U: urine
d) Numbers indicate the range of mean accuracy and precision of determination of spiked samples. The values cover letrozole and CGP 44645, within- and between-assay measurements and determinations at the LOQ.

The was based on antibodies raised in guinea-pigs and on a letrozole-horseradish peroxidase conjugate as a marker. The antibodies showed a strong cross-reaction with the carbinol metabolite CGP 44645 and its glucuronide. However, measurements of plasma samples from healthy subjects or breast cancer patients were in agreement with results, indicating that the metabolite or its glucuronide were present in plasma only in small amounts [Lit. 1]. In a specific study in breast cancer patients, measurements were about 40% higher than determinations [Protocol US01]. A nonspecific cross-reaction with the biological matrix would

produce such a result. Urine could not be analyzed by the partly due to the presence of CGP 44645. An increased sensitivity of the was achieved by concentrating the plasma samples using an extraction step [2]. The was only used for the determination of letrozole in plasma samples of early Phase I studies in man (Protocols HPL14/89, HPH9003, HPH9026, AR/HW1, AR/BC1 and part of US01) and in the warfarin drug interaction study (Protocol 017).

For the determinations by methods, letrozole and CGP 44645 were extracted from plasma or urine and separation was achieved on reverse phase C18 columns. For the assessment of total CGP 44645, the glucuronide was hydrolyzed enzymatically prior to extraction [5, 8]. A sensitivity close to that of the was finally achieved with fluorescence detection [6], allowing the replacement of the immunoassay for the determination of letrozole plasma concentrations in single dose studies.

Estrogen serum levels [estrone (El) and estradiol (E2)] were measured by means of [10, 11, 12, 13, Protocol AR/BC2]. The limits of quantification were 2.5 pg/mL (9.2 pmol/L) for El and 1 pg/mL (3.7 pmol/L) for E2. Estrogens were separated from serum by liquid-liquid extraction and assayed in buffer. Tritium-labeled El and a ^{125}I-histamine derivative of E2 were used as tracers in the two assays. Specificity of the antibodies was checked against several androgens, gestagens, corticoids, letrozole and megestrol acetate. The antibodies showed little cross-reactivity to any of the compounds tested [10, 11, 13, Protocol AR/BC2].

All analytical methods were validated before and during the analysis of study samples according to recommendations given in [Lit. 2].

Analytical methods and the concentration range of determination for each study are provide in Attachment 6 (Sponsor's analytical methods summary).

6. Pharmacokinetics

The pharmacokinetics of letrozole have been investigated after single doses (intravenous bolus and oral) in healthy male and postmenopausal volunteers [Protocols HPL14/89, HPH9003, HPH9026, AR/HW1, 003, 011], and after multiple dosing (a single 2.5 mg dose/day) to patients with advanced breast cancer [Protocols AR/BC1 and US01]. A mass balance study with ^{14}C-labeled letrozole has been performed in healthy postmenopausal women [Protocol 018]. The pharmacokinetics in subjects with renal and hepatic impairment [Protocols 006 and 007] and interactions with cimetidine, warfarin [Protocols 004 and 017] and with food [Protocol 005] have been studied. In the pivotal trial AR/BC2, the relationships between letrozole plasma concentrations and several covariates (age, body mass index, hepatic and renal impairment, co-medications) and pharmacodynamic and clinical effects (estrogen suppression, time to tumor progression, severity of adverse experiences) have been evaluated. The formulations used in the clinical trials have been compared to the final market image in a bioequivalence trial in healthy male volunteers [Protocol 010]. A summary of all studies is given below.

Summary of pharmacokinetic studies with letrozole

description	protocol	subjects	formulation[1]	analytical method
sd; tolerability	HPL14/89	HMV	solutions	
sd; tolerability	HPH9003	HMV	1	
sd; tolerability	HPH9026	HMV	1	
sd; tolerability	AR/HW1	HPMW	1	
dose over-proportionality	3	HPMW	4	
interaction; cimetidine	4	HV	2	
food effect	5	HMV	2	
renal	6	HPMW	2	
hepatic	7	HPMW	2	
BE	8	HMV	1, 2, 4	
BE	10	HMV	1, 2, 4	
absolute BA	11	HPMW	solution, 4	
interaction; warfarin	17	HMV	4	
mass balance	18	HPMW	^{14}C	
md; tolerability	AR/BC1	BCP	1	
md; tolerability	US01	BCP	1	
md; pivotal	AR/BC2	BCP	1	

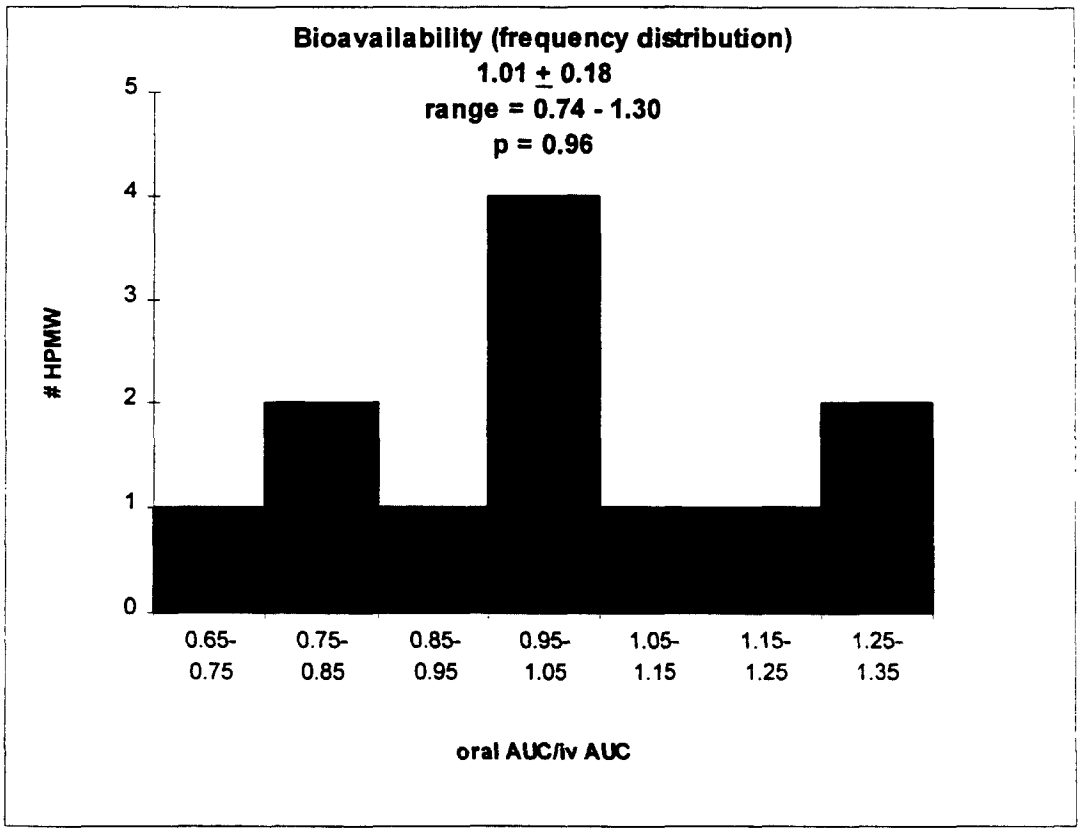
[1]formulation 4 is the Final Market Image

abbreviations: sd -- single dose, md -- multiple dose, BE -- bioequivalence, BA -- bioavailability, HMV -- healthy male volunteer, HPMW -- healthy postmenopausal women, HV -- healthy volunteers (male and female), BCP -- breast cancer patients, L -- letrozole, W -- warfarin

6.1. Healthy volunteers

6.1.1. Absorption

A two-way crossover study comparing systemic exposure after oral (p.o.) and intravenous (i.v.) administration of 2.5 mg of letrozole was performed in 12 healthy postmenopausal women [Protocol 011].



A comparison of AUC_{oral} to AUC_{iv} failed to show a significant difference between the two ($p = 0.96$ by two-tailed paired t-test). As the histogram shows, bioavailaility averages 101% but there is considerable variability about this mean.

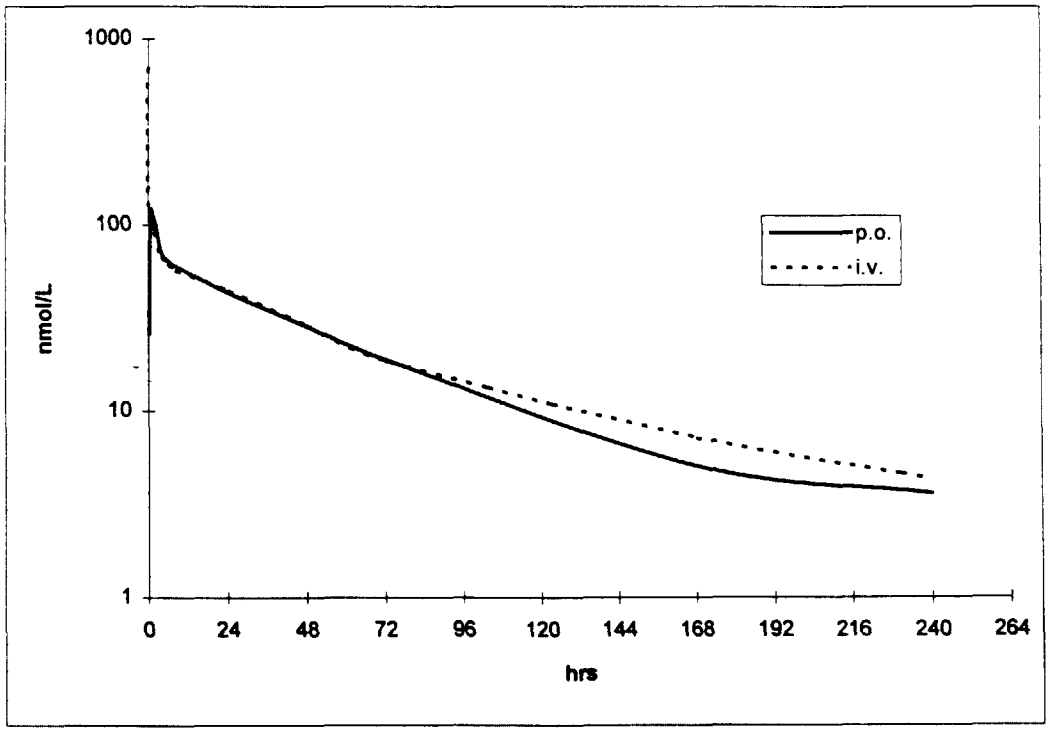
The table below gives a summary of the pharmacokinetic parameters for this bioavailability study. Maximum plasma concentrations were reached 1 hour after p.o. dosing. Absorption of letrozole is rapid, as plasma profiles after i.v. and p.o. administration were almost superimposable as early as 2 to 4 hours after dosing. In addition, dose proportionality of the

pharmacokinetics for single oral doses in the range of mg indicated that the absorption process is independent of the dose [Protocols HPL14/89, HPH9003, 003]. The absorption process did not increase the variability of the letrozole plasma kinetics, as after i.v. and p.o. administration similar variation coefficients for AUC were observed [Protocol 011]. The variability in the plasma kinetics seems, therefore, to lie in the variability of the disposition of letrozole.

Pharmacokinetic parameters after a single intravenous or oral dose of 2.5 mg letrozole to healthy postmenopausal women (N=12) [Protocol 011].

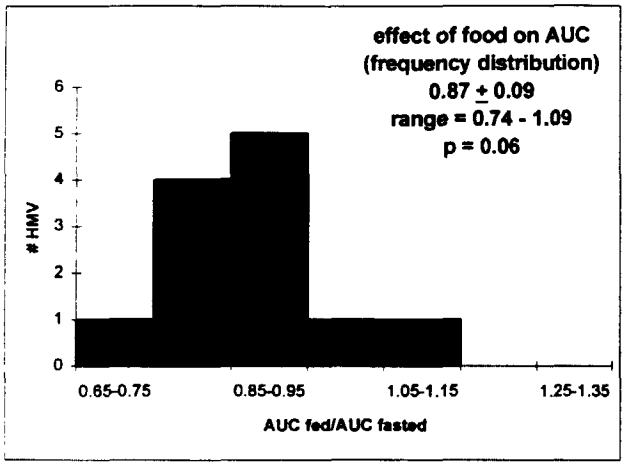
Parameter	Route of administration	
	p.o.	i.v.
Cmax (nmol/L)	128 ± 15	
tmax (h) (median)	1	
$t_{1/2}$ (h)	41.9 ± 15.2	
AUC (h * umol/L)	4.26 ± 1.39	
BAV (%)	99.9 ± 16.3	
Vdss (L/kg)		1.87 ± 0.47
CL (L/h)		2.21 ± 0.65
CL_R (L/h)		0.08 ± 0.02

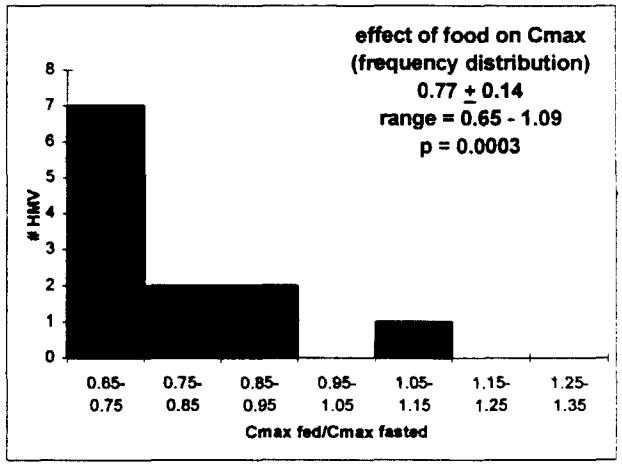
Mean plamsa profiles after single 2.5-mg doses of letrozole (N = 4 - 12/data point) Protocol 011

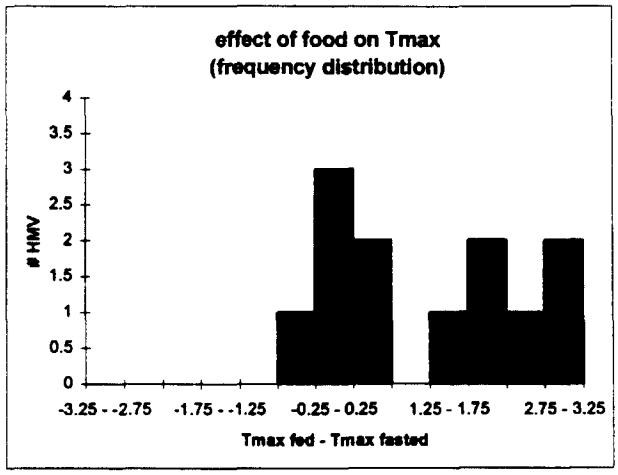


Oral administration of letrozole together with food to 12 healthy male volunteers in a randomized 2-way cross-over study resulted in a slightly reduced absorption rate as evidenced by an increased tmax and a decreased Cmax [Protocol 005]. The extent of absorption (AUC), while not different at $p < 0.05$, also appeared to be reduced by the concommitant intake of food. Considering the intended dosage regimen of letrozole (one 2.5 mg tablet daily for months) and the variability of the plasma levels attained at steady state, these food effects are likely of little or no clinical relevance.

Pharmacokinetic parameters after single oral 2.5-mg doses of letrozole to healthy male volunteers under fed and fasted conditions (N=12) [Protocol 005].







6.1.2. Bioequivalence

Three different formulations of film-coated tablets at the dose strength of 2.5 mg were used in clinical trials, F. 1, F.2 and F.4. F.1 was used in the pivotal trial AR/BC2, F.2 and F.4 in several other clinical trials. F.4 is the Final Market Image. The composition of the 3 formulations is given below.

Composition of the 2.5 mg film-coated tablets (in mg)

Ingredient	F.1	F.2	F.4 (FMI)
Core			
Letrozole	2.5	2.5	2.5
Colloidal Anhydrous Silica			
Microcrystalline Cellulose			
Lactose Monohydrate, cryst.			
Lactose Monohydrate, ground			
Lactose Monohydrate, spray-dried			
Magnesium Stearate			
Maize Starch			
Sodium Starch Glycollate			
Total weight			
Film-Coat			
Methylhydroxypropylcellulose			
Iron oxide, red			
Iron oxide, yellow			
Polyethylene Glycol 8000			
Talc			
Titanium Dioxide			
Total weight			

The FMI was bioequivalent (two one-sided tests procedure on log transformed data comparing $AUC_{0\text{-}Tlast}$ and Cmax) to the two clinical trial formulations as shown in a single-center, single-dose, open, balanced three-way cross-over study (washout period: 3 weeks) in 18 healthy male volunteers [Protocol 010].

Bioequivalence comparisons [Protocol 010].

0.5 mg tablet – formulation 1 vs 4				0.5 mg tablet – formulation 2 vs 4			
	90% Confidence Interval		n		90% Confidence Interval		n
AUC	0.96	1.05	17	AUC	0.95	1.05	17
Cmax	0.94	1.10	17	Cmax	0.96	1.11	17

2.5 mg tablet – formulation 1 vs 4				2.5 mg tablet – formulation 2 vs 4			
	90% Confidence Interval		n		90% Confidence Interval		n
AUC	0.90	1.01	18	AUC	0.92	1.03	18
Cmax	1.02	1.16	18	Cmax	0.99	1.12	18

Bioequivalence is also supported by the fact that the changes in the formulations had little effect on their dissolution profiles [14].

6.1.3. Disposition

6.1.3.1. Plasma profiles

The plasma profile of letrozole is characterized by a dominant terminal elimination phase with a half-life of about 2 days (see p. -- Protocol 011). Shortly after i.v. administration, plasma concentrations decreased rapidly (about 4-fold within 10 minutes) and showed, in some subjects, small secondary peaks within the first 4 - 8 hours. Thereafter, the decline was monoexponential with the half-life mentioned above. Small secondary peaks were also observed after oral administration [Protocols HPL14/89, AR/HW1, 003, 005, 010, 011, 018], and might be due to enterohepatic circulation, a phenomenon seen in animal experiments [15, 16]. This hypothesis is further supported by the fact that unchanged letrozole could still be detected in feces collected 72 to 96 hours after administration of 2.5 mg ^{14}C-labeled material [Protocol 018]. At this time point no unabsorbed compound should be excreted via feces. The rather slow elimination, together with the good absorption of letrozole, suggest that once-daily administration is sufficient to maintain adequate plasma levels.

6.1.3.2. Protein binding and distribution

Letrozole is only weakly bound to plasma proteins *(in vitro* approximately 60% and mainly to albumin, 55%) and its concentration in the erythrocyte fraction is about 80% of that in plasma

[17]. Protein binding is, therefore, considered to have little effect on the availability of letrozole for aromatase inhibition, and displacement of highly protein-bound compounds by letrozole would not be predicted. The weak protein binding and a volume of distribution at steady state (Vdss) of about 2 L/kg [Protocol 011] indicate that letrozole is extensively distributed into tissues. In addition, the about 4-fold decrease of the plasma concentration that occurs within 10 minutes after an i.v. bolus injection suggests that the distribution into tissue is rapid.

6.1.3.3 Metabolism, elimination and excretion

Unchanged letrozole is the predominant compound in human plasma. It accounted for 62 to 100% of the radioactivity in plasma (mean: 82%) after a single oral 2.5-mg dose of ^{14}C-labeled letrozole to 6 healthy postmenopausal women [Protocol 018]. Although studied at only two early time points, the AUC of letrozole in plasma represented 82 ± 7% of that of plasma radioactivity. Metabolites did not accumulate in plasma, as the ratio of unchanged letrozole to total radioactivity remained roughly constant over the collection period of 2 weeks. The main metabolite identified in these plasma samples was the glucuronic acid conjugate of CGP 44645.

Elimination of letrozole occurs mainly via metabolism i.e. loss of the triazole, oxidation and subsequent glucuronidation of the carbinol metabolite CGP 44645. The metabolite showed no activity as an aromatase inhibitor [18]. Formation of other unidentified metabolites and direct excretion of unchanged compound play only minor roles in the overall elimination. The excretion of metabolites and unchanged letrozole is predominantly via kidneys. Within 2 weeks after a single oral dose of ^{14}C-labeled letrozole (2.5 mg), 88.2 ± 7.6% of the radioactivity was recovered in urine while fecal excretion was only 3.8 ± 0.8% [Protocol 018]. Within 216 hours 63.2 ± 11.2% of the dose was excreted as the CGP 44645 glucuronide in urine, about 8% as two yet unidentified metabolites (6.9 ± 3.1 and 1.1 ± 0.2%) and 5.0 ± 2.4% was found to be unchanged letrozole. The radioactivity recovered in urine up to 216 hours represented 84.7 ± 7.8% of the dose.

Total plasma clearance of letrozole, CL, after i.v. bolus administration of 2.5 mg was low: 2.21 ± 0.65 L/h [Protocol 011]. Renal clearance (CL_R) and fecal excretion contribute very little to CL (CL_R = 0.08 ± 0.02 L/h and only about 2% of the dose is excreted as unchanged letrozole in feces [Protocol 018]). Thus, non-renal clearance is primarily metabolic clearance (CLm) and amounts to about 2.1 L/h. Considering the weak protein binding and a hepatic blood flow of about 90 L/h, it can be concluded that metabolic clearance is determined by slow enzyme kinetics (low intrinsic clearance) and not by a limited delivery of letrozole to the liver (extraction of letrozole from plasma water into liver). The low renal clearance of letrozole suggests considerable re-absorption after glomerular filtration. The free fraction in plasma is about 40% of total plasma concentration indicating a glomerular filtration rate of about 3 L/h for letrozole, which is far above its CL_R.

The pharmacokinetic parameters (AUC, half-life) showed considerable between-subject variability with variation coefficients in the range of 30 to 60%. A few subjects with half-lives longer than 100 hours have been observed [Protocols 006, 007 and 010]. Longer half-lives correlated significantly with higher AUC values (P-values: <0.0025 for data of Protocols 011 and 018) and larger AUC and

half-life values with lower amounts of metabolite excreted (Ae) in the urine (P-values: <0.0051). Thus it appears that longer half-lives and higher AUC values are associated with a decreased metabolic clearance rate of letrozole.

In vitro experiments have shown that the human cytochrome P450 isoenzymes CYP3A4 and CYP2A6 can catalyze the conversion of letrozole to CGP 44645 [19]. The affinity of letrozole for CYP3A4 is low, whilst that for CYP2A6 is high (for a discussion of *in vitro* metabolism see 7.3 below). In man, CYP3A4 is the most prominent P450 isoenzyme (approximately 30% of the P450 enzymes), whereas the abundance of CYP2A6 is low (approximately 4%) [Lit. 3, Lit. 4, Lit. 5]. Both isoenzymes show considerable inter-subject variability [Lit. 5], which may relate to the large inter-subject variability seen in the disposition of letrozole. However, the contribution of each isoenzyme to the overall metabolic clearance of letrozole and a possible involvement of other isoenzymes have not yet been investigated.

6.1.4. Dose proportionality after single doses

Results from early Phase I single dose studies [Protocols HPLI4/89, HPH9003] indicated that the pharmacokinetics of letrozole were dose proportional in the range of 0.01 to 10 mg but increased dose over-proportionally after 30 mg. Analysis of urine samples for unchanged letrozole and CGP 44645 from a few individuals indicated that the dose over-proportionality might be associated with saturation or inhibition of the metabolic elimination of letrozole [1, Lit. 1]. To test this hypothesis, a study was performed with single dose administrations of 5 and 30 mg to 12 healthy postmenopausal women (parallel group design, N = 6 per group) and sample collections over 2 and 4 weeks, respectively [Protocol 003]. In this trial, AUC values showed a slight over-proportional increase after the 30 mg dose (see table below), but no difference in the terminal elimination half-life was detected. Less of the metabolite CGP 44645 (58.0 ± 9.4% of dose) was recovered in the urine of the subjects receiving the 30 mg dose than in the urine of those receiving the 5 mg d'ose (74.6 ± 15.4%) (Table 4.i-4.-I). In addition, in the urine fractions collected 4 to 5 days after administration, the ratios of CGP 44645 over letrozole concentrations were about 40% lower in the 30 mg than in the 5 mg group. Thereafter the ratios in the 30 mg group returned to similar values as in the 5 mg group (table below). These results suggest that a slight saturation of the metabolic elimination process may have occurred during the first 4-5 days after the 30 mg dose, but that the metabolic clearance returned thereafter to levels comparable to that of the lower dose.

Plasma pharmacokinetic parameters and total urinary excretion of letrozole and CGP44645 in healthy postmenopausal women receiving single oral doses of letrozole [Protocol 003]. To calculate the ratio and the 90% confidence interval, the data were log-transformed.

	Dose (mg)	Mean ± SD	Ratio 30mg/5mg	90% C.I.	Expected ratio
Plasma AUC (h*umol/L)	30	97.0 ± 28.4	8.88	(6.79,11.6)	6
	5	10.8 ± 2.4			
Plasma half-life (h)	30	60.0 ± 18.8	1.2	(0.85.1.70)	1
	5	74.5 ± 32.7			
CGP 44645 urinary excretion (mg)	30	14.3 ± 2.3	4.68	(3.88,5.64)	6
	5	3.06 ± 0.63			
Letrozole urinary excretion (mg)	30	2.08 ± 1.38	7.4	(5.11,10.7)	6
	5	0.35 ± 0.07			

Ratio of CGP 44645/letrozole concentrations in urine fractions [Protocol 003]

Time (h)	5 mg (mean±SD)	N	30 mg (mean±SD)	N
	14.4 ± 6.2	6	6.5 ±1.3	6
	10.2 ± 3.8	6	6.9 t 2.2	6
	10.8 ± 2.3	6	6.5 ± 1.8	6
	10.4 ± 2.8	6	6.2 ± 2.5	6
	9.2 ± 3.3	6	6.5 ± 3.5	6
	11.8 ± 3.9	6	7.8 ± 3.3	6
	13.6 ± 3.4	4	10.6 ± 6.6	6
			9.6 ± 5.6	6
			10.6 ± 4.8	5
			12.3 ± 4.0	2

0 -168h ratio of 30 mg vs. 5 mg = 0.60, 90% C.I. (0.41, 0.87)

In vitro, the P450 isoenzyme CYP3A4, which was found to be capable of converting letrozole to CGP 44645 (see above), could not be saturated with letrozole at concentrations up to 100 μM [19], a concentration far above those observed in plasma after a 30 mg single dose (Cmax = 1.33 ± 0.14 μmol/L). This and the fact that the urinary excretion rate of 6-beta-hydroxycortisol, a marker of *in vivo* activity of CYP3A4, was not affected by the administration of 30 mg letrozole [Protocol 003], indirectly suggest that dose over-proportionality was not caused by a saturation of CYP3A4.

6.1.5. Effect of gender

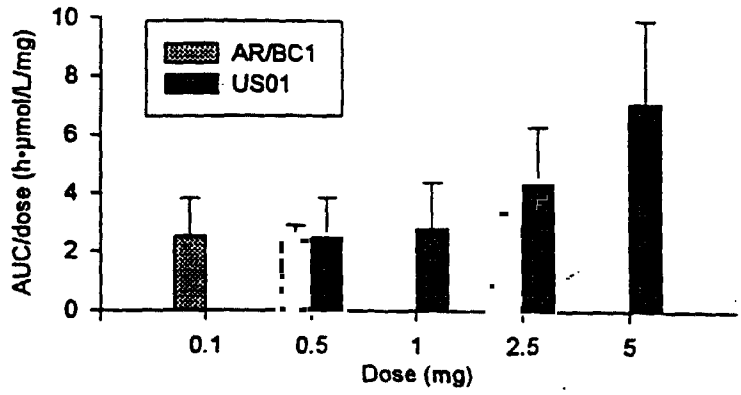
The effect of gender on the pharmacokinetics of letrozole was investigated by comparing the data of two early Phase I single dose studies (doses: 0. 1, 0. 5 and 2.5 mg), one performed in healthy male subjects (N=6) and the other in healthy postmenopausal volunteers (N=12), using a general linear regression model [Protocols AR/HW1, HPH9026. Assuming that there was no study effect, no effect of gender on the pharmacokinetics of letrozole was detected. In addition, the similarity of the pharmacokinetic parameters obtained in several studies in healthy male and healthy postmenopausal volunteers supports these findings [Protocols HPL14/89, HPH9003, AR/HW1, 003, 005, 010, 011].

6.2. Pharmacokinetics in patients

6.2.1. Multiple dose

Upon daily administration of letrozole in the dose range 0.1 to 1.0 mg to postmenopausal women with advanced breast cancer, steady state was reached after approximately 1 to 2 weeks [Protocols AR/BC1 and US01]. This is in line with a half-life of about 2 days. However, at doses of 2.5 or 5 mg/day, 2 to 6 weeks were needed to reach steady state. This was associated with a slight dose over-proportional increase of $AUC_{\tau}(0 - 24h)$ as assessed either after 4 or 6 weeks of treatment [Protocols AR/BC1 and US01]. As shown in the figure below, AUC_{τ} values increased proportional to the dose in the range of 0.1 to 1 mg/day, and were generally in agreement with $AUC_{0\text{-}inf}$ values after single doses. However, they increased about 3.8 and 12 fold instead of 2.5 and 5 fold for the 2.5 and 5 mg/day dosage regimen, respectively, when compared to the 1.0 mg/day dose. The 2.5 mg/day dose may thus be a borderline dose at which an onset of over-proportionality becomes apparent, whereas at 5 mg/day the over-proportionality is more pronounced.

Figure 4.2.1.-1: Dose normalized mean AUC values after repeated administration of letrozole to patients with advanced breast cancer (Protocols AR/BC1 and US01).



Monitoring of letrozole trough levels in the pivotal trial AR/BC2, involving 188 and 174 patients treated with 0.5 and 2.5 mg/day, respectively, confirmed the slight dose overproportionality for the 2.5 mg/day dose (7.8 fold higher in the 2.5 mg/day treatment arm instead of 5 fold) [Protocol AR/BC2]. However, despite this non-linear phannacokinetic behavior for doses ≥2.5 mg/day, steady state levels were maintained when the patients were treated over long time periods (up to 12 months or longer), indicating that continuous accumulation of the compound did not occur (see figures below). In addition, in the data set of AR/BC2 no correlation between letrozole levels and the severity of adverse experiences (AEs) was found (see p. 23).

Figure 4.2.1.-3: Inidvidual plasma trough levels of letrozole in patients with advanced breast cancer (Protocol US01).

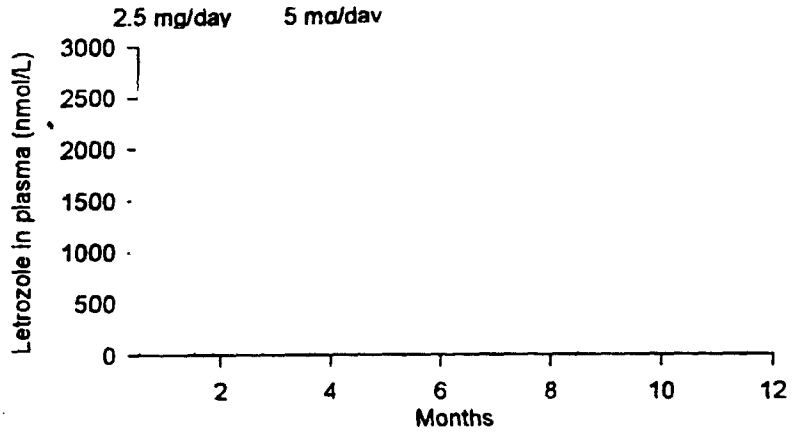
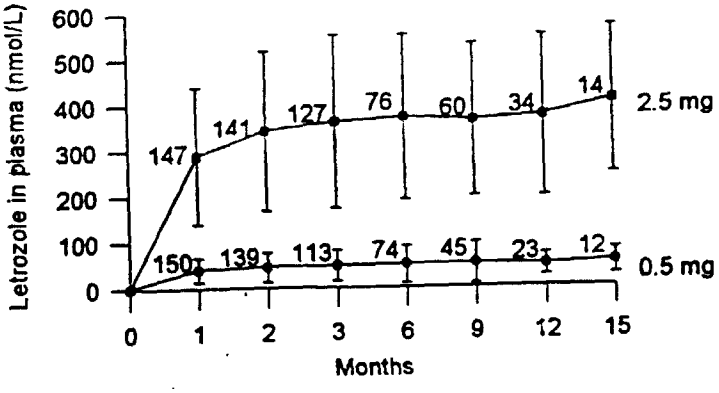


Figure 4.2.1.-4: Mean (±SD) letrozole plasma trough levels as measured in AR/BC2. The number of patients included in the mean calculation is indicated for each data point.



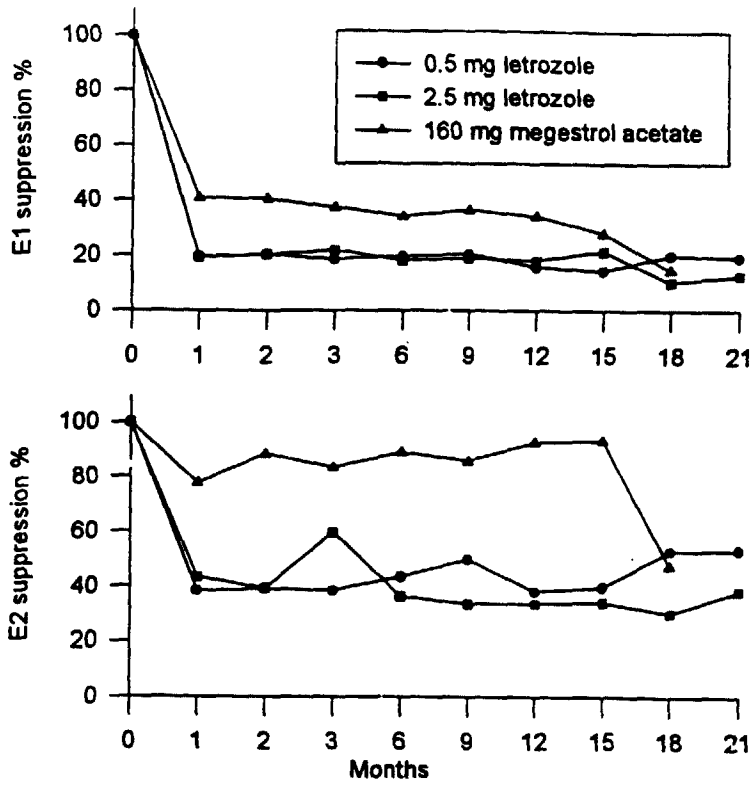
In a few patients the urinary excretion of letrozole and CGP 44645 was assessed at steady state [Protocol US01]. As after single doses, the bulk of the dose was excreted as the glucuronide of CGP 44645. Excretion of unchanged letrozole was, in some subjects, higher than expected from the single dose experiments and was in the range of 5.55 to 36.9% of the dose. A clear relationship between dose over-proportionality and the pattern of urinary excretion of letrozole and CGP 44645 could not be found. Conclusions on a correlation between a reduction in metabolic clearance and dose over-proportionality under steady state conditions could therefore not be drawn. This might be due to the high degree of variability in the data and the limited size of the data set.

6.2.2. Pharmacokinetics/Pharmacodynamics

The relationship between letrozole plasma concentrations and pharmacodynamic effects at steady state was investigated in the data set of AR/BC2. Correlations between letrozole trough levels and the suppression of estrogens [estrone (El) and estradiol (E2)], the time to (tumor) progression (TTP) and the severity of adverse experiences (AEs) were studied.

Spearman rank correlation coefficients were calculated to assess if a relationship between letrozole levels and estrogen suppression was present. No significant correlation was found between an increase in letrozole concentration and a higher degree of serum estrogen suppression. In addition, the El and E2 levels remained suppressed over time (see figure below). Hence, a similar degree of serum estrogen suppression was observed with both doses of letrozole and no effect of the dose on this surrogate marker could be detected. Thus, letrozole concentrations in the investigated concentration range could not be used as a predictor for the degree of serum estrogen suppression. However, as serum estrogen concentrations fell in many cases to levels below the quantification limits of the assays (ca. 40% of the El and ca. 15% of the E2 values in both letrozole arms), it is likely that the calculated hormone suppressions were underestimated. Thus, a dose effect or an effect of letrozole concentration on estrogen suppression might have been observable using analytical methods with higher sensitivities. Klein et al. have applied a more sensitive bioassay to determine E2 levels in plasma samples from Protocol US01 [Lit. 6]. However, they did not detect an effect of the letrozole dose (range 0. - 5.0 mg/day) on the plasma suppression of E2.

Figure 4.2.2.-1: Mean estrone (E1) and estradiol (E2) suppression as measured in AR/BC2.



To investigate the relationship between letrozole trough levels and TTP, patients were subdivided into the following mean concentration groups: ≤50, >50≤150, >150≤300 and ≥300 nmol/L (the mean was the within-patient letrozole level mean over visits). A Cox proportional hazard model was used to calculate the conditional risk ratio between pairs of groups and the corresponding 95% confidence intervals. A lower risk ratio indicated a longer TTP. A tendency to an increase in TTP for those patients with letrozole concentrations ≥300 nmol/L was found (see table below), confirming the observed dose effect of letrozole on TTP [Protocol AR/BC2].

Comparison of TTP among concentration groups [Protocol AR/BC2]

Comparison (Concentration groups)	Risk Ratio 95%	Confidence Interval	P-value
	1.12	(0.74,1.70)	0.60
	1.00	(0.69,1.46)	0.99
	0.90	(0.57,1.41)	0.63
	0.71	(0.48,1.04)	0.08
	0.63	(0.40,1.00)	0.05
	0.71	(0.46,1.07)	0.10

Thus, a relationship between a clinical efficacy parameter and the drug levels was found, but no correlation between a surrogate marker (serum estrogen suppression) and letrozole concentration could be established. Suppression of estrogens is thought to be a pre-requisite for the anti-tumor efficacy of letrozole [Lit. 7]. However, in view of-the above findings, it is unlikely that a significant relationship between the extent of estrogen suppression and a clinical efficacy parameter like TTP or objective response can be detected in the data set of AR/BC2, although no specific analysis has been performed.

The relationship between letrozole concentration and the severity of adverse experiences in AR/BC2 was modeled as an ordinal logistic regression. Adverse experiences were given the following four values: none, mild, moderate or severe (including death). Increasing letrozole plasma levels were not found to increase the severity of AEs (P-value=0.727).

6.3. Patients at increased risk

6.3.1 Elderly

A repeated measures linear mixed effects model was applied on the data of AR/BC2 to assess a possible effect of age as a covariate on the letrozole plasma trough levels. Patients were subdivided into the age groups: ≤55 years old, 56 to 69 years old, and ≥70 years old. In the table below the mean letrozole concentration values over visits (visits at 2 to 12 months of treatment were considered) of the individual patients (dose: 2.5 mg/day) are shown as a function of age. Among adult patients, it appears that patients older than 55 do not have steady state concentrations significantly different than those 55 or younger.

mean ± SD letrozole levels as a function of age [Protocol AR/BC2]

Age (years)	≤55	56 - 69	≥70
N	26	85	41
Letrozole (nmol/L)	309 ± 163	342 ± 174	372 ± 152

6.3.2 Renal impairment

The influence of renal function on letrozole pharmacokinetics was investigated in a single 2.5-mg dose study in 19 postmenopausal volunteers with varying degrees of renal impairment (24 hour creatinine clearance range: CL_{CR} = 9 - 116 mL/min) [Protocol 006]. Using regression analysis, no correlation between creatinine clearance and pharmacokinetic parameters of letrozole was found (table below). This is to be expected as letrozole is a drug for which renal clearance plays only a minor role (about 5% of total) in the overall elimination. In addition, a scatter plot of CL_{CR} versus amount of metabolite excreted in the urine did not reveal a relationship between these two parameters (see table below).

Mean SD pharmacokinetic parameters in volunteers with varying degrees of renal function [Protocol 006]				
Renal impairment group (mL/min)	≥90	60 - 90	30 - 60	≤30
N	3	2	11	3
Creatinine clearance (mL/min)	111.0 ± 6.2	72.0 ± 1.4	49.7 ±.8.4	11.0 ± 2.0
tmax (h) (median)	1.5	1.25	1.5	2
Cmax (nmol/L)	98.8 ± 20.0	119 ± 15	125 ± 46	68.0 ± 25.9
$t_{1/2}$ (h)	64 ± 42	43.1 ± 5.6	65.9 ± 28.3	43.9 ± 18.1
AUC(0-inf) (umol*h/L)	4.57 ± 2.82	4.63 ± 0.05	6.23 ± 1.63	3.33 ± 1.33
CL_R (mL/min)	3.2 ± 2.1	2.9 ± 0.2	2.0 ± 1.0	2.1 ± 0.6

In addition to the above evaluation a covariate analysis was performed on the data of AR/BC2. Calculated CL_{CR} (range: mL/min) showed no statistically significant association with letrozole plasma levels (P-value: 0.952).

6.3.3 Hepatic impairment

As mentioned above, elimination of letrozole depends mainly on intrinsic metabolic clearance. Thus, impairment of liver functions may have an influence on the elimination kinetics of letrozole. A single dose trial (2.5 mg) was therefore performed in 12 volunteers with normal and mild to moderately impaired liver functions (Child-Pugh classification A and B) [Protocol 007]. Mean pharmacokinetic parameters are given in the table below. The results were somewhat confounded by a subject (Child-Pugh A group) with distinctly higher AUC and half-life values than any other subject. The statistical analysis was therefore performed with and without inclusion of this subject.

Mean (± SD) pharmacokinetic parmeters in volunteers with different degrees of liver impairment [Protocol 007]				
PK parameter	Normal N=4	Child-Pugh A, N=5	Child-Pugh A, N=4	Child-Pugh B, N=3
		all subjects	M8683D/003 excluded	
tmax (h) (range)	1.50 (1.0-2.0)	1.50 (0.5-12)	1.75 (1.0-12)	2.00 (1.0-2.0)
Cmax (nmol/L)	124.5 ± 29.5	99.8 ± 29.4	90.7 ± 24.5	108 ± 22.3
$t_{1/2}$ (h)	49.2 ± 24.5*	80.5 ± 32.8	69.5 ± 25.2	79.3 ± 32.3
AUC(0-inf) (umol*h/L)	4.90 ± 1.59*	7.03 ± 5.02	4.82 ±1.06	6.72 ± 1.04
CL (L/h)	1.95 ± 0.76*	1.62 ± 0.70	1.88 ± 0.43	1.33 ± 0.22
CL_R (L/h)	0.114 ± 0.063	0.133 ± 0.043	0.121 ± 0.039	0.15 ± 0.072
CL_{NR} (L/h)	1.82 ± 0.76*	1.49 ± 0.73	1.76 ± 0.43	1.18 ± 0.29
Molar ratio (44645/20267)	14.8 ± 9.5	11.3 ± 6.5	13.4 ± 5.1	6.5 ± 3.4
* N = 3				

AUC and half-life tended to increase and total clearance (CL) and non-renal clearance (CL_{NR}) to decrease with increasing liver impairment. The pharmacokinetic parameters of the ChildPugh A group were closer to the normal group when subject M8683D/003 was excluded but they were comparable to the Child-Pugh B group when all subjects were considered. Systemic exposure in the Child-Pugh B group was about 37% higher than in the normal group.

In AR/BC2 patients with changes in transaminases (SGPT, SGOT), bilirubin or alkaline phosphatase (grade 3 or 4 of the NIH common toxicity criteria, >5 times normal values) showed no statistically significant alteration in their letrozole trough plasma levels [Protocol AR/BC2]. Thus, under repeated dosing, hepatic dysfunction did not result in significant changes in exposure to letrozole.

7. Interactions

Two interaction trials were performed, one investigating the effect of cimetidine on letrozole pharmacokinetics and the other looking at the influence of letrozole on the pharmacokinetics and pharmacodynamics of warfarin. In addition, the data set of AR/BC2 was statistically analyzed for correlations between co-medications and letrozole concentrations.

7.1 Cimetidine

Cimetidine is a known inhibitor of hepatic microsomal drug metabolism (CYP2C and 3A isoenzymes). The effect of a 400 mg b.i.d treatment with cimetidine for 7 days on the letrozole pharmacokinetics after a single 2.5-mg dose was investigated in 16 healthy subjects [Protocol 004]. A slight but statistically significant decrease in systemic exposure and an increase in Cmax were observed when letrozole was administered together with cimetidine (table below). This result is in contrast to an expected decrease in letrozole clearance due to an inhibition of metabolizing enzymes by cimetidine. In addition, although the data and analysis do not appear in the review, the sponsor claims that letrozole trough concentrations showed no significant change in patients with concomitant administration of cimetidine, benzodiazepines and omeprazole [Protocol AR/BC2].

Comparison of letrozole pharmacokinetic parameters after administration of letrozole alone and after administration of cimetidine 400 mg b.i.d. for 7 days [Protocol 004].

Parameter	Letrozole alone mean ± SD	Letrozole + Cimetidine mean ± SD	Ratio (L + C)/L	90% C. I.	P value
$AUC_{(0\text{-inf})}$ (h*umol/L)	6.07 ± 2.37	5.67 ± 2.48	0.92	(0.889, 0.956)	0.002
Cmax (nmol/L)	27.6 ± 4.8	29.6 ± 4.9	1.073	(1.002, 1.151)	0.091

7.2 Warfarin

Warfarin has a narrow therapeutic window and is a common co-medication in the target population of letrozole. Its clearance was found to be increased by the co-administration of the aromatase inhibitor aminoglutethimide, due to enzyme induction [Lit. 12]. A balanced two-way cross-over study was performed in 14 healthy male volunteers with warfarin administration as a single 25-mg dose, either alone or after 15 days of letrozole treatment at 2.5 mg/day (letrozole was continued up to the 20th day) [Protocol 017]. No statistically significant influence on the pharmacokinetics of (R)- or (S)-warfarin was observed (table below). There was also no change in the maximum prothrombin time (PTmax). However, a small but statistically significant increase in AUC_{PT} (approximately 4%) was found when warfarin was co-administered with letrozole.

Comparison of pharmacokinetic parameters of (R)- and (S)-warfarin and of pharmacodynamic parameters after administration of a single 25-mg dose of warfarin with and without concomitant administration of daily 2.5-mg doses of letrozole

Parameter	Warfarin alone	Warfarin + letrozole	Ratio (W + L)/W	90% C. I.	P
		(R)-Warfarin			
Cmax (mg/L)	1.33 ± 0.36	1.44 ± 0.34	1.09	(6.990,1.190)	0.1156
tmax (h) (median)	1.00	1.00	1.02	(0.934,1.112)	0.6710
AUC (mg*h/L)	78 ± 24	79 ± 21	1.00	(0.880,1.140)	0.9367
		(S)-Warfarin			
cmax (mg/L)	1.37 ± 0.41	1.52 ± 0.40	1.11	(1.003,1.223)	0.1092
tmax (h) (median)	1.00	1.00	1.05	(0.986,1.118)	0.1987
AUC (mg*h/L)	48 ± 11	50 ± 10	1.01	(0.940,1.090)	0.7809
		Prothrombin time			
PTmax (s)	31.2 ± 9.6	29.8 ± 9.1	1.04	(0.969,1.119)	0.3079
AUC_{PT} (s*h)	3191 ± 620	3051 ± 555	1.04	(1.019,1.068)	0.0075

7.3 *In vitro* metabolism

In order to assess possible interactions with other drugs, the dominant metabolic clearance of letrozole and its enzyme induction potential found in rats [27] have to be considered. The human CYP3A4 isoenzyme was found to be capable of converting letrozole to its main metabolite CGP 44645 [19]. CYP3A4 is responsible for the metabolism of a number of drugs, and is subject to enzyme inhibition and induction by drugs and diet [Lit. 3, Lit. 4, Lit. 8]. The low affinity of letrozole as a substrate of CYP3A4 (not saturable at concentrations up to 100 μmol/L), together with the fact that letrozole seems not to be able to inhibit CYP3A4 [19, 28], suggest that an influence on

the metabolic clearance of other drugs eliminated mainly by this isoenzyme is unlikely. However, inhibitors, inducers or competitive substrates of CYP3A4 may, theoretically, interfere with the metabolic clearance of letrozole.

In vitro, letrozole was found to be a substrate and an inhibitor (Ki = 0.12 μM) of CYP2A6, and also an inhibitor (Ki ≈ 9 μM) of CYP2C19 [28]. Inhibition of CYP2A6 by letrozole would be expected to inhibit the metabolism of coumarin and nicotine, but the toxicological consequences are likely to be insignificant because low levels of CYP2A6 or inhibition of CYP2A6 by another inhibitor does not appear to predispose individuals/patients to the adverse effects of coumarin or nicotine [28]. Inhibition of CYP2C19 would be expected to inhibit the metabolism of several drugs (e.g. omeprazole, diazepam) [28]. However, clinical consequences are likely to be insignificant as most of these drugs have a high therapeutic index and are well tolerated even in individuals who are genetically deficient in CYP2C19. A possible exception is diazepam which shows interactions (reduced metabolic clearance and higher systemic exposure) with inhibitors (omeprazole, cimetidine) of CYP2C19 and is usually prescribed at lower doses in orientals who are known to have a higher incidence of genetic deficiencies in CYP2C19 [Lit. 9]. In AR/BC2, patients taking benzodiazepines tended to have more severe adverse experiences than those without this co-medication [Protocol AR/BC2]. However, drug concentrations in these patients were not higher than in patients not treated with the drug combination. Letrozole plasma levels at steady state are in the range of 0.2 to 0.8 μmol/L. In rats and dogs, radioactivity concentrations in the liver after administration of ^{14}C-letrozole were about 4 to 6 times higher than in plasma [16], and in mice they were about 15 times higher [20]. Assuming a similar distribution in man, liver concentrations still below the Ki value of letrozole for CYP2C19 (ca. 9 μM) can be expected. Thus, an inhibition of diazepam metabolism by letrozole seems to be unlikely and a pharmacokinetic drug-drug interaction of letrozole and diazepam with clinical consequences seems unlikely.

The data of the interaction studies together with the above considerations suggest that co-administration with 2.5 mg letrozole is unlikely to result in clinically significant interaction with cytochrome P450 mediated metabolism of other drugs.

8. Dissolution

The Ciba Monograph dissolution test method uses USP apparatus II (paddle) at 100 rpm and 500 mL of dissolution medium (0.1 M HCl) at 37° ± 0.5°C. Paddle speeds less than 100 rpm, regardless of dissolution medium, result in incomplete dissolution. This incomplete dissolution at speeds < 100 rpm appears to be a function of the hydrodynamics of the testing apparatus rather than inadequate performance of the drug product (see Attachments 3 & 5). A validated with detection procedure is used to determine the amount of drug substance dissolved. The sponsor's preliminary dissolution specification of Q of [redacted]% in [redacted] minutes has recently been revised to Q of [redacted]% in [redacted] minutes, based on preliminary discussions at a May 23, 1996 meeting with the sponsor.

In the IND sumission number serial number 158, dated August 01, 1996, the sponsor

submitted limited information on solubility of letrozole in different media at two temperatures (25°C and 37°C), dissolution profiles of FEMARA tablets in USP apparatus II set at 75 and 50 rpm, and dissolution profiles of different batches in different media to justify the selection of dissolution specifications for FEMARA 2.5 mg tablets.

Based on the data submitted in the NDA as well in the IND the following dissolution specifications is recommended for FEMARA tablets.

Apparatus:	USP II (Paddle)
Dissolution Medium:	0.1 N HCl
Volume:	500 mL
Speed:	75 rpm
Temperature:	37°C
Q:	not less than [redacted]% in [redacted] minutes

The dissolution specifications should be considered as an **interim** specification. The sponsor is requested to generate the dissolution profiles of FEMARA tablets (12 units per lot) from the biobatch using the following conditions:

1] 900 mL 0.1 N HCl using USP II apparatus (Paddle) set at 50 and 75 rpm,

2] 900 mL 0.1 N HCl using USP I apparatus (Basket) set at 50 and 100 rpm,

3] 500 mL 0.1 N HCl using USP II apparatus set at 75 rpm,

4] Sampling time point at least up to [redacted] minutes.

The data generated should be submitted to the Agency for review and for setting up of a proper dissolution specifications for FEMARA 2.5 mg tablets.

A summary of the dissolution profile data and dissolution plots for 2.5 mg FEMARA tablets is provided as Attachment 5. Dissolution testing and methodology summaries are provided in this attachment.

9. Labeling revisions and General Comments

2 Pages (30-31)
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9. References

4 pages (31-34)
Deleted
Internal Reports

References to published literature

Lit. 1 Pfister CU, Duval M, Godbillon J, Gosset G, Gygax D, Marfil F, et al. Development, application and comparison of an enzyme immunoassay and a high-performance liquid chromatography method for the determination of the aromatase inhibitor CGS 20267 in biological fluids. J Pharm Sci 1994; 83: 520-524.

Lit. 2 Shah VP, Midha KK, Dighe S, McGilveray IJ, Skelly JP, et al. Analytical method validation: bioavailability, bioequivalence, and pharmacokinetic studies. J Pharm Sci 1992; 81: 309-312.

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Lit. 4 Cholerton S, Daly AK, Idle JR. The role of individual human cytochrome P450 in drug metabolism and clinical response. TiPS 1992; 13: 434-439.

Lit. 5 Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich PF. Interindividual variations in human liver cytochrome P450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharm Exp Ther 1994; 270: 414-423.

Lit. 6 Klein KO, Demers LM, Santner SJ, Baron J, Cutler GB, Santen RS. Use of ultrasensitive recombinant cell bioassay to measure estrogen levels in women with breast cancer receiving the aromatase inhibitor, letrozole. J Clin Endocron Metabol 1995; 80: 2658-2660.

Lit. 7 Stoll BA. Breast cancer: rationale for endocrine therapy. In: Stoll BA, editor. Hormone Management of Endocrine-related Cancer. London: Lloyd Luke, 1981: 77-91.

Lit. 8 Guengerich PF, Shimada T, Yun CH, Yamazaki H, Ranney R, Thier R, et al. Interactions of ingested food, beverage, and tobacco components involving human cytochrome P4501A2, 2A6, 2E1, and 3A4 enzymes. Environ Health Perspect 1994; 102 (Suppl 9): 49-53.

Lit. 9 Bertilsson L. Geographical/interracial differences in polymorphic drug oxidation. Current state of knowledge of cytochrome P450 (CYP) 2D6 and 2C19. Clin Pharmacokinet 1995; 29: 192-209.

Lit. 10 Andersson T, Andrén K, Cederberg C, Edvardsson G, Heggelund A, Lundborg P. Effect of omeprazole and cimetidine on plasma diazepam levels. Eur J Clin Pharmacol 1990; 39: 51-54

Lit. 11 Andersson T, Andrén K, Cederberg C, Edvardsson G, Heggelund A, Lundborg P. Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. Clin Pharmacol Ther 1990; 47: 79-85.

Lit. 12 Lønnig PE, Kvinnsland S, Jahren G. Aminoglutethimide and warfarin. A new important drug interaction. Cancer Chemother Pharmacol 1984; 73: 1392-1396.

Attachment 1

Sponsor's proposed labeling

19 Pages (1-19)
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Attachment 2

Sponsor's pharmacokinetic study synopses

1.2. Individual trial summaries

A telegraphic narrative summary of the design and results of each individual clinical pharmacology trial in Table 1 follows.

Title of the 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.**
Investigators:	Ph. Müller; P. Trunet, H. Howald.
Study center(s):	Human Pharmacology, Ciba-Geigy, Basle, CH
Publication (reference):	J. Clin. Endocrin & Metab. 1993. Vol 77, p 319-323.
Studied period / Clinical phase:	1989
Objectives:	1) To estimate tolerability and possible side effects. 2) To obtain preliminary information on magnitude and duration of decrease in estrogen levels and on possible effects on other hormones. 3) To estimate basic pharmacokinetics after single oral doses of CGS 20267 in the range of 0.02 and 30 mg.
Methodology:	Open pilot study with increasing doses, each dose tested in 3 subjects, each subject receiving one low and one higher single dose at an interval of at least 3 weeks. Subjects receiving the 2 highest doses had only one single administration. Monitoring of tolerability over 48 h. Determination of serum hormone levels up to three weeks after each dose. Sampling of plasma and urine for pharmacokinetics.
Number of subjects (total and for each treatment):	18
Diagnosis and criteria for inclusion:	Healthy male subjects, age 20-60 years, health screen perform at Medical Outpatients Department of University Hospital Basle, ability and willingness to cooperate, written informed consent obtained.
Test product, dose and mode of administration, batch no.:	CGS 20267. Doses tested: 0.02, 0.1, 0.25, 0.5, 1.0, 2.5, 5.0, 10, 30 mg (each dose n=3). Oral solution in distilled PEG 300 and demineralized water, volume 100 mL, 1.5 h after breakfast. Batch no.14/405/A-G, I, K.
Duration of treatment:	Single doses
Reference therapy, dose and mode of administration, batch no.:	Placebo (n = 3), administered as for active treatment. Batch no. 14/405/H
Criteria for evaluation:	Tolerability: subjective symptoms, blood chemistry, hematology, urinalysis, blood pressure, heart rate, ECG, body weight. Hormones: estrone, estradiol, LH, FSH, testosterone, aldosterone, cortisol. Pharmacokinetics: plasma and urinary concentrations of CGS 20267.
Statistical methods:	Descriptive: plots with individual data for all hormones and % changes from baseline for E1 and E2, tabulations of geometric means for all hormones.

Results

Efficacy:

Estrone: decrease with all doses within 2-4 h, maximum suppression by 70-85% from baseline at 24-48 h after administration, reaching limit of detection (2.5 pg/mL) with doses of 2.5 mg and higher. Slow return to baseline, suppression by 80% from baseline and more sustained for 2 days after 2.5 mg, for at least 3 days after 5, 10 and 30 mg. In 30 mg dose group suppression still by 50% from baseline at 3 weeks after administration.

Estradiol: decrease with all doses within 2-4 h, maximum suppression after 10-24 h with a clear-cut dose-dependency. At 24 h after dosing, suppression from baseline by 30% with 0.02 mg, by 50% with 0.1 and 0.25 mg, by 60% with 0.5 and 1.0 mg, by 75% with 2.5 and 5 mg, by 80% with 10 mg and by 90% with 30 mg CGS 20267. Return to baseline was faster as compared to E1, suppression by 80% from baseline for 2 days with 10 mg and 3 days with 30 mg doses. Testosterone, LH, FSH: dose-related increase; with highest dose of 30 mg between 6-13 days after administration, by 150% from baseline for testosterone after 13 days and by 250% from baseline for LH and FSH after 6 days.

Cortisol and aldosterone: no drug-related changes of both hormones with any of the doses tested.

Adverse experiences

Good systemic tolerability, only 4/18 subjects with symptoms after 5/30 mg administrations: one incidence of orthostatic collapse upon passive tilting already before and after 0.5 mg dose; same subject with moderate headache on day 1 and with migraine on day 3 after 5 mg dose and 2 subjects with mild headache on day 1 after 0.02 mg. No influence of treatment on blood pressure, heart rate, ECG and body weight detectable.

Safety monitoring results

Clinical laboratory evaluations:

No influence of treatment on clinical laboratory parameters.

Pharmacokinetics:

tmax (h): 1 (median)

t½: 0.1-10 mg: mean=43 (range 19-68); 30 mg: 236 (106-394)

Cmax (nmol/l): 0.1 mg: 3.82±0.95; 0.25 mg: 9.56±2.21; 0.5 mg: 22.7±11.9; 1.0 mg: 30.6±4.0; 2.5 mg: 103±7; 5.0 mg:206±56; 10 mg: 330±33; 30 mg: 1232±66)

AUC (h·µmol/l): 0.1 mg: 0.19±0.11; 0.25 mg: 0.46±0.04; 0.5 mg: 0.78±0.45; 1.0 mg: 1.54±0.65; 2.5 mg: 5.08±0.49;5.0 mg: 7.63±1.73; 10 mg: 18.34.7; 30 mg: 263±106.

Other outcomes (if appropriate):

Summary - Conclusions:

CGS 20267 is a well-tolerated, highly potent, selective and long-acting inhibitor of the aromatase enzyme system when administered in single oral doses between 0.02 and 30 mg to healthy male subjects.

Pharmacokinetics were dose proportional in the dose range of 0.1 to 10 mg (concentrations after 0.02 mg were below the quantification limit of the analytical method). For the 30 mg dose, AUC, but not Cmax, increased dose over-proportionally due to an increase of the apparent terminal plasma half-life of letrozole.

4 Pages (14-17)
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None Published
References

Title of the study:	**AR/HW1** **CGS 20267-Non steroidal aromatase inhibitor: Double-blind randomized single dose Phase I trial in healthy postmenopausal women.**
Investigators:	I.E. Smith; M. Dowsett
Study center(s):	Royal Marsden Hospital, London
Publication (reference):	J. Clin. Endocrinol. and Metab.77:324-331, 1993
Studied period / Clinical phase:	1991/Phase I
Objectives:	a) To establish the dose-response relationship between the administration of single doses of 0.1 mg, 0.5 mg, and 2.5 mg CGS 20267 and the suppression of estrogen synthesis. b) To determine the effect of each tested single dose CGS 20267 on other hormones (cortisol, aldosterone, testosterone, androstenedione, 17-OH-progesterone, LH, FSH, TSH. c) To assess the tolerability and safety of each tested single dose CGS 20267. d) To obtain pharmacokinetic information after single dose administration
Methodology:	Monitoring of tolerability (adverse experiences, clinical laboratory), determination of serum hormone levels up to 2 weeks after dosing, determination of urine hormones up to 72 h after dosing, sampling of plasma and urine for pharmacokinetics.
Number of subjects (total and for each treatment):	12
Diagnosis and criteria for inclusion:	Healthy postmenopausal women, age 55-70 years. Healthy status was essential and defined by normal liver and renal function together with normal hematology, blood chemistry, urinalysis, ECG, blood pressure and heart rate. Written informed consent.
Test product, dose and mode of administration, batch no.:	CGS 20267. Placebo (2 x placebo), 0.1 mg (1 x 0.1 mg + 1 x placebo), 0.5 mg (2 x 0.25 mg), 2.5 mg (1 x 2.5 mg + 1 x placebo)
Duration of treatment:	Single doses
Reference therapy, dose and mode of administration, batch no.:	
Criteria for evaluation:	Tolerability: subjective symptoms, blood chemistry, hematology, urinalysis, blood pressure, heart rate and ECG. Hormones: estrone, estradiol, aldosterone, cortisol, testosterone, androstenedione, 17-OH-progesterone, LH, FSH, TSH. Pharmacokinetics: plasma and urinary concentrations of CGS 20267.
Statistical methods:	Logarithmic transformation of hormone data; analysis of variance for balanced incomplete block design; comparisons between means using Bonferroni's method; for serum E1 and E2 level of significance adjusted for multiple testing to p = 0.00119.

Results

Efficacy:	Estrone: decrease within 2 h after all 3 doses, maximum suppression at 48-72 h for 0.1 and 0.5 mg by 75% from baseline and 7 days for 2.5 mg by 78%. Dose-dependent recovery towards baseline between 7-14 days but baseline values not reached within this time. Effect statistically significant compared with placebo for all doses between 24-72h. No statistically significant difference between doses. Statistical significance was still seen after 7 days for the 2 higher doses. Estradiol: decrease within 4-8 h after all 3 doses, maximum suppression at 72h for 0.1 and 0.5 mg, by 75-78% from baseline; maximum suppression at 48 h for 2.5 mg by 78% from baseline. Return to baseline not achieved within 14 days. Suppression statistically significant from placebo for 0.1 and 0.5 mg at 24 and 72 h. for 2.5 mg at 48 and 72h. No statistically significant difference between doses. No significant effect on other hormones
Adverse experiences	Good systemic tolerability. No unwanted endocrine effects. Headache reported 11 times in 7 subjects including 3 following placebo; drug-related causality appears remote.
Safety monitoring results	No influence of test drug on ECG, pulse rate and blood pressure.
Clinical laboratory evaluations:	Deviations observed in serum biochemistry and hematology were mostly present at baseline or mild and transient and without relationship to the trial drug.
Pharmacokinetics:	tmax (h): 1 (median) t½ (h): 51 (range 25-87) Cmax (nmol/l): 0.1 mg: 4.47±0.65; 0.5 mg: 23.8±2.05; 2.5 mg: 130±20 AUC (h·nmol/l): 0.1 mg: 160±60; 0.5 mg: 1040±220; 2.5 mg: 6210±2200

Summary - Conclusions:

The results of this double-blind randomized trial with single oral doses of CGS 20267 (0.1, 0.5, 2.5 mg and placebo) administered to healthy postmenopausal female volunteers show that the compound is a well tolerated, selective, long acting and very potent aromatase inhibitor.

Pharmacokinetics in healthy postmenopausal women were comparable to those observed in healthy man. No effect of sex on the pharmacokinetics was detected.

Title of the study:	**AR/BC1 Core** **CGS 20267: Non-steroidal oral aromatase inhibitor. Open, Phase I trial in postmenopausal patients with advanced breast cancer.**
Investigators:	I.E. Smith.
Study center(s):	Royal Marsden Hospital, London, GB
Publication (reference):	Cancer Res. 1993; 53: 266-270
Studied period / Clinical phase:	11/03/1991- 12/11/91
Objectives:	To assess the tolerability and toxicity of CGS 20267 after multiple administration and to observe suppression of estrogens, effects on other hormones and pharmacokinetic behavior.
Methodology:	Objective tumor response according to UICC criteria. Adverse experiences, hematology, blood chemistry, blood pressure, pulse rate. Plasma concentration of CGS 20267- samples taken during core and extension trial.
Number of subjects (total and for each treatment):	7 pts (0.1 mg trial drug), 7 pts (0.5 mg trial drug), 7pts (2.5 mg trial drug).
Diagnosis and criteria for inclusion:	Compliant postmenopausal women under the age of 80 years with loco-regional recurrence or progression of metastatic breast cancer no longer responding to conventional treatment, i.e. chemotherapy, and with a WHO performance status of 0-2
Test product, dose and mode of administration, batch no.:	CGS 20267; 0.1 mg (4 x 0.025 mg), 0.5 mg (2 x 0.025), 2.5 mg (1 x 2.5 mg). Oral administration. 0.025 mg tablets (batch no. 14/737/1; 0.25 mg tablets (batch no. 15/187/1); 2.5 mg tablets (batch no. 15/218/1).
Duration of treatment:	28 days: Patients who got benefit from the treatment could continue until disease progression or any other reason necessitated discontinuation.
Reference therapy, dose and mode of administration, batch no.:	
Criteria for evaluation:	Tolerability: Adverse experiences, hematology, blood chemistry, urinalysis, body temperature, ECG, blood pressure, pulse rate. Hormones: Estrone (E1), estradiol (E2), cortisol, aldosterone, androstenedione, 17-OH-progesterone, FSH, LH, TSH. Pharmacokinetics: Plasma concentrations of CGS 20267.
Statistical methods:	Logarithmic transformation of hormone data, within-dose comparisons using a series of sample t-tests with Bonferroni corrections for multiple testing, to keep the overall within-dose significance level to < 5%. Summary statistics for safety data.

Results

Efficacy:

Hormones: Estrone (E1) suppression (0.1 mg) was ± 61 % from baseline (day 1), with further decrease to ± 78% (day 28). 78 % suppression was seen at day 7 with 0.5 mg decreasing further to 83% at day 28. Maximal suppression of ± 80% was seen at day 7 with 2.5 mg. Changes from baseline were statistically significant at each time for each dose. Several individual estrone values reached the limit of the detection assay (6 with 0.1 mg, 11 with 0.5 mg, and 19 with 2.5 mg CGS 20267). Maximal Estradiol (E2) suppression of 80 % was seen at day 7 with 0.1 and 2.5 mg. This was for 0.5 mg 77% at day 14. Changes from baseline were statistically significant and several values reached the limit of the detection assay (8 with 0.1 mg, 7 with 2.5 mg CGS 20267). Other hormones: No statistically significant changes were seen in cortisol, aldosterone, androstenedione, 17-OH-progesterone, FSH, LH and TSH.

Adverse experiences

No patient died or stopped due to tolerability problems within the 28-day treatment period. Including the SAEs from the extension part of the trial, 6 patients reported 21 AEs (0.1 mg), 7 patients 16 AEs (0.5 mg) and 6 patients 12 AEs (2.5 mg). Most AEs were mild, some of moderate severity. With the exception of one possible trial drug related mild headache, all others were reported as not or unlikely related. The most commonly reported AEs were: headache (6 pts), constipation (3 pts), pain back (3 pts), nausea (2 pts), leukorrhea (2 pts), pain musculo-skeletal (2 pts), pneumonitis (2 pts), dyspnea (2 pts),-some of which were due to underlying disease.

Four patients experienced serious adverse experiences in the trial extension period (2 death, 1 skin rash, 1 hospitalization for puncture of pleural effusion). Relationship to trial drug was considered as none (3) or unlikely (1).

Safety monitoring results

Clinical laboratory evaluations:

Pharmacokinetics (if appropriate):

Plasma kinetics were in general as expected from single dose kinetics observed in previous trials with healthy volunteers. A slight dose over-proportional increase in systemic exposure was observed in the 2.5 mg dose group.

Other outcomes (if appropriate): >

Summary - Conclusions:

CGS 20267 is a well tolerated drug in the dose range tested. The reported AEs were mainly of mild severity. No clinically related changes related to CGS 20267 were seen in vital signs, ECG, body weight, hematology and blood chemistry. A significant suppression in estrone and estradiol levels were observed without affecting other hormone levels. CGS 20267 can therefore be considered as a safe and active drug in terms of estrogen suppression for the treatment of postmenopausal patients with advanced breast cancer.

Title of the study:	**P01 Core** **Open-label dose range finding trial of CGS 20267 in postmenopausal women with metastatic breast cancer.**
Investigators:	A. Lipton
Study center(s):	Hershey Medical Center, Hershey (US)
Publication (reference):	Cancer 1995; 75: 2132-8
Studied period / Clinical phase:	21/10/91-30/9/92
Objectives:	Core trial: To determine safety, efficacy, selectivity of letrozole and the effects of various doses of letrozole on estrogen suppression. Determination of multiple dose pharmacokinetics. Extension trial: To provide continued treatment to patients responding to letrozole during participation in Protocol 01.
Methodology:	This was a single center, open-label dose-range finding trial using 6 dose levels of letrozole. Patients received 2 ascending doses of letrozole over a 12-week period; patients were assigned to groups sequentially in order of entry into the trial (Treatment sequence I, 0.1 mg/ 0.25 mg; Treatment sequence II, 0.5/1.0 mg; Treatment sequence III, 2.5/5.0 mg). Serum was collected prior to the morning of each visit for determination of estrogen levels. Additionally at visits 2, 5 and 8, 24-hour serial collections for estradiol and estrone were obtained. Urinary estradiol and estrone: 24-h urine samples were collected at all visits except visit 1. Additionally: at visits 2, 5 and 8, a 2nd 24-h collection was obtained. Continued treatment in the extension protocol was allowed for responding patients who had completed all trial visits.
Number of subjects (total and for each treatment):	Patients who completed core trial: Sequence I (6); Sequence II (5); Sequence III (6). Patients who received drug at visit 2: Sequence I (8); Sequence II (7); Sequence III (8). 23 patients were evaluated for hormones/ECOG and safety; 21 patients for tumor response. 14 patients continued in the extension trial.
Diagnosis and criteria for inclusion:	Postmenopausal patients ($\geq$ 18 years) with progressive metastatic breast cancer. Patients with evaluable disease, non-responsive to conventional hormonal therapy. ER+ or unknown status of the breast tumor. Patients with a life expectancy of $\geq$ 16 weeks and ECOG status $\leq$ 2. Normal or specified renal, hepatic, and hematological profiles. Extension trial: any patient who completed core trial and who could benefit from continued treatment.
Test product, dose and mode of administration, batch no.:	Letrozole (0.1 mg; Batch No. E-14702, Formulation No, H-3468/ 0.25 mg; Batch No. E-14703, Formulation No, H-3469/ 1.0 mg; Batch No. E-14704, Formulation No, H3470/ 2.5 mg; Batch No. E-14705, Formulation No, H-3471), oral administration.
Duration of treatment:	Core trial: 12 weeks. Extension trial: until disease progression or discontinuation otherwise.

Reference therapy, dose and mode of administration, batch no.:	Comparative control and placebo, dose and mode of administration, batch and formulation nos.: none.
Criteria for evaluation:	Primary: serum estradiol, estrone, estrone sulfate. Secondary: pain and narcotic scores, ECOG performance status and unconfirmed tumor response (core trial) or confirmed response (extension trial).
Statistical methods:	Within-treatment comparisons were performed at visits 3, 4, 5, 6, 7 and 8 for each primary efficacy variable: serum estradiol, estrone and estrone sulfate, and urinary estradiol and estrone.
Results	
Efficacy:	Core trial: Serum estradiol and estrone levels were suppressed by $\geq$ 63% within 24 h of the first dose of 0.1, 0.5 and 2.5 mg. Estrogen suppression was 85 - 94 % for 0.5 and 2.5 mg doses after 6 weeks of treatment. Dose increases per treatment sequence to 0.25 mg, 1.0 mg and 5.0 mg respectively, showed slight incremental increases in percent estrogen suppression during the initial 6 weeks (89 -95% suppression). Serum estrone sulfate ($\pm$ 95 % suppression at all visits for all treatment sequences) and urinary estrone and estradiol (at least 80% suppression during all treatment sequences) were significantly affected. One patient had a partial response and 7 patients had stable disease. A second partial response was seen in the extension trial. 18 (78%) patients received letrozole as $\geq$ 3rd line hormonal therapy. Extension trial: No further decreases in serum and urinary estrogens were observed. During core and extension trials; 2 patients attained confirmed partial response and 6 patients had stable disease.
Adverse experiences	Core trial: Most commonly reported adverse experiences were bone pain, nausea, hot flushes and vomiting. Trial drug related events included nausea (5 pts), hot flushes (5 pts), hair thinning (2 pts), diarrhea (2 pts) dyspepsia (2 pts), and increased sweating (2 pts). One patient showed an increase in bone pain to grade 4 which was considered as a possible trial drug related flare. Most adverse experiences mild to moderate likely disease related. No patient discontinued treatment due to adverse experiences. No clinically relevant changes were seen in vital signs, chest X-rays, ECGs or in any other endocrine parameter evaluated. Serum urinary cortisol and serum androgen levels were not affected. Cortisol and aldosterone response to ACTH challenge remained within the biologically normal range. No clinical significant changes were seen for plasma renin levels or for serum and urinary electrolytes. Thyroid function (TSH, T4 and T3 uptake) appeared unaltered. Extension trial: New trial drug related events included one case of nausea, hot flushes and peripheral edema. No patient discontinued the trial due adverse experiences or died during the extension period. Other parameters were not further affected.

Safety monitoring results

Clinical laboratory evaluations:

Pharmacokinetics:

AUC values within a dose interval after 6 weeks of treatment increased dose proportionally in the dose range of 0.25 to 1.0 mg/day. They increased clearly dose over-proportionally after 5 mg/day (by a factor of 12 instead of 5 compared to 1.0 mg/day) and after 2.5 mg/day they increased slightly over-proportionally. Thus, 2.5 mg/day seems to be a border line dose at which non-linearity of the plasma pharmacokinetics starts to become apparent. However, all patients which remained for longer periods of time under treatment attained steady state letrozole plasma levels, indicating that no continuous accumulation occurred.

In urine (24 h at 6 weeks of treatment) letrozole was excreted mainly as its metabolite CGP 44645 (range 18.7-99.0% of dose) and to a lesser extent as unchanged compound (range 5.55-36.9% of dose).

Other outcomes (if appropriate):

Summary - Conclusions:

The results demonstrate that letrozole is an active, potent and specific aromatase inhibitor. At all doses tested (0.1-5 mg), letrozole markedly suppresses estrogens without affecting other hormones involved in the steroidogenic pathway. Higher doses did not show a trend towards a greater degree of estrogen suppression.

Eight patients did benefit from letrozole treatment in terms of tumor response (2 partial response, 6 stable disease). This was achieved in spite of the fact that these patients had advanced metastatic disease which was refractory to multiple conventional therapies.

In summary: the good systemic and subjective tolerability of letrozole seen in earlier Phase I trials was confirmed in this trial of heavily pretreated postmenopausal women with advanced breast cancer. Letrozole also appears active in terms of antitumor activity in some of the patients in this trial.

28 Pages (25-52)
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None Published
References

11 Pages (Attach. 3)

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30 Pages Deleted

Attachments 4 & 5

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20,726 **Submission Date**: July 24, 1996

Type of Submission: original new drug application; this review is for the file/refuse-to-file meeting

Generic Name: Letrozole

Formulation: oral, tablet

Sponsor: Ciba-Geigy Corporation
556 Morris Avenue
Summit, New Jersey 07901-1398

Reviewer: Gene M. Williams, Ph.D.

Background

This NDA is for the use of letrozole (Femara®, CGS 20267) for treatment of advanced breast cancer in postmenopausal women.

The submission for Item 6 of the NDA appears to be organized in a manner that will allow for review. As requested, the sponsor has included electronic submission of pharmacokinetic data.

The submission is incomplete; incompleteness in the submission has been brought to the attention of the sponsor and the sponsor has responded by supplying some of the data requested. Some of the incompleteness has only recently been identified by the reviewer and has not yet been submitted by the sponsor. The sponosr has agreed to provide all of the data requested. A listing of the reviewer's requests and the sponsor's responses to date is attached to this review.

Comment to the clinical division

The package submitted by the sponsor is organized in a manner that allows for review. The submission is incomplete, but to date the sponsor has shown willingness to submit data that has been omitted. Based upon what's been submitted to date, and the apparent good will of the sponsor, we find the Human Pharmacokinetics and Bioavailability portion of the NDA reviewable.

FT

Atiqur Rahman, Ph.D. 2/9/96
Team Leader
Division of Pharmaceutical Evaluation I

Gene M. Williams, Ph.D. 2/7/96
Reviewer
Division of Pharmaceutical Evaluation I

cc:

NDA 20,726	original
HFD-150	division file
HFD-150	Spillman, Schechter, JJohnson
HFD-340	Viswanathan
HFD-850	Lesko
HFD-860	Malinowski, Mehta, Rahman