SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
MALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.1 mg/kg	1.0 mg/kg	10 mg/kg	TEST FOR TREND P-VALUE
INTEGUMENTARY SYSTEM (continued)					
SKIN (continued)					
NERVE SHEATH TUMOR, MALIGNANT [M]	0/60	0/60	1/60	1/60	
OBS/EXP:	0.00	0.00	2.01	1.98	0.189
OSTEOSARCOMA [M]	0/60	0/60	1/60	0/60	
OBS/EXP:	0.00	0.00	3.24	0.00	0.569
PAPILLOMA [B]	1/60	1/60	0/60	1/60	
OBS/EXP:	1.57	1.38	0.00	1.27	0.746
MUSCULOSKELETAL SYSTEM					
BONE					
CHONDROSARCOMA [M]	0/60	0/60	1/60	0/60	
OBS/EXP:	0.00	0.00	3.00	0.00	0.565
OSTEOSARCOMA [M]	1/60	1/60	1/60	0/60	
OBS/EXP:	1.72	1.37	1.02	0.00	0.896
SKELETAL MUSCLE					
NERVE SHEATH TUMOR, MALIGNANT [M]	0/60	0/60	0/60	1/60	
OBS/EXP:	0.00	0.00	0.00	3.78	0.264
RHABDOMYOSARCOMA [M]	0/60	1/60	0/60	0/60	
OBS/EXP:	0.00	4.17	0.00	0.00	0.827
SARCOMA [M]	1/60	0/60	0/60	0/60	
OBS/EXP:	3.93	0.00	0.00	0.00	1.000
NERVOUS SYSTEM					
BRAIN					
ASTROCYTOMA [M]	0/60	3/60	0/60	2/60	
OBS/EXP:	0.00	2.48	0.00	1.63	0.438

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
MALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.1 mg/kg	1.0 mg/kg	10 mg/kg	TEST FOR TREND P-VALUE
NERVOUS SYSTEM (continued)					
BRAIN (continued)					
MENINGIOMA [M]	0/60	0/60	0/60	1/60	
OBS/EXP:	0.00	0.00	0.00	3.70	0.271
SPINAL CORD					
ASTROCYTOMA [M]	0/60	0/60	0/60	1/60	
OBS/EXP:	0.00	0.00	0.00	3.87	0.259
REPRODUCTIVE SYSTEM					
TESTIS					
INTERSTITIAL-CELL TUMOR [B]	0/60	0/60	0/60	1/60	
OBS/EXP:	0.00	0.00	0.00	4.41	0.227
RESPIRATORY SYSTEM					
LUNG					
ADENOCARCINOMA [M]	0/60	0/60	0/60	1/60	
OBS/EXP:	0.00	0.00	0.00	4.41	0.227
MESOTHELIOMA [M], pleural	0/60	0/60	0/60	1/60	
OBS/EXP:	0.00	0.00	0.00	3.96	0.253
SPECIAL SENSE ORGANS					
LACRIMAL GLAND					
MYOEPITHELIOMA [B]	0/59	0/60	1/60	0/60	
OBS/EXP:	0.00	0.00	3.03	0.00	0.588
ZYMBAL'S GLAND					
ADENOCARCINOMA [M]	0	1	1	1	

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
MALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.1 mg/kg	1.0 mg/kg	10 mg/kg	TEST FOR TREND P-VALUE
URINARY SYSTEM					
KIDNEY					
ADENOMA [B]	0/60	0/60	2/60	0/60	
OBS/EXP:	0.00	0.00	2.78	0.00	0.451
OTHER/NOT CLASSIFIED					
OTHER TISSUE(S)					
MELANOMA, AMELANOTIC [M], gingival	0	0	1	0	
COMBINATIONS					
ADRENAL GLAND					
CORTICAL ADENOMA [B] OR CARCINOMA [M]	2/60	1/59	1/60	1/60	
OBS/EXP:	1.78	0.82	0.73	0.78	0.774
PHEOCHROMOCYTOMA, BENIGN OR MALIGNANT	9/60	11/59	9/60	9/60	
OBS/EXP:	1.10	1.19	0.83	0.92	0.758
BONE OR SKIN					
OSTEOSARCOMA [M]	1/60	1/60	2/60	0/60	
OBS/EXP:	1.30	1.03	1.55	0.00	0.822
LIVER					
HEPATOCELLULAR ADENOMA OR CARCINOMA	4/60	3/60	8/60	5/60	
OBS/EXP:	0.92	0.62	1.40	0.99	0.296
MAMMARY GLAND					
ADENOMA OR FIBROADENOMA	1/49	3/45	0/44	0/41	
OBS/EXP:	1.14	3.02	0.00	0.00	0.959
ADENOMA, FIBROADENOMA OR ADENOCARCINOMA	2/49	3/45	0/44	0/41	
OBS/EXP:	1.77	2.42	0.00	0.00	0.986

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
MALES

BODY SYSTEM ORGAN FINDING		DOSE GROUPS 0 mg/kg	 0.1 mg/kg	 1.0 mg/kg	 10 mg/kg	TEST FOR TREND P-VALUE
COMBINATIONS (continued)						
PANCREAS						
ISLET CELL ADENOMA OR CARCINOMA		3/60	2/60	4/60	7/60	
	OBS/EXP:	0.84	0.51	0.90	1.70	0.079
PITUITARY						
ADENOMA (PARS DISTALIS) OR CARCINOMA		18/58	32/59	33/60	37/59	
	OBS/EXP:	1.12	0.95	0.82	1.00	0.952
SKIN						
FIBROMA OR FIBROSARCOMA		2/60	4/60	3/60	2/60	
	OBS/EXP:	0.81	1.51	1.00	0.70	0.640
PAPILLOMA OR KERATOACANTHOMA		4/60	2/60	2/60	1/60	
	OBS/EXP:	2.11	0.93	0.76	0.44	0.950
SKIN OR SKELETAL MUSCLE						
NERVE SHEATH TUMOR, BENIGN OR MALIGNANT		1/60	0/60	1/60	2/60	
	OBS/EXP:	1.11	0.00	0.93	1.91	0.296
THYROID						
C-CELL ADENOMA OR CARCINOMA		5/60	2/60	2/59	1/60	
	OBS/EXP:	2.06	0.81	0.79	0.39	0.965
FOLLICULAR ADENOMA OR ADENOCARCINOMA		1/60	3/60	0/59	2/60	
	OBS/EXP:	0.80	2.06	0.00	1.31	0.586

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.1 mg/kg	1.0 mg/kg	10 mg/kg	TEST FOR TREND P-VALUE
DIGESTIVE SYSTEM					
LIVER					
CHOLANGIOMA (B)	1/60	1/60	0/60	0/60	
OBS/EXP:	1.90	2.24	0.00	0.00	0.897
HEPATOCELLULAR ADENOMA (B)	8/60	4/60	8/60	8/60	
OBS/EXP:	1.10	0.65	1.14	1.05	0.421
HEPATOCELLULAR CARCINOMA (M)	1/60	2/60	3/60	4/60	
OBS/EXP:	0.38	0.89	1.23	1.52	0.082
PANCREAS					
ISLET CELL ADENOMA (B)	1/60	0/60	0/60	2/60	
OBS/EXP:	1.29	0.00	0.00	2.46	0.239
ISLET CELL CARCINOMA (M)	0/60	1/60	0/60	1/60	
OBS/EXP:	0.00	2.02	0.00	2.24	0.377
SALIVARY GLAND					
MYOEPITHELIOMA, MALIGNANT (M)	0/60	1/60	0/60	0/60	
OBS/EXP:	0.00	4.05	0.00	0.00	0.765
SMALL INTESTINE					
ADENOCARCINOMA (M)	0/60	1/60	0/60	0/60	
OBS/EXP:	0.00	4.05	0.00	0.00	0.765
STOMACH					
SQUAMOUS CELL CARCINOMA (M)	0/60	1/60	0/60	0/60	
OBS/EXP:	0.00	4.05	0.00	0.00	0.765

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NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING		DOSE GROUPS 0 mg/kg	0.1 mg/kg	1.0 mg/kg	10 mg/kg	TEST FOR TREND P-VALUE
ENDOCRINE SYSTEM						
ADRENAL GLAND						
CORTICAL ADENOMA (B)		1/60	1/60	0/60	2/60	
	OBS/EXP:	1.00	1.14	0.00	1.86	0.359
CORTICAL CARCINOMA (M)		0/60	0/60	0/60	1/60	
	OBS/EXP:	0.00	0.00	0.00	4.30	0.233
PHEOCHROMOCYTOMA (B)		5/60	4/60	4/60	8/60	
	OBS/EXP:	0.90	0.82	0.79	1.45	0.182
PHEOCHROMOCYTOMA (M)		0/60	0/60	0/60	1/60	
	OBS/EXP:	0.00	0.00	0.00	4.05	0.247
PARATHYROID						
ADENOMA (B)		2/58	2/56	2/56	0/58	
	OBS/EXP:	1.33	1.51	1.29	0.00	0.887
PITUITARY						
ADENOMA (B), pars distalis		42/59	47/60	38/59	43/60	
	OBS/EXP:	0.98	1.25	0.90	0.90	0.875
ADENOMA (B), pars intermedia		1/59	0/60	0/59	0/60	
	OBS/EXP:	4.25	0.00	0.00	0.00	1.000
CARCINOMA (M)		3/59	1/60	1/59	0/60	
	OBS/EXP:	2.36	0.88	0.80	0.00	0.981
THYROID						
C-CELL ADENOMA (B)		5/60	2/60	3/60	3/60	
	OBS/EXP:	1.45	0.67	0.95	0.87	0.743

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING		DOSE GROUPS 0 mg/kg	0.1 mg/kg	1.0 mg/kg	10 mg/kg	TEST FOR TREND P-VALUE
ENDOCRINE SYSTEM (continued)						
THYROID (continued)						
FOLLICULAR ADENOCARCINOMA [M]		0/60	0/60	1/60	0/60	
	OBS/EXP:	0.00	0.00	3.40	0.00	0.518
FOLLICULAR ADENOMA [B]		0/60	0/60	0/60	1/60	
	OBS/EXP:	0.00	0.00	0.00	4.47	0.224
GANGLIONEUROMA [B]		1/60	0/60	0/60	0/60	
	OBS/EXP:	4.25	0.00	0.00	0.00	1.000
HEMATOPOIETIC-LYMPHORETICULAR SYSTEM						
LYMPH NODE						
LEIOMYOSARCOMA [M]		1/60	0/60	0/60	0/60	
	OBS/EXP:	3.84	0.00	0.00	0.00	1.000
SYSTEMIC						
HISTIOCYTIC SARCOMA [M]		1/60	0/60	0/60	0/60	
	OBS/EXP:	3.69	0.00	0.00	0.00	1.000
LYMPHOMA, MALIGNANT [M]		3/60	0/60	5/60	0/60	
	OBS/EXP:	1.43	0.00	2.61	0.00	0.733
THYMUS						
ADENOCARCINOMA [M]		0/58	0/58	1/59	0/59	
	OBS/EXP:	0.00	0.00	4.06	0.00	0.502
THYMOMA [M]		0/58	0/58	0/59	1/59	
	OBS/EXP:	0.00	0.00	0.00	3.78	0.264

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NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING		DOSE GROUPS 0 mg/kg	0.1 mg/kg	1.0 mg/kg	10 mg/kg	TEST FOR TREND P-VALUE
INTEGUMENTARY SYSTEM						
MAMMARY GLAND						
ADENOCARCINOMA [M]		8/60	0/60	0/58	0/54	
	OBS/EXP:	3.82	0.00	0.00	0.00	1.000
ADENOMA [B]		3/60	1/60	0/58	0/54	
	OBS/EXP:	2.91	1.14	0.00	0.00	0.996
FIBROADENOMA [B]		35/60	6/60	1/58	0/54	
	OBS/EXP:	3.75	0.58	0.09	0.00	1.000
FIBROMA [B]		1/60	0/60	0/58	0/54	
	OBS/EXP:	3.74	0.00	0.00	0.00	1.000
SKIN						
BASAL CELL EPITHELIOMA [B]		0/60	0/60	1/60	0/60	
	OBS/EXP:	0.00	0.00	4.06	0.00	0.514
FIBROMA [B]		1/60	1/60	3/60	0/60	
	OBS/EXP:	0.78	0.90	2.47	0.00	0.680
FIBROSARCOMA [M]		0/60	0/60	0/60	1/60	
	OBS/EXP:	0.00	0.00	0.00	3.90	0.257
HEMANGIOSARCOMA [M]		0/60	0/60	1/60	0/60	
	OBS/EXP:	0.00	0.00	4.16	0.00	0.494
KERATOACANTHOMA [B]		0/60	3/60	0/60	0/60	
	OBS/EXP:	0.00	4.78	0.00	0.00	0.854

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NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING		DOSE GROUPS 0 mg/kg	0.1 mg/kg	1.0 mg/kg	10 mg/kg	TEST FOR TREND P-VALUE
INTEGUMENTARY SYSTEM (continued)						
SKIN (continued)						
LEIOMYOSARCOMA [M]		0/60	0/60	1/60	0/60	
	OBS/EXP:	0.00	0.00	4.05	0.00	0.513
LIPOMA [B]		2/60	1/60	1/60	0/60	
	OBS/EXP:	2.02	1.13	0.94	0.00	0.949
OSTEOSARCOMA [M]		0/60	1/60	0/60	0/60	
	OBS/EXP:	0.00	1.97	0.00	0.00	0.748
PILOMATRICOMA [B]		0/60	0/60	1/60	0/60	
	OBS/EXP:	0.00	0.00	4.05	0.00	0.513
TRICHOEPITHELIOMA [B]		1/60	0/60	0/60	1/60	
	OBS/EXP:	1.95	0.00	0.00	1.85	0.639
MUSCULOSKELETAL SYSTEM						
BONE						
SQUAMOUS CELL CARCINOMA [M]		0/60	0/60	0/60	1/60	
	OBS/EXP:	0.00	0.00	0.00	4.47	0.224
NERVOUS SYSTEM						
BRAIN						
ASTROCYTOMA [M]		0/60	1/60	1/60	0/60	
	OBS/EXP:	0.00	2.02	1.70	0.00	0.630
GLIOMA [M]		0/60	0/60	0/60	1/60	
	OBS/EXP:	0.00	0.00	0.00	3.92	0.255

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NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING		DOSE GROUPS 0 mg/kg	0.1 mg/kg	1.0 mg/kg	10 mg/kg	TEST FOR TREND P-VALUE
NERVOUS SYSTEM (continued)						
BRAIN (continued)						
GRANULAR CELL TUMOR [M]		1/60	0/60	0/60	0/60	
	OBS/EXP:	4.25	0.00	0.00	0.00	1.000
REPRODUCTIVE SYSTEM						
OVARY						
GONADAL STROMAL TUMOR [B]		0/60	0/60	0/60	3/60	
	OBS/EXP:	0.00	0.00	0.00	4.47**	0.010**
LUTEAL CELL TUMOR [B]		0/60	2/60	0/60	0/60	
	OBS/EXP:	0.00	3.88	0.00	0.00	0.753
THECA-CELL TUMOR [B]		1/60	0/60	0/60	0/60	
	OBS/EXP:	4.25	0.00	0.00	0.00	1.000
UTERUS						
ADENOMA [B]		1/60	0/60	0/60	0/60	
	OBS/EXP:	4.25	0.00	0.00	0.00	1.000
ENDOMETRIAL STROMAL SARCOMA [M]		1/60	0/60	0/60	0/60	
	OBS/EXP:	3.70	0.00	0.00	0.00	1.000
POLYP [B]		9/60	1/60	0/60	0/60	
	OBS/EXP:	3.40	0.44	0.00	0.00	1.000
VAGINA						
POLYP [B]		1/60	0/60	0/60	0/60	
	OBS/EXP:	4.25	0.00	0.00	0.00	1.000

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FEMALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.1 mg/kg	1.0 mg/kg	10 mg/kg	TEST FOR TREND P-VALUE
SPECIAL SENSE ORGANS					
ZYMBAL'S GLAND					
ADENOCARCINOMA (M)	0	1	0	0	
URINARY SYSTEM					
KIDNEY					
ADENOCARCINOMA (M)	1/60	0/60	0/60	0/60	
OBS/EXP:	4.00	0.00	0.00	0.00	1.000
LIPOSARCOMA (M)	0/60	0/60	1/60	0/60	
OBS/EXP:	0.00	0.00	3.40	0.00	0.518
NEPHROBLASTOMA (M)	0/60	1/60	0/60	0/60	
OBS/EXP:	0.00	3.96	0.00	0.00	0.735
URINARY BLADDER					
PAPILLOMA (B)	0/60	4/60	3/60	2/60	
OBS/EXP:	0.00	1.81	1.24	0.91	0.237
TRANSITIONAL CELL CARCINOMA (M)	0/60	1/60	0/60	0/60	
OBS/EXP:	0.00	3.88	0.00	0.00	0.742
OTHER/NOT CLASSIFIED					
ADIPOSE TISSUE					
LIPOMA (B)	2	0	0	0	
COMBINATIONS					
ADRENAL GLAND					
CORTICAL ADENOMA (B) OR CARCINOMA (M)	1/60	1/60	0/60	3/60	
OBS/EXP:	0.81	0.88	0.00	2.34	0.188

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FEMALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.1 mg/kg	1.0 mg/kg	10 mg/kg	TEST FOR TREND P-VALUE
COMBINATIONS (continued)					
ADRENAL GLAND (continued)					
PHEOCHROMOCYTOMA, BENIGN OR MALIGNANT	5/60	4/60	4/60	9/60	
OBS/EXP:	0.86	0.78	0.75	1.56	0.118
BRAIN					
ASTROCYTOMA OR GLIOMA	0/60	1/60	1/60	1/60	
OBS/EXP:	0.00	1.39	1.17	1.42	0.314
KIDNEY					
ADENOCARCINOMA OR NEPHROBLASTOMA (M)	1/60	1/60	0/60	0/60	
OBS/EXP:	1.94	2.18	0.00	0.00	0.934
LIVER					
HEPATOCELLULAR ADENOMA OR CARCINOMA	9/60	6/60	11/60	11/60	
OBS/EXP:	0.92	0.73	1.19	1.12	0.212
MAMMARY GLAND					
ADENOMA OR FIBROADENOMA	35/60	7/60	1/58	0/54	
OBS/EXP:	3.68	0.67	0.09	0.00	1.000
ADENOMA, FIBROADENOMA OR ADENOCARCINOMA	37/60	7/60	1/58	0/54	
OBS/EXP:	3.81	0.63	0.08	0.00	1.000
PANCREAS					
ISLET CELL ADENOMA OR CARCINOMA	1/60	1/60	0/60	3/60	
OBS/EXP:	0.79	0.92	0.00	2.21	0.181
PITUITARY					
ADENOMA (PARS DISTALIS) OR CARCINOMA	45/59	48/60	39/59	43/60	
OBS/EXP:	1.05	1.24	0.89	0.87	0.969

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.1 mg/kg	1.0 mg/kg	10 mg/kg	TEST FOR TREND P-VALUE
COMBINATIONS (continued)					
SKIN					
FIBROMA OR FIBROSARCOMA	1/60	1/60	3/60	1/60	
OBS/EXP:	0.65	0.74	2.09	0.60	0.387
TRICHOEPITHELIOMA (B) OR PILOMATRICOMA (B)	1/60	0/60	1/60	1/60	
OBS/EXP:	1.29	0.00	1.36	1.24	0.517
SKIN OR ADIPOSE					
LIPOMA (B)	4/60	1/60	1/60	0/60	
OBS/EXP:	2.64	0.77	0.65	0.00	0.988
THYROID					
FOLLICULAR ADENOMA OR ADENOCARCINOMA	0/60	0/60	1/60	1/60	
OBS/EXP:	0.00	0.00	1.70	2.24	0.181
URINARY BLADDER					
PAPILLOMA OR TRANSITIONAL CELL CARCINOMA	0/60	5/60	3/60	2/60	
OBS/EXP:	0.00	2.04	1.02	0.84	0.322
UTERUS					
POLYP OR ENDOMETRIAL STROMAL SARCOMA	10/60	1/60	0/60	0/60	
OBS/EXP:	3.45	0.40	0.00	0.00	1.000

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T/P (US) 96001 CGS 20267:104-week oral carcinogenicity study in mice (MIN 934020) Conducted by Preclinical Safety, Pharmaceuticals Division, Ciba-Geigy Corporation, Summit, NJ and Rueil- Malmaison, France, in 1995 according to GLP.

Methods

species:	mice (70/sex/dose-main study; 5/sex/control group and 15/sex/dose group-toxicokinetics)
drug:	CGS 20267 (lot no. 800192)
vehicle:	aqueous 3% corn starch (dosing volume 10mg/kg body weight)
dosage:	vehicle, 0.06, 0.6, and 6.0mg/ml [0.6, 6.0 and 60mg/kg]
age; weight:	6 weeks, 20.9-30.2♂, 17.4-25.2♀
route:	oral gavage

Observations

mortality/clinical signs	2X/day on days of dosing
physical/auditory examinations	2weeks prior to dosing, week 13, 26, 38, 52, 65, 78, 91, 104
body weights	weekly from 2 weeks prior to dosing to week 13, monthly from week 17 to week 101 and during week 104
food consumption	weekly from 1 week prior to dosing to week 13, monthly from week 17 to week 101 and during week 104
hematology	determined from 6-10 mice/sex/dose at study termination (early termination week 94, 5HD mice/sex/group used for hematologic determinations)
clinical chemistry	determined from 6-10 mice/sex/dose at study termination (early termination week 94, 5♂ and 4♀mice/group used for clinical chemistry)
urinalyses	not determined
ophthalmoscopy	conducted on all animals predose weeks 1 and 2, control and HD at week 52, control, MD, HD at week 93 and control and MD at week 103
palpable mass examination	every 4 weeks week 4-40, every 2 weeks week 42-terminal necropsy
toxicokinetics	weeks 26, 54 and 78 to determine plasma levels of unchanged letrozole (see Pharmacokinetics section for review)
organ weights	not determined
gross pathology	at week 94 for HD and 104 for control, LD, MD
histopathology	at week 94 for HD and 104 for control, LD, MD

Results

Mortality/clinical signs -males

Dose Group (mg/kg)	Mortality[a]	Sacrificed Moribund/ humane sacrifice	Terminal sacrifice (% survival)	Clinical signs
Control	41	12	17 (24)	Ocular discharge, perineal staining, lacrimation, dehydration
0.6	41	17	12 (17)	"
6	37	12	21 (30)	"
60	40	20	10 (14)	", skin abrasion*, blepharitis, alopecia*, swollen neck and appendages*, prolapsed penis*

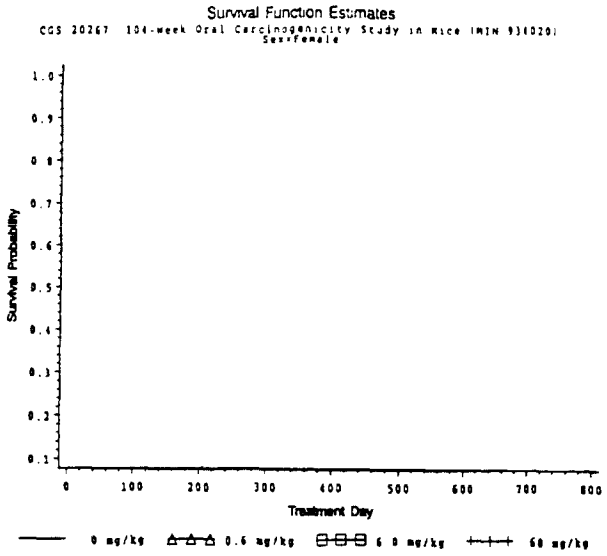
[a]Includes animals which died as result of dosing technique
*Change occurs in all groups but incidence >> in HD group

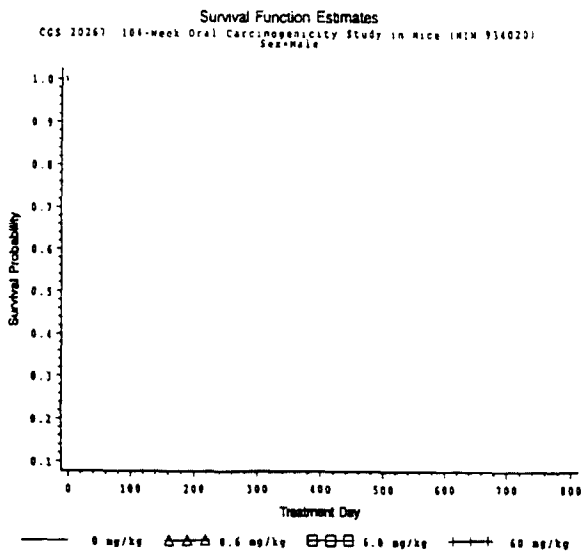
Mortality/clinical signs-Females

Dose Group (mg/kg)	Mortality[a]	Sacrificed Moribund/ humane sacrifice	Terminal sacrifice (% survival)	Clinical signs
Control	44	13	13 (19)	Ocular discharge, perineal staining, lacrimation, dehydration
0.6	33	21	16 (23)	"
6	38	13	19 (27)	"
60	42	19	9 (13)	", skin abrasion*, blepharitis, alopecia*, swollen neck and appendages*

[a]Includes animals which died as result of dosing technique
*Change occurs in all groups but incidence >> in HD group

Significant reductions in survival of ♂ and ♀HD animals necessitated early terminal sacrifice at week 94.





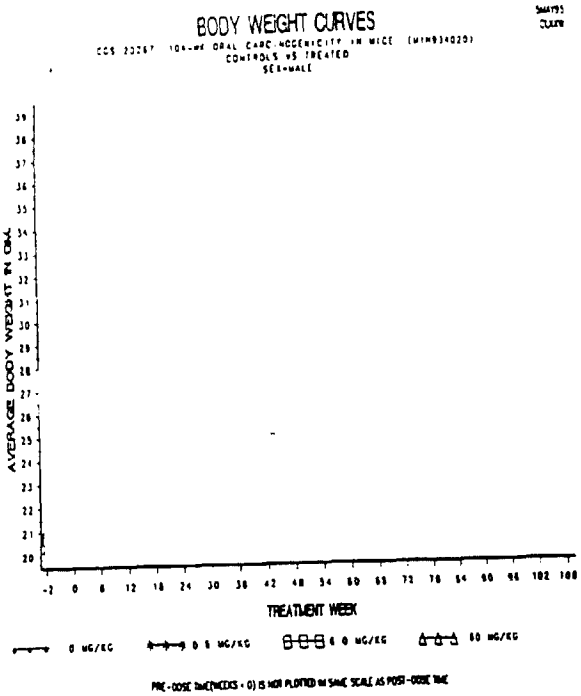
Ophthalmology

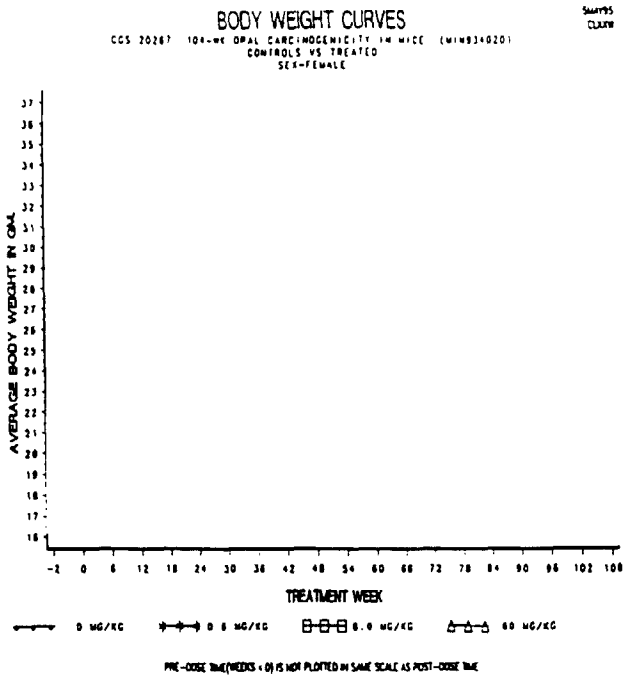
An infection of the Harderian and lacrimal glands resulting in dacryoadenitis, conjunctivitis and blepharitis with lacrimation was observed at 52 weeks in HD ♂ and ♀. The lacrimation contributed to dermatitis with alopecia which was exacerbated by scratching. The sponsor considered this infection to be incidental to dosing.

Body weight

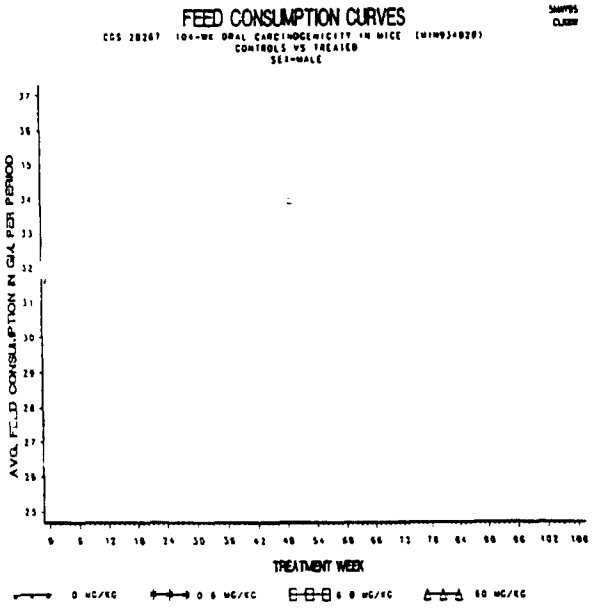
Comparative change in body weights of males and females administered letrozole for 94 to 104 weeks						
Dose (mg/kg)	Males			Females		
	Body weight (g)		% change	Body weight (g)		% change
	baseline	week 104		baseline	week 104	
control	26.3	35.0	33.1	22.2	33.4	50.5
0.6	25.8	35.8	38.8 (14.9)[a]	21.8	31.5	44.5 (-13.4)
6.0	26.4	34.8	31.8 (-3.4)	21.5	34.4	60 (15.2)
60	26.2	33.3	25.1 (-18.4)	21.6	32.3	49.5 (-4.5)

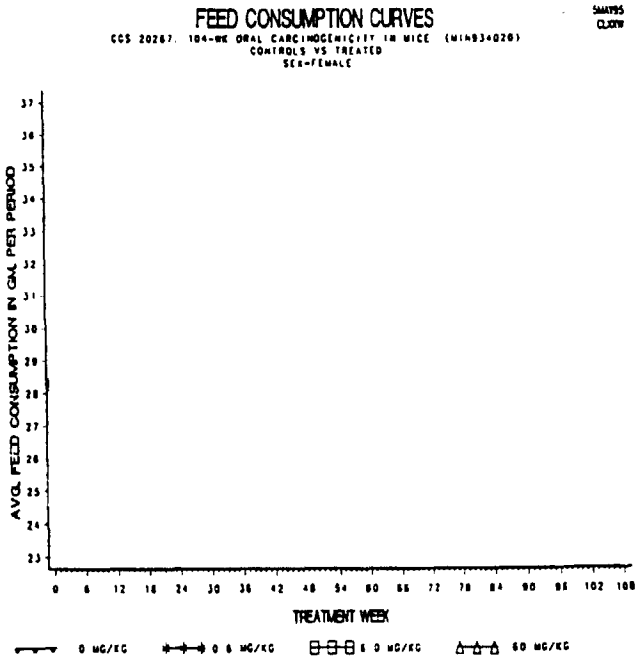
[a]Percent gain relative to control ($\frac{\text{weight gain of group-weight gain of control}}{\text{weight gain of control}}$ X 100)





Food Consumption: HD males appeared to have ↑ food consumption and ↓ body weights compared to other dosed males (see figures).





Hematology

Percent change from control in hematological parameters at study termination (>10%)			
Parameter	dose	Day 730	
		males	females
WBC	0.6	↓22	↑61
	6.0	↓12	-
	60.0	↑36	↑70
Platelets	0.6	↓33	↑75
	6.0	↓37	[a]
	60.0	↓36	↑38
reticulocytes	60.0	-	↓24

[a] N=1 for group; comparison not valid

Clinical chemistry

Since blood chemistry was determined only at study termination, it is difficult to determine a pattern of change. The toxicological effects of these changes are probably minor and can be attributed to metabolic change resulting from aromatase inhibition and P-450 induction.

Percent change in blood chemistry at study termination (>10%)						
Parameter	LD		MD		HD	
	♂	♀	♂	♀	♂	♀
AST	↓63	↓21	↓9	↑4	↓65	↓44
ALT	↓19	↓6	-	↑42	↓18	↓34
Alk Phos	↓17	↓37	↑70	↓34	↓38	↓35
Creatinine	-	-	-	-	↓74	↓58

Toxicokinetics Study reviewed in Pharmacokinetics/Toxicokinetics section

Palpable mass examination

Palpable masses included many sites of skin inflammation and abcess, especially in females. The inhibition of aromatase and low circulating estrogen levels may have contributed to thinning of the skin with predisposition to infection.

Gross and histopathology

Gross pathology data were not tabulated. The study sponsor indicated that the small ovaries, uterus, and testes, and ovaries with tissue masses observed macroscopically, correlated with the histopathology of atrophy of these organs and the benign ovarian stromal tumors (granulosa theca cell tumors) observed in LD, MD and HD females. The increased incidence of ovarian granulosa theca cell tumors showed a significant trend with dose ($p \leq 0.001$, time adjusted trend test, incidence of 34-53% at the MD and HD). A significant trend with dose was maintained when the HD was excluded ($p \leq 0.01$). The LD incidence was significant when compared pairwise with the controls ($p \leq 0.01$). When recalculated by the Division of Biometrics, the positive trend was confirmed. Historically, the spontaneous incidence of granulosa theca cell tumors in control female mice of this strain is 2.21% with a range of 0-6.67% (7/317) (Lang, P. Spontaneous neoplastic lesions in the mouse. 1995. Pub. :

These changes likely resulted from the inhibition of estrogen synthesis, the lack of negative feedback by estrogen to the pituitary and the resulting increase in FSH and LH stimulating proliferation of the ovarian stroma. The same mechanism was probably responsible for the atrophy of the genital tract at all doses. The increased incidence of mandibular salivary gland hypertrophy in dosed females was also the result of the inhibition of estrogen synthesis. In female mice administered testosterone, this epithelium enlarges to resemble that in males.

Microscopic findings related to inhibition of estrogen synthesis following administration of letrozole to mice for 94-104 weeks.								
Tissue/finding	Males				Females			
	contr	LD	MD	HD	contr	LD	MD	HD
Ovary (#examined)	-	-	-	-	69	70	70	70
/Benign ovarian stromal tumor (granulosa theca cell tumor)	-	-	-	-	1	11	37	24
/Atrophy	-	-	-	-	3	14	18	8
/Hemorrhage	-	-	-	-	6	23	14	12
/Pigmented	-	-	-	-	2	39	28	38
/Cyst	-	-	-	-	44	24	14	16
Uterus (# examined)	-	-	-	-	70	70	70	70
/Atrophy	-	-	-	-	1	38	48	40
/Cystic glandular hyperplasia	-	-	-	-	52	32	3	4
Vagina (# examined)	-	-	-	-	70	70	65	69
/Atrophy	-	-	-	-	3	25	33	29
Testes (# examined)	70	70	69	70	-	-	-	-
/Atrophy	15	26	31	21	-	-	-	-
/Mineralization	7	15	14	17	-	-	-	-
Epididymides (# examined)	70	70	69	70	-	-	-	-
/Oligospermia	10	22	27	21	-	-	-	-
Mandibular Salivary Gland (# examined)[a]					70	69	70	70
/Ductal hypertrophy					0	51	51	20

Dermal inflammation was associated with alopecia and included head and neck ulceration, abscess formation, acanthosis and pyogranulomatous inflammation involving the eyes, ears, Harderian and lacrimal glands. Systemic inflammation was observed as abscess, thrombosis, and systemic amyloidosis of the heart, lung, brain, liver and skeletal muscle. The sponsor has

indicated a propensity for letrozole to accumulate and persist in the skin, especially in the head and neck regions.

Skin lesions in mice administered letrozole for 104 weeks [a]								
Finding	Males				Females			
	cont	LD	MD	HD	cont	LD	MD	HD
Erosion and ulceration	2	9	7	33	3	3	10	29
Abscess and other inflammation	3	6	3	25	4	3	10	33

[a] N=70

The incidence of follicular adenoma of the thyroid in HD females was significant ($p \leq 0.05$; One-sided test, Peto and Lagakos; significant trend of 0.024, Mantel's trend test) when compared to control mice of the study. The sponsor indicated that the incidence was comparable to the historical incidence in control mice in the laboratory. The incidence of this finding (2/70, 2.9%) was compared to the incidence of thyroid follicular adenoma as spontaneous neoplastic lesions of female mice of this strain following 21-24 months on control diet (Lang, P. Spontaneous neoplastic lesions in the mouse. , pub.) The historical control incidence in 460 mice examined was 0.2% with a range of 0-2.0%. The historical incidence of the sponsor's laboratory should be submitted for review.

The incidence of hepatocellular adenoma and carcinoma in LD and MD males and females was not significant when considered individually; however, combined adenoma and carcinoma in MD females was significant ($p \leq 0.05$, One-sided test of Peto and Lagakos; significant trend of 0.039, Mantel's trend test) when compared to control mice of the study. The incidence of this finding (5/70, 7.1% in MD females) was compared to the incidence of hepatocellular adenoma and carcinoma as spontaneous lesions of female mice of this strain following 21-24 months on control diet (Lang, P., Spontaneous neoplastic lesions in the mouse, The historical incidence of 482 mice examined was 0.8% with a range of 0-2.8% for hepatocellular adenoma and 1% with a range of 0-2.8% for hepatocellular carcinoma. The incidence of foci of cellular alteration of the liver was not increased in these animals; focal hepatocellular hyperplasia was not listed under non-neoplastic histopathology for females of this study. Since the incidence of hepatocellular adenoma and carcinoma in HD animals was $\leq$ control animals, the biological significance of this finding is uncertain. The increased incidence of the combined lesion is unusual for this strain. It may be appropriate to exclude these data since the HD appeared to exceed the MTD. The hepatocellular hypertrophy observed in dosed mice was consistent with microsomal enzyme induction.

The increased incidence of nephropathy observed in dosed males and females could result from lowered estrogen levels and elevated androgenic precursors. The increased incidence of

hyperplasia of the parathyroid in MD and HD females was probably the result of the nephropathy observed in these animals.

Liver, kidney, thyroid and parathroid findings in mice administered letrozole for 104 weeks								
Organ/finding	Males				Females			
	cont	LD	MD	HD	cont	LD	MD	HD
Liver[a]/ hypertrophy	0	13	17	15	1	2	3	6
/ hepatocellular adenoma	3	2	6	2	1	0	5	1
/ hepatocellular carcinoma	4	6	4	2	1	1	5	0
/combined hepatocellular adenoma and carcinoma[c]	7	8	10	4	2	1	10	1
Kidney[a]/nephropathy	17	34	37	29	15	22	25	26
Thyroid[a]/ follicular adenoma	-	-	-	-	0	0	0	2
Parathroid[b]/hyperplasia	-	-	-	-	0	0	1	3

[a]N=70

[b]N=60, cont; 64, LD; 62, MD, HD

[c] Statistical method of collection of neoplastic combinations was not identified

Summary of Neoplastic Findings in Male and Female Mice (See following pages)

SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
MALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
DIGESTIVE SYSTEM					
GALL BLADDER					
ADENOMA (B)	1/50	2/59	1/59	0/51	
OBS/EXP:	0.86	1.74	0.68	0.00	0.659
LARGE INTESTINE					
ADENOCARCINOMA (M)	1/70	0/70	0/70	0/70	
OBS/EXP:	3.56	0.00	0.00	0.00	1.000
LIVER					
HEMANGIOMA (B)	0/70	0/70	0/70	1/70	
OBS/EXP:	0.00	0.00	0.00	5.87	0.170
HEMANGIOSARCOMA (M)	3/70	3/70	2/70	2/70	
OBS/EXP:	1.08	1.10	0.65	1.44	0.514
HEPATOCELLULAR ADENOMA (B)	3/70	2/70	6/70	2/70	
OBS/EXP:	0.85	0.56	1.53	1.02	0.222
HEPATOCELLULAR CARCINOMA (M)	4/70	6/70	4/70	2/70	
OBS/EXP:	0.91	1.35	0.81	0.89	0.606
SALIVARY GLAND			-		/
MYOEPITHELIOMA (B)	0/70	0/70	0/70	1/70	
OBS/EXP:	0.00	0.00	0.00	9.60	0.104
SMALL INTESTINE					
ADENOCARCINOMA (M)	0/69	1/69	0/70	0/68	
OBS/EXP:	0.00	3.41	0.00	0.00	0.753

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
MALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
DIGESTIVE SYSTEM (continued)					
STOMACH					
LEIOMYOSARCOMA (M)	0/70	1/70	0/70	0/70	
OBS/EXP:	0.00	3.49	0.00	0.00	0.735
ENDOCRINE SYSTEM					
ADRENAL GLAND					
CORTICAL ADENOMA (B)	2/70	1/70	4/70	0/70	
OBS/EXP:	1.08	0.53	2.01	0.00	0.597
HEMATOPOIETIC-LYMPHORETICULAR SYSTEM					
SYSTEMIC					
GRANULOCYTIC LEUKEMIA (M)	1/70	0/70	0/70	1/70	
OBS/EXP:	1.96	0.00	0.00	2.65	0.571
HISTIOCYTIC SARCOMA (M)	2/70	1/70	1/70	0/70	
OBS/EXP:	1.79	0.91	0.82	0.00	0.908
LYMPHOMA, MALIGNANT (M)	5/70	1/70	3/70	2/70	
OBS/EXP:	1.60	0.35	0.80	1.60	0.634
INTEGUMENTARY SYSTEM					
SKIN					
BASAL-CELL EPITHELIOMA (B)	0/70	0/70	1/70	0/70	
OBS/EXP:	0.00	0.00	2.83	0.00	0.461
HEMANGIOSARCOMA (M)	1/70	1/70	1/70	0/70	
OBS/EXP:	1.17	1.25	0.96	0.00	0.768
LEIOMYOSARCOMA (M)	0/70	0/70	1/70	0/70	
OBS/EXP:	0.00	0.00	3.19	0.00	0.424

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
MALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
INTEGUMENTARY SYSTEM (continued)					
SKIN (continued)					
NERVE SHEATH TUMOR, BENIGN (B)	0/70	0/70	1/70	0/70	
OBS/EXP:	0.00	0.00	2.67	0.00	0.479
NERVE SHEATH TUMOR, MALIGNANT (M)	1/70	0/70	1/70	0/70	
OBS/EXP:	1.78	0.00	1.45	0.00	0.771
SEBACEOUS GLAND ADENOMA (B)	0/70	1/70	0/70	0/70	
OBS/EXP:	0.00	3.49	0.00	0.00	0.737
MUSCULOSKELETAL SYSTEM					
BONE					
OSTEOMA (B)	1/70	0/70	0/70	0/70	
OBS/EXP:	3.56	0.00	0.00	0.00	1.000
NERVOUS SYSTEM					
BRAIN					
ASTROCYTOMA (M)	0/70	1/70	0/70	0/70	
OBS/EXP:	0.00	3.75	0.00	0.00	0.753
REPRODUCTIVE SYSTEM					
BULBOURETHRAL GLAND					
RHABDOMYOSARCOMA (M)	0	1	0	0	
EPIDIDYMIS					
LEIOMYOSARCOMA (M)	0/70	0/70	0/69	1/70	
OBS/EXP:	0.00	0.00	0.00	9.50	0.105
SEMINAL VESICLE					
ADENOMA (B)	0/70	0/69	1/70	0/69	
OBS/EXP:	0.00	0.00	2.64	0.00	0.484

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
MALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
REPRODUCTIVE SYSTEM (continued)					
SEMINAL VESICLE (continued)					
LEIOMYOSARCOMA (M)	0/70	1/69	0/70	0/69	
OBS/EXP:	0.00	3.40	0.00	0.00	0.723
TESTIS					
HEMANGIOSARCOMA (M)	1/70	0/70	0/69	0/70	
OBS/EXP:	3.52	0.00	0.00	0.00	1.000
INTERSTITIAL-CELL TUMOR (B)	0/70	0/70	2/69	0/70	
OBS/EXP:	0.00	0.00	3.27	0.00	0.161
RESPIRATORY SYSTEM					
LUNG					
ADENOCARCINOMA (M)	12/70	6/70	6/70	4/70	
OBS/EXP:	1.57	0.77	0.69	1.04	0.909
ADENOMA (B)	8/70	10/70	11/70	3/70	
OBS/EXP:	0.92	1.13	1.14	0.63	0.615
SPECIAL SENSE ORGANS					
HARDERIAN GLAND					
ADENOMA (B)	3/70	2/70	6/70	0/70	
OBS/EXP:	0.96	0.66	1.62	0.00	0.472
URINARY SYSTEM					
KIDNEY					
ADENOCARCINOMA (M)	1/70	3/70	1/70	0/70	
OBS/EXP:	0.71	2.45	0.51	0.00	0.808

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
MALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
URINARY SYSTEM (continued)					
KIDNEY (continued)					
ADENOMA [B]	0/70	0/70	1/70	0/70	
OBS/EXP:	0.00	0.00	2.67	0.00	0.479
LIPOMA [B]	0/70	1/70	0/70	0/70	
OBS/EXP:	0.00	3.88	0.00	0.00	0.723
URINARY BLADDER					
LEIOMYOSARCOMA [M]	0/70	2/69	1/70	1/68	
OBS/EXP:	0.00	1.83	0.76	2.19	0.163
TRANSITIONAL CELL CARCINOMA [M]	0/70	2/69	0/70	0/68	
OBS/EXP:	0.00	3.74	0.00	0.00	0.750
COMBINATIONS					
KIDNEY					
ADENOMA OR ADENOCARCINOMA	1/70	3/70	2/70	0/70	
OBS/EXP:	0.59	2.05	0.86	0.00	0.617
LIVER					
HEPATOCELLULAR ADENOMA OR CARCINOMA	7/70	8/70	10/70	4/70	
OBS/EXP:	0.88	1.00	1.13	0.95	0.372
LUNG					
ADENOMA OR ADENOCARCINOMA	20/70	16/70	17/70	7/70	
OBS/EXP:	1.23	0.96	0.93	0.81	0.892
TOTAL BODY					
HEMANGIOMA	0/70	0/70	0/70	1/70	
OBS/EXP:	0.00	0.00	0.00	5.87	0.170

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
MALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
COMBINATIONS (continued)					
TOTAL BODY (continued)					
HEMANGIOMA OR HEMANGIOSARCOMA	5/70	4/70	3/70	3/70	
OBS/EXP:	1.19	0.99	0.64	1.48	0.558
HEMANGIOSARCOMA	5/70	4/70	3/70	2/70	
OBS/EXP:	1.25	1.05	0.66	1.19	0.697
NERVE SHEATH TUMOR, BENIGN OR MALIGNANT	1/70	0/70	2/70	0/70	
OBS/EXP:	1.16	0.00	1.79	0.00	0.546

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING		DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
CARDIO-VASCULAR SYSTEM						
HEART						
HEMANGIOSARCOMA [M]		0/70	0/70	1/70	0/70	
	OBS/EXP:	0.00	0.00	2.83	0.00	0.463
DIGESTIVE SYSTEM						
GALL BLADDER						
ADENOMA [B]		0/53	1/54	0/55	0/48	
	OBS/EXP:	0.00	3.55	0.00	0.00	0.769
LARGE INTESTINE						
ADENOCARCINOMA [M]		0/68	1/70	0/69	0/70	
	OBS/EXP:	0.00	3.28	0.00	0.00	0.734
POLYP [B]		0/68	0/70	1/69	0/70	
	OBS/EXP:	0.00	0.00	2.83	0.00	0.463
LIVER						
HEMANGIOSARCOMA [M]		3/70	1/70	2/70	3/70	
	OBS/EXP:	1.26	0.37	0.69	2.99	0.198
HEPATOCELLULAR ADENOMA [B]		1/70	0/70	5/70	1/70	
	OBS/EXP:	0.54	0.00	2.36	1.01	0.074
HEPATOCELLULAR CARCINOMA [M]		1/70	1/70	5/70	0/70	
	OBS/EXP:	0.53	0.46	2.08	0.00	0.155
STOMACH						
LEIOMYOSARCOMA [M]		0/70	0/68	1/70	0/69	
	OBS/EXP:	0.00	0.00	3.90	0.00	0.483

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
DIGESTIVE SYSTEM (continued)					
STOMACH (continued)					
SQUAMOUS CELL CARCINOMA [M]	0/70	0/68	1/70	0/69	
OBS/EXP:	0.00	0.00	2.79	0.00	0.469
ENDOCRINE SYSTEM					
ADRENAL GLAND					
CORTICAL ADENOMA [B]	1/70	0/69	1/70	0/70	
OBS/EXP:	1.87	0.00	1.61	0.00	0.672
GANGLIONEUROMA [B]	0/70	0/69	1/70	0/70	
OBS/EXP:	0.00	0.00	3.28	0.00	0.432
HEMANGIOSARCOMA [M]	0/70	1/69	0/70	0/70	
OBS/EXP:	0.00	3.36	0.00	0.00	0.748
PHEOCHROMOCYTOMA [B]	0/70	0/69	0/70	1/70	
OBS/EXP:	0.00	0.00	0.00	9.00	0.111
SPINDLE CELL TUMOR, BENIGN [B]	0/70	0/69	1/70	0/70	
OBS/EXP:	0.00	0.00	2.79	0.00	0.469
PITUITARY					
ADENOMA [B], pars distalis	1/69	0/69	0/69	0/68	
OBS/EXP:	4.05	0.00	0.00	0.00	1.000
ADENOMA [B], pars intermedia	1/69	0/69	0/69	0/68	
OBS/EXP:	4.05	0.00	0.00	0.00	1.000
MYXOSARCOMA [M]	0/69	1/69	0/69	0/68	
OBS/EXP:	0.00	3.52	0.00	0.00	0.753

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING		DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
ENDOCRINE SYSTEM (continued)						
THYROID						
FOLLICULAR ADENOCARCINOMA (M)		0/70	1/70	0/70	0/70	
	OBS/EXP:	0.00	3.42	0.00	0.00	0.756
FOLLICULAR ADENOMA (B)		0/70	0/70	0/70	2/70	
	OBS/EXP:	0.00	0.00	0.00	4.13*	0.024*
HEMATOPOIETIC-LYMPHORETICULAR SYSTEM						
LYMPH NODE						
HEMANGIOMA (B)		1/70	0/69	0/69	0/70	
	OBS/EXP:	3.68	0.00	0.00	0.00	1.000
SPLEEN						
HEMANGIOMA (B)		0/70	0/69	0/70	1/70	
	OBS/EXP:	0.00	0.00	0.00	7.81	0.128
HEMANGIOSARCOMA (M)		0/70	0/69	1/70	0/70	
	OBS/EXP:	0.00	0.00	2.83	0.00	0.463
SYSTEMIC						
HISTIOCYTIC SARCOMA (M)		2/70	0/70	0/70	0/70	
	OBS/EXP:	3.87	0.00	0.00	0.00	1.000
LYMPHOMA, MALIGNANT (M)		13/70	9/70	8/70	3/70	
	OBS/EXP:	1.51	0.92	0.80	0.65	0.960
INTEGUMENTARY SYSTEM						
SKIN						
NERVE SHEATH TUMOR, BENIGN (B)		0/70	0/70	1/70	0/70	
	OBS/EXP:	0.00	0.00	3.35	0.00	0.429

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
MUSCULOSKELETAL SYSTEM					
BONE					
OSTEOMA [B]	2/70	1/70	2/70	0/70	
OBS/EXP:	1.64	0.68	1.13	0.00	0.844
OSTEOSARCOMA [M]	0/70	1/70	0/70	0/70	
OBS/EXP:	0.00	3.89	0.00	0.00	0.743
NERVOUS SYSTEM					
BRAIN					
EPENDYMOMA [M]	1/70	0/70	0/70	0/70	
OBS/EXP:	3.74	0.00	0.00	0.00	1.000
REPRODUCTIVE SYSTEM					
CERVIX					
LEIOMYOMA [B]	1	1	0	0	
SQUAMOUS CELL CARCINOMA [M]	1	0	0	0	
OVARY					
ADENOMA [B]	1/69	1/70	2/70	2/70	
OBS/EXP:	0.66	0.64	1.27	1.50	0.190
GRANULOSA-THECA CELL TUMOR [B]	1/69	11/70	37/70	24/70	
OBS/EXP:	0.05	0.52**	1.82**	2.05**	0.000**
GRANULOSA-THECA CELL TUMOR [M]	0/69	1/70	0/70	0/70	
OBS/EXP:	0.00	2.86	0.00	.	.
HEMANGIOMA [B]	2/69	0/70	0/70	0/70	
OBS/EXP:	3.86	0.00	0.00	0.00	1.000

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
REPRODUCTIVE SYSTEM (continued)					
OVARY (continued)					
HEMANGIOSARCOMA [M]	0/69	0/70	1/70	0/70	
OBS/EXP:	0.00	0.00	2.83	0.00	0.463
OVIDUCT					
ADENOCARCINOMA [M]	0	0	1	0	
ADENOMA [B]	0	0	1	1	
UTERUS					
ENDOMETRIAL STROMAL SARCOMA [M]	1/70	0/70	0/70	0/70	
OBS/EXP:	4.10	0.00	0.00	0.00	1.000
HEMANGIOMA [B]	1/70	0/70	0/70	0/70	
OBS/EXP:	3.95	0.00	0.00	0.00	1.000
LEIOMYOMA [B]	1/70	1/70	0/70	0/70	
OBS/EXP:	2.03	2.05	0.00	0.00	0.906
LEIOMYOSARCOMA [M]	2/70	0/70	0/70	0/70	
OBS/EXP:	3.90	0.00	0.00	0.00	1.000
NERVE SHEATH TUMOR, MALIGNANT [M]	1/70	0/70	0/70	0/70	
OBS/EXP:	3.67	0.00	0.00	0.00	1.000
POLYP [B]	6/70	1/70	0/70	0/70	
OBS/EXP:	3.25	0.50	0.00	0.00	0.999
VAGINA					
FIBROSARCOMA [M]	1/70	0/70	0/65	0/69	
OBS/EXP:	1.62	0.00	0.00	0.00	1.000

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
REPRODUCTIVE SYSTEM (continued)					
VAGINA (continued)					
POLYP [B]	2/70	0/70	0/65	0/69	
OBS/EXP:	4.00	0.00	0.00	0.00	0.973
RESPIRATORY SYSTEM					
LUNG					
ADENOCARCINOMA [M]	4/70	4/70	5/70	3/70	
OBS/EXP:	0.93	0.82	0.96	1.83	0.224
ADENOMA [B]	11/70	8/70	5/70	4/70	
OBS/EXP:	1.50	1.03	0.63	0.80	0.953
SPECIAL SENSE ORGANS					
HARDERIAN GLAND					
ADENOCARCINOMA [M]	1/70	0/70	0/70	0/69	
OBS/EXP:	3.66	0.00	0.00	0.00	1.000
ADENOMA [B]	3/70	2/70	2/70	0/69	
OBS/EXP:	1.63	1.01	0.99	0.00	0.905
URINARY SYSTEM					
URINARY BLADDER					
LEIOMYOSARCOMA [M]	0/68	1/70	1/70	0/70	
OBS/EXP:	0.00	1.66	1.49	0.00	0.547
COMBINATIONS					
BONE					
OSTEOMA OR OSTEOSARCOMA	2/70	2/70	2/70	0/70	
OBS/EXP:	1.35	1.16	0.99	0.00	0.812

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
COMBINATIONS (continued)					
CERVIX OR UTERUS					
LEIOMYOMA	2/70	2/70	0/70	0/70	
OBS/EXP:	1.91	1.78	0.00	0.00	0.956
LEIOMYOMA OR LEIOMYOSARCOMA	4/70	2/70	0/70	0/70	
OBS/EXP:	2.54	1.13	0.00	0.00	0.993
HARDERIAN GLAND					
ADENOMA OR ADENOCARCINOMA	4/70	2/70	2/70	0/69	
OBS/EXP:	1.90	0.89	0.87	0.00	0.957
LARGE INTESTINE					
POLYP OR ADEONCARCINOMA	0/68	1/70	1/69	0/70	
OBS/EXP:	0.00	1.67	1.53	0.00	0.526
LIVER					
HEPATOCELLULAR ADENOMA OR CARCINOMA	2/70	1/70	10/70	1/70	
OBS/EXP:	0.53	0.24	2.25*	0.63*	0.039*
LUNG					
ADENOMA OR ADENOCARCINOMA	15/70	12/70	10/70	7/70	
OBS/EXP:	1.28	0.95	0.77	1.05	0.826
OVARY					
GRANULOSA-THECA CELL TUMOR, BENIGN OR MALIGNANT	1/69	12/70	37/70	24/70	
OBS/EXP:	0.05	0.56**	1.77**	2.04**	0.000**
OVIDUCT					
ADENOMA OR ADENOCARCINOMA	0	0	2	1	

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SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
FEMALES

BODY SYSTEM / ORGAN / FINDING	DOSE GROUPS 0 mg/kg	0.6 mg/kg	6.0 mg/kg	60 mg/kg	TEST FOR TREND P-VALUE
COMBINATIONS (continued)					
THYROID					
FOLLICULAR ADENOMA OR ADENOCARCINOMA	0/70	1/70	0/70	2/70	
OBS/EXP:	0.00	1.21	0.00	3.56	0.058
TOTAL BODY					
HEMANGIOMA	4/70	0/70	0/70	1/70	
OBS/EXP:	3.21	0.00	0.00	0.90	0.970
HEMANGIOMA OR HEMANGIOSARCOMA	7/70	2/70	5/70	4/70	
OBS/EXP:	1.49	0.38	0.92	1.54	0.495
HEMANGIOSARCOMA	3/70	2/70	5/70	3/70	
OBS/EXP:	0.87	0.51	1.16	2.30	0.089
NERVE SHEATH TUMOR, BENIGN OR MALIGNANT.....	1/70	0/70	1/70	0/70	
OBS/EXP:	1.83	0.00	1.68	0.00	0.764
UTERUS					
LEIOMYOMA OR LEIOMYOSARCOMA	3/70	1/70	0/70	0/70	
OBS/EXP:	2.89	0.89	0.00	0.00	0.989
UTERUS OR VAGINA					
POLYP	8/70	1/70	0/70	0/70	
OBS/EXP:	3.42	0.41	0.00	0.00	1.000
POLYP OR ENDOMETRIAL STROMAL SARCOMA	9/70	1/70	0/70	0/70	
OBS/EXP:	3.44	0.36	0.00	0.00	1.000

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Summary of Carcinogenicity

The carcinogenic potential of letrozole was assessed in mice and rats. Administration of letrozole to mice at doses of 1.8, 18 and 180mg/m^2/day (about 1, 10 and 100 times the recommended human dose on a mg/m^2 basis) resulted in a dose-related increased incidence of granulosa theca cell tumors and atrophy of the reproductive tract in males and females. These changes can be attributed to the pharmacological inhibition of estrogen synthesis, either directly or through feedback mechanisms increasing the secretion of gonadotropins. At 1.8, 18 and 180mg/m^2, the letrozole C_{max} was 0.78, 8.5 and 70.7μmol/L, respectively, at 6 weeks; the dose normalized AUC was 8.9, 10.7 and 10.2μmol·h/L, respectively. The carcinogenicity study in rats at doses of 0.6, 6 and 60mg/m^2/day (about 4/10, 4 and 40 times the recommended human dose on a mg/m^2 basis) produced a lower incidence of benign ovarian stromal tumors compared to the incidence of ovarian tumors in mice, but the result was still highly significant. This may be a result of the species difference in proliferative response of the ovarian stroma. The incidence of ovarian stromal hyperplasia was increased in the rat study. At 0.6, 6 and 60mg/m^2, the letrozole C_{max} was 0.2-1.4, 3.3-7.7 and 12.7-44μmol/L, respectively, at 78 weeks; the dose normalized AUC was 103(♂)-245(♀), 140(♂)-170(♀) and 73(♂)-89(♀)μmol·h/L, respectively.

Hepatocellular hypertrophy was observed in subchronic rodent studies as well as carcinogenicity studies in rats and mice possibly as a result of microsomal enzyme induction. The incidence of combined hepatocellular adenoma and carcinoma was significantly increased in LD and MD female mice when compared to concurrent controls. The incidence of the combined tumors in male rats showed a dose dependent trend, but the finding was not significant when analyzed by the Division of Biometrics, FDA. The incidence of chronic progressive nephropathy and parathyroid hyperplasia was increased in female mice and rats treated for 104 weeks.

An increased incidence of head and neck skin lesions were observed in rats dosed for 6 months at 30mg/kg as well as mice treated for 104 weeks. A 30-day radiolabeled distribution study in rats indicated that letrozole accumulated primarily in skin samples from the neck region with decreasing incidence following termination of the 30-day treatment. The dermal and systemic inflammation were a cause of the increased mortality in HD mice.

Summary of Toxicology

Male and female mice readily tolerated doses of 600mg/m^2 letrozole. At single doses of 6000mg/m^2 letrozole in mice and 12,000mg/m^2 in rats, effects of depressed motor activity, irregular respiration, muscular hypotonia, inhibition of pain response, hyperemia of mucosa and skin, ruffled coat and salivation were exhibited; recovery occurred within 3-5 days. Mortality occurred at 6000mg/m^2 in female mice. Administration of a single dose of 4000mg/m^2 letrozole to a beagle dog resulted in death due to to respiratory failure within 48 hrs of dosing; tonic-clonic convulsions were observed at 2000 and 4000mg/m^2.

Subchronic and chronic toxicity studies were conducted in mice, rats and dogs. Short term intravenous administration of letrozole appeared to be more toxic to female rats whcn compared to oral administration. Major findings in multiple dose studies were attributable to the

inhibition of estrogen synthesis by letrozole, causing estrogen depletion, and the lack of negative feedback by estrogen to the pituitary. In general, end-organ toxicities were directed primarily to the reproductive organs and the liver. Atrophy of uterine and vaginal epithelium was observed in female rodents and dogs and leydig cell hyperplasia was observed in male rodents and dogs, while testicular atrophy was exhibited in mice and dogs. Hyperplasia of the mammary gland was observed in rats and dogs. Hepatocellular changes were likely a result of enzyme induction. Changes in the kidney and adrenal in rats and dogs may indicate interference with steroid synthesis or lowered estrogen levels. Hypercellularity of the bone marrow and stimulation of hematopoiesis in the spleen is probably attributed to the inhibition of estrogen synthesis.

Bone fractures were observed in female rats administered 180mg/m^2 letrozole 8 to 9 months following dosing; this finding was not exhibited after two years of treatment at doses up to 60mg/m^2. Bone fragility has been observed in rodents administered antiestrogenic agents but not with other aromatase inhibitors (ie. Arimidex). Adrenal atrophy has not been observed with treatment of toremifene, an antiestrogenic agent or arimidex, an aromatase inhibitor.

Hyaline droplets were observed in the kidneys of male and female dogs administered $\geq$0.6mg/m^2 letrozole for 12 months and 1 month following termination of dosing. Crystals were observed in the kidneys of female rats following 2 years of dosing. Hyaline droplets and crystals are ususally observed in the male gender. Erosion, abcess and ulceration of the skin of the head and neck was exhibited in mice dosed orally for 2 years at 18mg/m^2 and rats dosed orally for 6 months at 180mg/m^2; in rodents, this site was indicated to be predisposed to external contamination by letrozole.

Hepatocellular hypertrophy was observed in subchronic rodent studies as well as carcinogenicity studies in rats and mice and was likely a result of microsomal enzyme induction. The incidence of combined hepatocellular adenoma and carcinoma was significantly increased in LD and MD mice when compared to concurrent controls. The incidence of the combined tumors in male rats showed a dose dependent trend, but the finding was not significant when analyzed by the Division of Biometrics. The incidence of chronic progressive nephropathy and parathyroid hyperplasia was increased in female mice and rats treated for 104 weeks.

Histopathology Inventory NDA 20-726

Study	91-6010	91-6015	95059	96001
Species	RAT	DOG	RAT	MOUSE
Adrenals	X	X	X	X
Aorta	X	X	X	X
Bladder	X	X	X	X
Bone Marrow smear	X	X	X	X
Bone (femur)	X	X	X	X
Brain	X	X	X	X
Cecum	X	X	X	X
Cervix				
Colon	X	X	X	X
Duodenum	X	X	X	X
Epididymis	X	X	X	X
Esophagus	X	X	X	X
Eye	X	X	X	X
Fallopian tube				
Gall bladder		X		X
Harderian gland	X		X	X
Heart	X	X	X	X

Hypophysis				
Ileum	X	X	X	X
Injection site				
Jejunum	X	X	X	X
Kidneys	X	X	X	X
Lachrymal gland		X	X	X
Larynx				
Liver	X	X	X	X
Lymph nodes,axillary	X	X	X	
Lymph nodes mandibular/submaxillary	X	X		X
Lymph nodes, mesenteric	X	X	X	X
Lungs	X	X	X	X
Mammary Gland	X	X	X	X
Nasal cavity				
Optic nerves	X	X	X	X
Ovaries	X	X	X	X
Pancreas	X	X	X	X
Parathyroid	X	X	X	X
Peripheral nerve		X		X
Pharynx				
Pituitary	X	X	X	X
Prostate	X	X	X	X
Rectum	X	X	X	X
Salivary gland		X		X
Sciatic nerve	X	X	X	X
Seminal vesicles	X		X	X
Skeletal muscle	X	X	X	X
Skin	X	X	X	X
Spinal cord	X	X	X	X
Spleen	X	X	X	X
Sternum	X	X	X	X
Stomach	X	X	X	X
Testes	X	X	X	X
Thymus	X	X	X	X
Thyroid	X	X	X	X
Tongue	X	X	X	X
Trachea	X	X	X	X
Uterus	X	X	X	X
Vagina	X	X	X	X
Zymbal gland				
Knee Joint	X		X	
Lymph node, cervical, popliteal, inguinal		X		
Nictitating membrane		X		

VI. REPRODUCTIVE TOXICITY

T/P (US) 95046 CGS 20267: An oral dose-rangefinding study for effects on embryo and fetal development in rabbits (MIN 954024) Conducted by Ciba-Geigy Corporation, Summit, NJ in 1995; GLP status not indicated

Methods

species: New Zealand White female rabbits (NZW)] (8 animals/group)
drug: Letrozole [lot # 800192] in aqueous 3% corn starch
dosage: 0.006, 0.06, 0.6, 2, and 6mg/kg on gestation days 7-19
age, wt: 26 wks, 2.87-4.05kg
route: gavage 1X daily

Results

All ♀ survived to scheduled sacrifice on gestation day 29. Clinical observations included bleeding in 7/8 ♀ administered 0.06, 0.6, and 2mg/kg and 3/8 ♀ administered 6mg/kg; bleeding was associated with resorption and regression of the corpora lutea. Fecal changes (↓and soft) were observed in 3/8 HD ♀. Body weights of HD ♀(6mg/kg) were depressed 18-21% from study days 10-29; food consumption of these animals was reduced 28-50% from study days 7 to 21 and 15% from study day 22 to study termination(study day 29). Body weight gains were slightly and sporadically depressed in ♀ administered ≥0.6mg/kg. Food consumption of other dosed animals were similar to concurrent controls. Ovarian cysts were observed in 1/8 control and dosed ♀ administered >0.06mg/kg.

The number of early resorptions was significantly increased (8.5-12-fold) in ♀ administered ≥0.06mg/kg letrozole when compared to concurrent controls; the number of live fetuses were reduced by 85, 98, and 100% in ♀ administered 0.06, 0.6, and ≥2mg/kg. Due to 100% resorption in all ♀ administered ≥2mg/kg, there was no fetal examination at the higher doses. There were no macroscopic teratogenic abnormalities of live fetuses at 0.6mg/kg; individual data of fetal examination was not submitted.

Reproductive parameters (/doe/dose group) of rabbits administered letrozole on gestation days 7-19

Parameters	Dose level (mg/kg/day)					
	0	0.006	0.06	0.6	2	6
Implantations	8.88	7.43	7.71	8.38	10.75	9.13
Early resorptions	0.75	0.43	6.43	7.75	10.75	9.13
Late resorptions	0	0.29	0	0.38	0	0
Live fetuses	8.13	6.71	1.29	0.13	0	0
Dead fetuses	0	0	0	0.13	0	0
Postimplantation loss	0.75	0.71	6.43	8.25	10.75	9.13

T/P (US) 95042 CGS 20267: An oral dose-rangefinding study for the effects on embryo and fetal development in rats (MIN 954026) Conducted by Ciba-Geigy Corporation, Summit, NJ in 1995; GLP status not indicated.

Methods

species: ♀Sprague-Dawley rats (8 animals/group)
drug: Letrozole [lot # 800192] in aqueous 3% corn starch
dosage: 0.005, 0.03, 0.3, and 1mg/kg on gestation days 6-17
age, wt: 12 wks, 235-298g on gestation day 0
route: gavage 1X daily

Results

2/8 HD ♀ were found dead on gestation days 19 and 20; prior to death one animal exhibited vaginal bleeding. Vaginal bleeding was also observed in 2/8, 1/8, and 2/8 ♀ administered 0.005, 0.03 and 0.3mg/kg. Alopecia was observed in 1-2 animals/group administered 0.005, 0.03 and 1mg/kg. Body weights of HD dams were depressed up to 6% during dosing when compared to concurrent controls; food consumption was depressed 6-24% at 0.005mg/kg from gestational days 1-20, 10-15% at 0.03mg/kg from gestational days 15-20, 1-20% at 0.3mg/kg from gestational days 12-20 and 1-14% at 1mg/kg from gestational days 6-20. Effects of letrozole on dams included enlarged placenta, fluid-filled uteri, eroded uterus lining, and rigid or ruptured uteri.

Incidence of maternal necropsy observations					
	Dose level (mg/kg/day)				
Observation	0	0.005	0.03	0.3	1.0
Placenta -enlarged	0	1/8	1/8	0	0
- surrounded w/blood	0	0	2/8	0	0
Uterus - fluid-filled	0	0	1/8	3/8	2/8
-lesion/eroded lining	0	0	1/8	0	0
-rigid	0	0	0	5/8	2/8
-ruptured	0	0	0	1/8	1/8

The incidence of early and late resorptions was increased at doses ≥0.03mg/kg; the incidence of total resorptions was increased 3.5-, 4-, and 2-fold at 0.03, 0.3 and 1mg/kg when compared to concurrent controls. Concurrently, the number of live fetuses was depressed 17, 16 and 40% at 0.03, 0.3 and 1mg/kg; postimplantation loss was increased at these same doses. Fetal weights were slightly increased (up to 5%↑) at ≥0.03mg/kg.

Reproductive parameters (dams/dose group) of rats administered letrozole on gestation days 6-17					
Parameters	Dose level (mg/kg/day)				
	0	0.005	0.03	0.3	1
Implantations	15.3	15.8	16.0	17.1	11.3
Early resorptions	1.25	1.4	2.5	4.25	1.5
Late resorptions	0	0	1.83	1.13	1.0
Live fetuses	14	14.4	11.67	11.75	8.5
Dead fetuses	0	0	0	0	0.25
Postimplantation loss	1.25	1.4	4.3	5.4	2.8

Single findings of fetal anomalies were observed at doses ≥0.3mg/kg; each finding occurred in a separate fetus from 3 dams (dam #[redacted] administered 0.3mg/kg with 14 fetuses, 2 anomalies; dam [redacted] administered 1mg/kg with 5 fetuses, 1 anomaly; dam #[redacted] administered 1mg/kg with 9 fetuses, 2 anomalies).

Incidence of fetal gross observations at 0.3 and 1.0mg/kg		
Observation	0.3mg/kg	1.0mg/kg
Fluid filled mass on head	0	1
Fluid filled shoulder/foreleg	0	1
Hyperextension of hindleg	1	0
Swollen anogenital area	1	0
Umbilical hernia	0	1
Litters with anomalies	1/8	2/8

T/P (US) 96010 CGS 20267: An oral study for effects on embryo and fetal development in rats. Conducted by Ciba-Geigy Corporation, Preclinical Safety, Research Dept., Summit, NJ in 1996 according to GLP.

Methods

species: Sprague-Dawley
drug: CGS 20267, Lot # 800192
dosage: 0, 0.003, 0.01, 0.03mg/kg, dosing volume 5ml/kg, dosing concentrations 0.0006,

0.002, 0.006mg/ml in 3% corn starch, 26 mated ♀/group
age, wt: 12-14 weeks; 238-310g on gestation day 0
route: gavage 1X/day from gestation days 6-17 (12 days)
background: only 1 of 2 rangefinding studies referenced in the text of this study was received by the agency; study # 94023, An oral pilot Segment II study in rats, has not been submitted

Observations

Mortality	once daily
Clinical signs	once daily
Body weight and food consumption	gestation days 0, 6, 9, 12, 15, 18, 20
Sacrifice	gestation day 20

Results

Mortality and clinical observations

1/26 HD dam was found dead on gestation day 20. There were no clinical observations observed prior to death of this animal although necropsy revealed a ruptured uterine horn. Vaginal bleeding was observed in 12, 11 and 19 LD, MD and HD animals, respectively; this was a result of increased resorptions observed at all doses. Alopecia was observed in 1-2 control and test animals and is unlikely to be a result of letrozole administration.

Body weight and food consumption

Corrected body weight (terminal body weights of dams minus weights of uterus, ovaries, oviducts, placentas and fetuses) and body weight gain were similar in dosed and control animals. Food consumption was depressed in all dosed dams from gestational days 12-20; reduction in dosed animals was 5-9% between days 12-15, 15-19% between days 15-18 and 18-27% between days 18-20.

Maternal necropsy There were no findings in control or LD dams.

Incidence of gross pathological findings in dams administered letrozole (N=26)		
Organ/finding	Dose Level (mg/kg)	
	0.01	0.03
Uterus/eroded	0	5
/fluid filled		11
/rigid		9
/ruptured		2
Placenta/fused	1	
Liver/pale	1	

Reproductive parameters

Reproductive parameters of rats (dams/dose group) administered letrozole from gestational days 6-17					
Parameters	Dose level (mg/kg)				Historical Data[c] (range)
	0	0.003	0.01	0.03	
Implantation	16.27	16.13	16.12	16.78	15.45
Early resorptions	0.73	4.08	3.52	2.96	1 (0.1-2.2)
Late resorptions	0	2.29	3.08	4.04	0 (0-0.6)
Live fetuses	15.54	9.75	9.44	9.57	14.8 (11.4-17.2)
Dead fetuses	0	0	0.08	0.22	0
Postimplantation loss	0.73	6.38	6.68	7.22	
% postimplantation loss	4.58	38.58	42.38	43.56	6.08 (1-20)
♂ fetal weights[a] (mg/kg)	3.70	4.09	4.10	3.90	3.58 (3.10-3.94)
♀ fetal weights[b] (mg/kg)	3.50	3.83	3.79	3.71	3.38 (2.94-3.68)

[a] ♂ only pups from 1 dam (LD)
[b] ♀ only pups from 3 dams (MD, HD)
[c] Reference: Historical control data, 1990-1992, N= 2565 dams

Fetal observations

Fetal gross, visceral and skeletal malformations and variations (by fetus and litter)					
	Dose level (mg/kg)				Historical Fetal Incidence (%)[d]
	0	0.003	0.01	0.03	
No. of fetuses examined grossly	404	234	236	220	88270
Gross malformations					
Domed head				5[a] (2)[b]/0.023[c]	0.001
Exencephaly				1 (1)/0.0045	0.03
Gastroschisis	1 (1)/0.002				0.01
Hyperflexure of hindlimbs				1 (1)/0.0045	
Umbilical hernia		1 (1)/0.0043			0.01
Gross variations					
Edemic/swollen				5 (4)/0.023	0.01
Hematoma	1 (1)0.002			2 (2)/0.009	0.02
Irregular tongue				1 (1)/0.0045	
Pale				1 (1)/0.0045	0.002
Visceral malformations					
# of fetuses examined viscerally	197	110	112	107	
Dilated ventricles	1 (1)			1 (1)	
Irregular shaped eye				1 (1)	
Visceral variations					
Renal papilla absent	3 (2)/0.015	6 (6)/0.054	4 (4)/0.035	7 (6)/0.065	
Renal papilla short	34 (11)/ 0.172	42 (19) /0.382	40 (16)/ 0.357	40 (17)/0.374	
Ureter dilated	23 (12)/ 0.117	39 (14)/ 0.354	50 (18)/ 0.446	45 (18)/0.420	
Bladder enlarged				1 (1)	

Skeletal malformations					
# fetuses examined skeletally	207	124	124	113	
Fused centrum/vertebrae				2 (2)/0.0177	0.018
Skeletal variations					
Bipartite (split) sternebrae		3 (3)/0.024	5 (5)/0.040	5 (4)/0.0442	0.126
Incomplete ossification of frontal skull	2 (2)/ 0.0096	3(2)/0.0242	4(2)/0.032	4 (2)/0.0354	
Cervical rib				1 (1)/0.0088	0.394
Incomplete ossification of metatarsals of hindleg	1 (1)/0.005	1 (1)/0.008	4 (2)/ 0.0323	3 (3)/0.0265	

[a] #fetuses/dose group with malformation or variation

[b] (# of litters with malformations or variations)

[c] incidence

[d] Reference: Historical Control Data for Development and Reproductive Toxicity Studies using the rat. 1993. Compiled by Middle Atlantic Reproduction and Teratology Association.

Letrozole is embryotoxic and fetotoxic when administered to rats at 0.003, 0.01 and 0.03mg/kg. Reproductive parameters were compared to concurrent control and historical control data. Embryotoxic and fetotoxic effects include increased early, late and total resorptions, increased postimplanatation loss, and decreased number of live fetuses at all doses. The number of dead fetuses was increased at 0.01 and 0.03mg/kg. The study author found all parameters to be significant using the Chi-bar square test or Mantel's trend test. LD and MD ♂ and ♀ fetal weights were found to be significantly increased compared to concurrent controls using the Student's T-Test ($p<0.001$)(Note: *ANOVA is the appropriate analysis*) . HD ♀ fetal weights were significantly increased ($p<0.005$) and HD ♂ fetal weights were not significantly increased compared to controls using the same statistical test.

Letrozole also exhibited potential teratogenicity; HD letrozole fetuses exhibited domed head, exencephaly, hyperflexture of hindlimbs, fused vertebra, cervical rib, edema, hematoma, and increased incidence of shortened or absent renal papilla, split sternebrae and incomplete ossification of frontal skull. Absence and shortening of renal papilla, dilation of ureter, split sternebrae and incomplete ossification of frontal skull and metatarsals were observed in all treated animals. The study author indicated that skull deformities were observed at 5mg/kg in the rat rangefinding study which was not submitted to the agency. In addition, the study authors indicated that the observed visceral variations were representative of developmental delays reversible following birth. The study author found the number of litters with gross variations to be significant at the HD ($p<0.005$) using Mantel's trend test. All doses were found to be

significant for number of litters with visceral variations, shortened renal papilla and dilated ureter using the Chi-bar square test. In addition, MD and HD were found to be significant for skeletal split sternebrae using Mantel's trend test.

Evidence of maternal toxicity included 1 HD mortality, vaginal bleeding at all doses, and fluid-filled, rigid, eroded and ruptured uteri at the HD.

T/P (US) 96025 CGS 20267: An oral study for the effects on embryo and fetal development in rabbits. Conducted by Research Department, Pharmaceuticals Division, Ciba-Geigy Corporation, Summit, NJ in 1996 according to GLP.

Methods

species: New Zealand White ♀ rabbits [NZW]
drug: CGS 20267, Lot # 800192
dosage: 0, 2, 6 and 20µg/kg, dosing volume 4ml/kg, dosing concentrations 0.5, 1.5 and 5µg/ml in 3% corn starch, 20 rabbits/group
age, wt: 25 weeks; 3.02-4.35kg at time of insemination
route: gavage 1X/day from gestation days 7-19 (13 days)
background: rangefinding study for effects of embryo and fetal development in rabbits

Observations

Mortality	once daily
Clinical signs	once daily
Body weight	gestation days 0,7, 10, 13, 16, 20, 24 and 29
Food consumption	daily from gestation days 5-29
Sacrifice	gestation day 28-29

Results

Mortality and clinical observations

There were no mortalities during the study. However, 1 control and 1LD doe aborted their fetuses and were sacrificed on gestation days 21 and 22, respectively. The LD abortion is unlikely to be drug-related. Clinical observations included vaginal bleeding and ↓stool in all dosed animals; the incidence of these findings was increased at the HD. The vaginal bleeding was the result of increased resorptions in MD and HD animals. The study authors indicated that the vaginal bleeding in LD rabbits was not associated with resorption since the does were not pregnant. Does were not confirmed for pregnancy prior to dosing.

Body weight and food consumption

Corrected body weight (terminal body weights of dams minus weights of uterus, ovaries, oviducts, placentas and fetuses) was similar in dosed and control animals. A significant body weight loss was observed at the HD on gestation day 20 when compared to concurrent controls; this was the result of the weight loss of one doe. Body weight gains of dosed animals were similar to controls by gestational day 24.

Food consumption in LD does was reduced up to 7% from day 14-16 and 23-26,

consumption at the MD was depressed up to 11% from day 13 to 28 and consumption at the HD was depressed up to 17% from day 11 to 27 when compared to control does.

Maternal necropsy

Incidence of gross pathological findings in does administered letrozole				
Organ/finding	Dose Level (µg/kg) N=20			
	0	2	6	20
Uterus/black corpora lutea		1	1	6
Ovary + uterus/ cysts		1		2
/detached and misshapen uterine horn				1
Kidney nodule				1

Reproductive parameters

Reproductive parameters of rabbits administered letrozole					
Parameters	Dose level (µg/kg)				
	0	2	6	20	Historical Data (range)
Implantation sites	7.94	7.88	8.33	7.81	7.8(4.5-11.5)
Corpora lutea	11.0	11.5	12.44	9.75	10.6(7-14)
Early resorptions	0.31	0.75	0.89	1.31	0.4(0-2.2)
Late resorptions	0.06	0	0.11	0.38	0.2(1-1.4)
Live fetuses	7.56	7.13	7.33	6.06	7.2(3-10.5)
Dead fetuses	0	0	0	0.06	0
Postimplantation loss	0.38	0.75	1.0	1.75	
% postimplantationloss	3.74	15.17	14.72	26.28	
♂ fetal weights[a]	46.9	46.0	42.5	44.4	44.6(34-52.5)
♀ fetal weights[b]	44.0	44.2	44.0	44.5	43.4(31.8-47.8)

[a] ♂ only pups from 2 does
[b] ♀ only pups from 3 does
[c] Reference: Historical control data, 1992-1994, N=678 does

Fetal observations

Gross malformations observed in 2/97 (2%) fetuses from 1/14 HD does included blepharia (absence/eyelids), acrania (partial or complete absence of skull), agenesis pinna (missing ear), brachdactyly (shortness of fingers and toes), oligodactyly (↓number of fingers and toes), exencephaly, and gastroschisis (protrusion of intestines). One additional fetus from this same litter exhibited omphalocele (protrusion of the intestine). These findings were not observed in other fetuses. Historical incidence for exencephaly and gastroschisis is 1.6 and 1.1%, respectively; historical incidence of these other findings could not be determined. (reference: Historical Control Data for External Malformations in NZW Rabbits. Compiled by

Historical data are not available for the majority of fetal observations; for this reason, visceral and skeletal malformations and variations of treated animals are compared to concurrent controls.

Fetal visceral and skeletal malformations and variations (by fetus and litter)				
No. of fetuses examined	Dose level (µg/kg)			
	0	2	6	20
	121	114	132	97
Visceral malformations				
Diaphramatic hernia[a]			1 (1)[b]/0.0075[c]	
Visceral variations				
Gallbladder/ coagulated blood	1 (1)	6 (3)	2 (2)	1 (1)
Skeletal variations				
Skull/incomplete ossification	18 (7)	21 (7)	36 (10)	16 (6)
/bowed hyoid	1(1)	5 (5)	3 (2)	0
Sternebrae/incompl ossification	17(10)	21(9)	24(10)	14(4)
Metacarpals of foreleg/incompl ossification	1(1)	0	3(2)	0
Mid phalanges of foreleg/incompl ossification	9(6)	7(6)	12(7)	11(4)
Proximal phalanges of foreleg/incompl ossification	0	0	6(2)	1(1)

Patella of hindleg/ incompl ossifica	25(9)	36(8)	47(14)	44(9)

[a] Historical fetal incidence 1.1%, 9089fetuses examined, Historical Control Data for Visceral Malformations in NZW Rabbits. Compiled by

[b] # of malformations or variations/litter in parentheses

[c] % incidence

Letrozole is embryotoxic at 2, 6, and 20μg/kg and fetotoxic when administered to rabbits at 20μg/kg. Reproductive parameters were compared to concurrent control and historical control data. Embryotoxic and fetotoxic effects include increased early and total resorptions, and increased postimplantation loss at all doses; the increase was dose-related. Increased late resorptions, increase in number of dead fetuses, and decrease in number of live fetuses occurred at the HD. The number of total resorptions, depressed number of live fetuses, and post-implantation loss were found to be significant by the study author using the Chi-Bar Square Test and Mantel's Trend Test; post-implantation loss was significant to 0.01.

Findings of gross, visceral and skeletal variations in dosed fetuses were not found to be significant by the study author using Mantel's Trend Test. The most common fetal variation was an increased incidence of incomplete ossification of skull, sternebrae, and fore- and hindlegs at the LD and MD.

Slight to moderate maternal effects were observed at all doses.

Summary of Reproductive Toxicity

Letrozole is embryotoxic and fetotoxic when administered to rats at ≥0.018mg/m^2. Significant changes in reproductive parameters included increased early, late and total resorptions (↑ by 2- to 4-fold), increased postimplantation loss, and decreased number of live fetuses. Fetal anomalies (eg. absent or shortened renal papilla, dilation of ureter, split sternebrae and incomplete ossification of frontal skull and metatarsals) were observed following dosing of dams at ≥0.018mg/m^2. Additional fetal anomalies including domed head, exencephaly, hyperflexure of hindlimbs, and fused vertebra and cervical rib were observed following dosing of dams at 0.18mg/m^2. Evidence of maternal toxicity included mortality at 0.18(1/26) and 6.0 (2/8) mg/m^2, vaginal bleeding at doses ≥0.018mg/m^2 and fluid-filled, rigid, eroded and ruptured uteri at doses ≥0.18mg/m^2.

Rabbits appeared to be equally sensitive to the effects of letrozole compared to rats; embryotoxicity and fetotoxicity was observed at ≥0.02mg/m^2 and 0.2mg/m^2, respectively. Postimplantation loss and increased resorptions were increased in a dose related manner. Increased number of dead fetuses and depressed number of live fetuses were exhibited at 0.2mg/m^2. The incidence of fetal anomalies was not significant in rabbits; the most common fetal variation was incomplete ossification of skull, sternebrae and fore-and hindlegs.

VII. GENETIC TOXICITY

AFP 12 **Bacterial mutagenicity test on CGS 20267** Conducted by The study was not conducted according to GLP.

Letrozole did not exhibit mutation in three strains of *Salmonella typhimurium* (TA100, TA1537 and TA98) with or without metabolic activation or in a tryptophan-requiring strain of *Escherichia coli* (wP2 uvrA) at concentrations of 15.8-5000µg/plate in the absence of S-9 or 5-1580µg/plate in the presence of S-9. The number of revertants/plate observed for each strain was comparable to the number exhibited in the concurrent solvent control. In addition, letrozole did not exhibit mutation when 1, 1, 1-trichloropropene oxide, an epoxide hydrolase inhibitor and glutathione depletor, was added to the S-9 mix with strain TA98 in order to increase the sensitivity of the test to drugs activated to mutagenic epoxides. The study authors indicated that letrozole precipitated at 1580 and 5000µg; cytotoxicity was increased by 10% at 5000µg/plate. Positive controls included benzo(a)pyrene 4,5-oxide, N-methyl-N'-nitro-N-nitrosoguanidine and N-ethyl-N'-nitro-N-nitrosoguanidine for direct mutagenicity, and 3-methylchloanthrene, 2-aminocholanthrene, benzo(e)pyrene and benzo(a)pyrene 4,5-oxide in the activated tests. DMSO was the solvent.

896031 **Salmonella/Mammalian-microsome mutagenicity test.** Conducted by Ciba-Geigy, Basle, Switzerland in 1989 according to OECD GLP. Previously reviewed by HR Prasanna in 1991.

Letrozole did not exhibit mutation in *S.typhimurium* strains TA98, TA100 or TA1535 with or without metabolic activation at concentrations of 313-5000µg/plate. Cytotoxicity was observed at 5000µg.

956144 **Salmonella and Escherichia/Mammalian-microsome mutagenicity test.** Conducted by Genetic Toxicology, Ciba-Geigy, Basle, Switzerland in 1995 according to OECD and Japanese GLP.

Letrozole did not exhibit mutation in five strains of *Salmonella typhimurium* (TA98, TA100, TA102, TA1535, and TA1537) with or without metabolic activation or in a tryptophan-requiring strain of *Escherichia coli* (wP2 uvrA) at concentrations of 312.5-5000µg/plate in the presence or absence of S-9. The number of revertants/plate observed for each strain was comparable to the number exhibited in DMSO, the concurrent solvent control. Positive controls included 2-aminoanthracene and cyclophosphamide for tests with metabolic activation, and sodium azide, 4-nitroquinoline, mitomycin-C, 2-nitrofluorene and 9-aminoacridine for tests without metabolic activation. Cytotoxicity was observed at 5000µg/plate.

Concentrations of letrozole in test solutions were analytically determined in order to confirm cell exposure to the test drug and the stability of the test material in DMSO; concentrations were reported at 88.6 and 97.9% for the original and confirmatory test,

respectively.

926313 **Cytogenetic test on Chinese hamster cells in vitro (EC-Conform).**
Conducted by Genetic Toxicology, Ciba-Geigy, Basle, Switzerland in 1993 according to OECD and Swiss GLP.

drug: CGS 20267, batch #800189, purity 99.8%
vehicle: DMSO
positive controls: Mitomycin C (0.2µg/ml) without metabolic activation, cyclophosphamide (20µg/ml) with metabolic activation

Chinese hamster ovary (CHO K1) cells were exposed to letrozole at concentrations of 145-1160µg/ml in the absence (18 and 42 hrs of incubation) and presence (3hr of incubation followed by recovery periods of 15 and 39hr) of metabolic activation. Confirmatory studies were performed at incubation and recovery periods of original tests and at extended incubation and recovery periods.

Cytotoxicity was observed at 290, 580 and 1160µg/ml, the three highest letrozole concentrations (see table). Letrozole caused 29.1 and 26.6% suppression of mitotic activity following 18hr incubation without metabolic activation at 580 and 1160µg/ml, respectively; and 40.2 and 34.3% suppression following 3hr incubation and 15hr recovery with metabolic activation, respectively. Following 42hr incubation without metabolic activation, mitotic activity was suppressed 56.7, 25.6, and 53.3% at 1160, 580 and 290µg/ml, respectively. There was no cytotoxicity observed at these concentrations with 3hr incubation and 39hr recovery with metabolic activation.
Letrozole concentrations were limited to 1160µg/ml based on solubility.

The incidence of chromosomal aberrations was increased in letrozole-exposed cells compared to vehicle controls (see table). In the original study, a significant increase ($0.01 \geq p \geq 0.001$) was observed (4.5-5.5-fold) in the incidence of cells with aberrations at concentrations of 290 and 580µg/ml letrozole with metabolic activation. The incidence of chromosomal aberrations was not increased at 1160µg/ml, the highest concentration tested. Similar statistical results were not repeated in confirmatory studies; however, the number of cells with chromatid and chromosome gaps, chromatid and chromosome deletions, chromosome exchanges and polyploid metaphases
were increased following letrozole exposure. Many chromosomal aberrations were increased relative to concentration.

The incidence of chromosomal aberrations in chinese hamster ovary cells exposed to letrozole				
Exposure/chromosomal aberration	Vehicle control[a]	Letrozole concentration (µg/ml)[a] 290	580	1160
18h w/o S9/chromatid del	1(0.5%)	5 (2.5%)	5 (2.5%)	6(3%)
/polyploid metaph	3 (1.5%)	3 (1.5%)	4 (2%)	6 (3%)
3h, 15h recov w S9/ chromatid gaps	5 (2.5%)	6 (3%)	8 (4%)	5 (2.5%)
/chromatid del	0	5 (3%)	5 (3%)	3 (1.5%)
/chromosome del	1(0.5%)	4 (2%)	4 (2%)	2 (1%)
18h w/o S9 (confirmatory)/ chromatid gaps	2 (1%)	6 (3%)	10 (5%)	5 (2.5%)
18h w/o S9 (confirmatory)/ chromatid gaps/	6 (3%)	6(3%)	10 (5%)	5 (2.5%)
/chromosome del	0	2 (1%)	4 (2%)	1 (0.5%)
/polyploid metaph	2 (1%)	7 (3.5%)	3 (1.5%)	2 (1%)
3h, 39h recov w S9 (confirmatory)/chromatid gaps	5 (2.5%)	6 (3%)	9 (4.5%)	4 (2%)
/polyploid metaph	5 (2.5%)	5	5	8 (4%)
42h w/o S9 (confirmatory) /chromatid gaps	2 (1%)	Letrozole concentration (µg/ml) 145 290 580		
		3 (1.5%)	6 (3%)	4 (2%)
/chromosome del	3 (1.5%)	4 (2%)	1 (0.5%)	2 (1%)
/chromosome exchanges	1 (0.5%)	3 (1.5%)	2 (1%)	1 (1.5%)
/polyploid metaph	1 (0.5%)	3 (1.5%)	4 (2%)	4 (2%)

[a] N=200 cells examined

896032 **Chromosome studies on chinese hamster ovary cell line CCL 61 in vitro.** Conducted by Ciba-Geigy, Basle, Switzerland in 1990 according to GLP. Previously reviewed by HR Prasanna in 1991; rereviewed and summarized below.

Chinese hamster ovary (CCL 61) cells were exposed to letrozole at concentrations of 200-800µg/ml in the absence and presence (3hrs incubation, 21hrs recovery) of metabolic activation. In addition, concentrations of 50-200µg/ml in the absence of metabolic activation were incubated for 24hrs without recovery.

Twelve to 16% suppression of mitotic activity was observed at a concentration of 400µg/ml letrozole with 3hrs exposure with and without metabolic activation, respectively; there was no cytotoxicity at 800µg/ml. Concentrations of ≥100µg/ml were cytotoxic (61-94% suppression of mitotic activity) following 24hrs exposure without metabolic activation.

The incidence of cells with chromatid gaps was increased at the highest concentration (800µg/ml) compared to vehicle controls when exposure was limited to 3hrs without metabolic activation and at all letrozole concentrations tested (50, 100 and 200µg/ml) when treated in the presence of metabolic activation. In addition, the incidence of chromatid gaps was increased to a greater extent at all letrozole concentrations tested when cells were exposed for 24hrs without metabolic activation; the increase was not dose related. The incidence of cells with chromatid fragments was increased for cells exposed to a concentration of 100µg/ml letrozole for 24hrs without metabolic activation. The incidence of chromosomal aberrations in letrozole-exposed cells was below the incidence of postive controls in all studies. Statistical analyses were not performed.

The incidence (%) of chromosomal aberrations in chinese hamster ovary cells CCL 61 exposed to letrozole					
Exposure/chromosomal aberration	Vehicle control[a]	Letrozole concentration (µg/ml)[a] 200	400	800	positive control [b]
3h w/o S9/chromatid gaps	4 (2%)	5 (2.5%)	1 (0.5%)	8 (4%)	6 (12%)
3h w S9/ chromatid gaps	3 (1.5%)	5(2.5%)	9 (4.5%)	6 (3%)	11 (22%)
24h w/o S9/chromatid gaps	5 (2.5%)	Letrozole concentration (µg/ml) 50	100	200	8 (16%)
		12 (6%)	11(5.5%)	11(5.5%)	
/chromatid fragm	0	3 (1.5%)	6 (3%)	4 (2%)	6(12%)
/total unspecific aberrations	3.5 (1.8%)	6.5 (3.3%)	7.5 (3.8%)	6.5(3.3%)	5.5(11%)

[a] N=200 metaphases

[b] 0.8µg/ml mitomycin-C, N=50 metaphases

896033 **Gene mutation test with chinese hamster cells V79.** Conducted by Ciba-Geigy, Basle, Switzerland in 1990 according to GLP. Previously reviewed by HR Prasanna in 1991; data were rereviewed.

Letrozole did not induce mutations in chinese hamster cells at doses up to the cytotoxic limit of 60 to 1200µg/ml with microsomal activation and 90 to 1080µg/ml without metabolic activation.

896030 **Micronucleus test, rat.** Conducted by Ciba-Geigy, Basle, Switzerland in 1990 according to GLP. Previously reviewed by HR Prasanna in 1991; data were rereviewed.

Tif: rats were administered 40, 80 and 160mg/kg letrozole by gavage following tolerability testing; additional animals were administered vehicle control (CMC) and positive control (cyclophosphamide).

The incidence of micronucleated polychromatic erythrocytes (PCEs) was increased at 160mg/kg at 24 (0.24-0.26% compared to negative contols, 0.10-0.12%) and 48hrs (0.18% compared to negative controls, 0.04-0.06%) postdosing. The sponsor indicated the critical level of significance to be 0.2%. When the study was repeated, the increase of PCEs was marginal at 48hrs only (0.10%) at the same dose. There was no increase observed when multiple doses were examined at 24 and 48 hrs. When comparing all studies, there was no biologically significant increase in the incidence of micronucleated polychromatic erythrocytes in letrozole-treated animals.

Summary of Genetic Toxicity

Letrozole was not found to be mutagenic in bacterial strains or V79 chinese hamster cells with or without metabolic activation. However, letrozole was found to be a potential clastogen in chinese hamster ovary cells (CHO K1 and CCL 61). The number of cells with chromatid and chromosome gaps, chromatid and chromosome deletions, chromosome exchanges and polyploid metaphases were significantly increased following exposure to letrozole at varying concentrations and study durations. All treatments also induced some degree of cytotoxicity. There was no biologically significant increase in the incidence of micronucleated polychromatic erythrocytes in the rat micronucleus test. The threshold of cytotoxicity was 580µg/ml in chinese hamster ovary cells.

VIII. SPECIAL TOXICITY STUDIES

896324 **Test for abnormal toxicity in mice (EC-conform).** Conducted by Ciba-Geigy, Basle Switzerland in 1990.

Letrozole did not exhibit abnormal toxicity in mice.

The following studies indicated that Letrozole was not a venous, ocular, or dermal irritant in rabbits.

946105 **5-day intravenous irritation study in rabbits.** Conducted by Ciba-Geigy, Basle Switzerland in 1995.

946922 **Acute eye irritation/corrosion study in the rabbit.** Conducted by Ciba-Geigy, Basle Switzerland in 1994.

946923 **Acute dermal irritation/corrosion in the rabbit.** Conducted by Ciba-Geigy, Basle Switzerland in 1994.

OVERALL SUMMARY AND EVALUATION

Letrozole is a potent and selective non-steroidal competitive inhibitor of aromatase. The inhibitory activity of the drug is primarily attributed to the parent drug and not to its metabolites. Letrozole effectively inhibits the conversion of androgens to estrogens both *in vitro* and *in vivo* without significant effect on adrenal steroidogenesis. The drug is suitable for confering antitumor activity in estrogen dependent malignancies of postmenopausal women whose main source of estrogen is via peripheral aromatization of androgen precursors.

Oral absorption of letrozole was indicated to be complete but prolonged in the mouse and male rat, approximately 85% in the female rat, and 80-90% in the dog. Following a single oral dose, the peak plasma concentration was highest for rats (males and females) followed by mouse and dog for equivalent mg/m^2 doses. Plasma concentrations were higher and the clearance of letrozole from blood, plasma and tissues was markedly slower in female compared to male rats. Absolute bioavailability was ~80% in mice, 100% in male rats and 50-100% in the dog. Following iv and oral dosing with letrozole, tissue distribution was similar in all species, with the highest levels of the drug observed in the adrenals and liver. The ratio of renal to fecal excretion of letrozole varied between species; the ratio was ~1:1 in male or female rats, ~2:1 in the dog and ~8:1 in mice. Unchanged CGS 20267 was the major component in the urine of mice with smaller amounts of the glucuronide conjugate, 4,4'-methanolbisbenzonitrile (CGP 44645) and unconjugated CGP 44645. The ratio of unchanged letrozole to total carbinol metabolite was ~4:1 in the urine of male mice, ~1:6 in the urine of male rats and ~2:3 in the urine of male dogs. CGP 44645 did not exhibit any aromatase activity *in vitro*. Excretion in the mouse and dog was primarily renal while the rat excretion was equally divided between urine and feces. Clearance of parent drug from plasma decreased in the order: mouse >male rat >female rat >dog. Following single doses, the t½ of letrozole was appproximately 4-5h in mice, 7-10h in male rats, 20-5-h in female rats and 60-90h in dogs. Letrozole is 50-56% bound to plasma proteins in all species. Arimidex inhibits P450 2A and 3A isozymes. The induction of metabolism is a probable explanation for the hepatocellular hypertrophy observed in rat and dog toxicology studies.

The proposed oral dose of letrozole in humans is 1.54mg/m^2. Mice readily tolerated doses of 600mg/m^2. Oral doses of 6000 and 4000mg/m^2 were lethal to mice and dogs, respectively. In rats administered daily doses for 12 months, reversible toxicities were observed at doses ≥1.8mg/m^2, corresponding to an AUC of 32-123µmol.h/L. Toxicities exhibited in female rats did not appear to be increased as a result of increased systemic exposure. In dogs administered multiple daily doses, toxicities were observed at doses ≥0.6mg/m^2, corresponding to an AUC of 99-146µmol.h/L. Major findings observed in multiple dose studies could be attributed to disturbances in steroid hormone biochemistry from aromatase inhibition and the induction of P450 metabolism. In general, end-organ toxicities were directed primarily to the reproductive organs and the liver. Letrozole depressed body weights in male rats and dogs, but increased body weights in female rats. Food consumption of rats was consistent with body weight changes. Atrophy of the uterine and vaginal epithelium was observed in female rodents and dogs and Leydig cell hyperplasia was observed in male rodents and dogs, while testicular atrophy was exhibited in mice and dogs. Hyperplasia of the mammary gland was observed in rats and dogs. The findings can be explained by the inhibition of estrogen synthesis by letrozole due to aromatase inhibition, causing estrogen depletion and resulting in the lack of negative feedback

to aromatase inhibition, causing estrogen depletion and resulting in the lack of negative feedback inhibition from estradiol to the pituitary resulting in Leydig cell testosterone production and hyperplasia. Depressed adrenal weights occurred in female rats administered $\geq 1.8mg/m^2$; depressed weights and adrenal atrophy were observed in female dogs dosed with $0.6mg/m^2$ for 12 months. This may have been a result of interference with steroid synthesis. Hepatocellular hypertrophy was exhibited in multiple dose rodent studies and is attributable to microsomal enzyme induction. Bone fractures were observed in female rats administered $180mg/m^2$ letrozole following 8-9 months of treatment, but were not exhibited after two years of treatment at doses up to $200mg/m^2$. Bone fragility has been observed in rodents administered antiestrogenic agents but not with other aromatase inhibitors.

The carcinogenic potential of letrozole was assessed in mice and rats. Administration of letrozole to mice at doses of 1.8, 18 and $180mg/m^2$/day (C_{max} = 0.78, 8.5 and 70.7µmol/L, respectively, dose normalized AUC = 8.9, 10.7 and 10.2µmol·h/L, respectively) resulted in a dose-related increase in the incidence of granulosa theca cell tumors and atrophy of the reproductive tract in males and females. As indicated above, these findings can be attributed to disturbances in steroid hormone biochemistry resulting from the aromatase inhibition of letrozole. The study in rats at doses of 0.6, 6 and $60mg/m^2$/day (C_{max} = 0.2-1.4, 3.3-7.7 and 12.7-44µmol/L, respectively, the dose normalized AUC = 103(♂)-245(♀), 140(♂)-170(♀) and 73(♂)-89(♀)µmol·h/L, respectively) produced only a low incidence of ovarian stromal tumors compared to the incidence of this finding in mice. This may be a result of the species difference in proliferative response of the ovarian stroma. The incidence of hepatocellular adenoma and carcinoma were increased in female mice administered $\geq 18mg/m^2$/day; the comparative incidence in rats was not significant when analyzed by the Division of Biometrics. The incidence of chronic progressive nephropathy was increased in female mice and rats treated for 104 weeks.

Letrozole is embryotoxic and fetotoxic when administered to rats at $\geq 0.018mg/m^2$. Postimplantation loss and the number of resorptions were increased and the number of live fetuses was decreased. Fetal anomalies at this dose included absent or shortened renal papilla, dilation of the ureter, split sternebrae and incomplete ossification of the frontal skull and metatarsals. Additional fetal anomalies including domed head, exencephaly, hyperflexure of hindlimbs and fused vertebra and cervical rib were observed at $0.18mg/m^2$. Evidence of maternal toxicity was observed at doses $\geq 0.018mg/m^2$. Rabbits appeared to be equally sensitive to the effects of letrozole compared to rats; embryotoxicity and fetotoxicity was observed at $\geq 0.02mg/m^2$ and $0.2mg/m^2$, respectively. Postimplantation loss and increased resorptions were increased in a dose related manner. Increased number of dead fetuses and depressed number of live fetuses were exhibited at $0.2mg/m^2$. The incidence of fetal anomalies was not significant in rabbits; the most common fetal variation was incomplete ossification of skull, sternebrae and for- and hindlegs.

Letrozole was not mutagenic in bacterial strains or V79 Chinese hamster cells. However, letrozole was found to be a potential clastogen in Chinese hamster ovary cells (CHO K1 and CCL 61). Significantly increased chromatid and chromosome gaps, chromatid and chromosome deletions, chromosome exchanges and polyploid metaphases were exhibited at varying letrozole concentrations and study durations, which also cause some cytotoxicity. Letrozole was not clastogenic in the rat micronucleus test.

In summary, letrozole is a specific inhibitor of aromatase. At therapeutic doses, Letrozole is expected to have a low potential for systemic or local toxicities. Letrozole is embryotoxic and fetotoxic at maternally toxic doses and is a potential clastogen.

RECOMMENDATIONS Approval

Discussed with Medical Officer: Mortality in cats due to cardiotoxicity.

Margaret Brower June 19, 1997

Margaret E. Brower, Ph. D. Date
Pharmacology

History
1st draft May 21, 1997
Returned June 4/9, 1997
Final draft June 10, 1997

cc
NDA ORIG. and Div. File
HFD-150
/GSchechter
/PAndrews
/MBrower
/DSpillman
HFD-900
/JContrera
HFD-002
/JDeGeorge

concur Paul A. Andrews 6/10/97

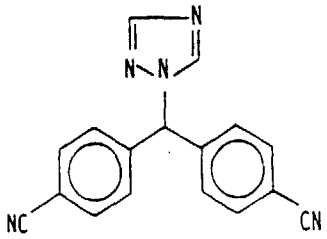
SEP 12 [illegible]

45-DAY FILABILITY REVIEW
PHARMACOLOGY/TOXICOLOGY

NDA No. 20-726

Drug Name: Letrozole (Femara)

Structure:



CGS 20 267

Molecular Weight and Formula: 285.3 $C_{17}H_{11}N_5$

Sponsor: Ciba-Geigy Corporation, Summit NJ

Related INDs: IND , IND

Class: Aromatase inhibitor

The ability of letrozole to inhibit estrogen synthesis and deplete estrogens in plasma should confer antitumor activity in estrogen-dependent malignancies.

Indication: Metastatic breast cancer in postmenopausal women

Route of Administration: oral tablet

Proposed Dosage: 2.5mg (1.85mg/m^2 based on 50kg human) administered daily until tumor progression

Filability: There are currently no filability issues for Pharm/Tox. The Segment II teratology study in rabbits was received following submission of the NDA and has been reviewed.

Chemistry has submitted a request for evaluation of toxicity of in the drug product. Additional data is expected from the sponsor regarding leaching of these chemicals from the container.

Pharm/Tox submission: Completed sections of the letrozole submission include subchronic and chronic toxicity, reproductive toxicity and genetic toxicity. The carcinogenicity studies are currently being reviewed. Pharmacokinetics and pharmacology will be completed following carcinogenicity. Rereview of studies submitted with the initial IND in 1991 have been found to be necessary and are included in the NDA.

Margaret Brower, Ph.D.
Sept. 6, 1996

9/12/96