CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-319

PHARMACOLOGY REVIEW

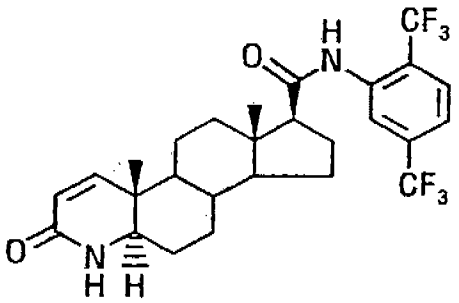
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21319
Review number: 2 (previous review by Jeri El-Hage attached)
Serial number/date/type of submission: 000/ 21December 2000/ original submission
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: Glaxo Wellcome Inc., Five Moore Drive (R&D 0-2029), Research Triangle Park, North Carolina 27709
Manufacturer for drug substance: Glaxo Wellcome Inc.

Reviewer name: Laurie McLeod
Division name: Division of Reproductive and Urologic Drug Products
HFD-580
Review completion date: 21 September 2001

Drug:

Trade name: Duagen
Generic name: Dutasteride
Code name: Gl198745X
Chemical name: (5α, 17β)-N {2,5-bis(trifluoromethyl)phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide
CAS registry number:
Mole file number:
Molecular formula/molecular weight: $C_{27}H_{30}N_2F_6O_2$/528.54
Structure:



Relevant INDs/NDAs/DMFs: [redacted]

Drug class: 5-α-reductase inhibitor

Indication: benign prostatic hyperplasia

Clinical formulation: Soft Gelatin Capsules contain 0.5 mg Dutasteride dissolved in a mixture of mono-di-glycerides of caprylic/capric acid and butylated hydroxytoluene. The inactive excipients in the capsule shell are gelatin (from certified, BSE-free, non-porcine sources), glycerin, ferric oxide (yellow), edible printing ink containing ferric oxide (red), purified water, and titanium oxide

Route of administration: oral

Proposed use: 0.5 mg/day for treatment of symptomatic benign prostatic hyperplasia in men with an enlarged prostate gland

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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

OVERALL SUMMARY AND EVALUATION:

Introduction:

Dutasteride is a new 5-α-reductase inhibitor being developed for treatment of benign prostatic hyperplasia. A total of 4324 patients have been enrolled in three large phase III studies for up to two years followed by a two-year open-label extension period. It was estimated that 3500 subject-years of safety data were completed at the time of the 120-Day Safety Update. Dutasteride inhibits both types 1 and 2 5-α-reductases.

Safety evaluation:

Dutasteride has been tested chronically in rats and dogs at multiples of parent drug greater than 200 times the expected clinical exposure. However, it was discovered relatively late in drug development that metabolism is extensive in humans and low in the animal species used for toxicity testing. Although human exposure levels of all known major metabolites have been shown to be present in rats given very high doses of parent drug, the metabolites, which constitute a major proportion of human exposure, have been minimally studied for carcinogenicity, genotoxicity, and reproductive effects. In addition, it is possible that up to 55% of the fate of this drug in humans is still unknown. No information regarding metabolites in rabbits or monkeys is available.

In rats, after multiple administrations of GI19845X resulting in blood levels higher than 17000 ng/ml, centrally mediated neurotoxicity was observed (hypoactivity, dilated pupils, uncoordinated behavior), with no histopathological correlate. Clinical signs disappeared when the drug was withdrawn and serum concentrations dropped below the critical levels. Because of the long half-life of the drug, several weeks were required for serum levels to drop low enough to eliminate clinical signs.

In dogs, neurotoxicity (unsteady gait, crouching, shaking, hypoactivity, and hunched posture) was also observed at blood levels above 12000 ng/ml, with no histopathological correlate. Clinical signs reversed after the drug was withdrawn (up to several weeks).

Adrenal effects were observed in dogs and mice at relatively high doses. Effects on the thyroid, pituitary, female reproductive organs, mammary glands, spleen, bone marrow, lungs, and liver were also observed at high doses in dogs. In rats and mice, the highest apparent concentrations of Dutasteride-associated radiolabel were in the adrenals at all measured times.

Cardiology measurements were inconclusive in a 1-year dog study since 4/8 high dose males and 5/8 females exhibited wandering pacemaker and 1 of 8 high dose females experienced an incidence of sinus arrest before the initiation of dosing. Although extended sinus (wandering pacemaker) arrhythmia was later observed in 2/8 males and 1/7 females, the effect could not be definitively attributed to the drug. No treatment related effects were observed in the low or mid dose groups. The mid dose had blood levels ranging from about 100 to about 200 times the clinical dose of parent drug, while the high dose had blood levels ranging from 200 to about 400 tomes. Exposure to the 4-OH metabolite at the high dose in dogs is about equal to the

concentration experienced by humans at the clinical dose. None of the other major human metabolites were detected in dog serum. (Note: A human QT study at the maximally tolerated dose was conducted.) GI198745X (parent drug) caused reductions in action potential, maximum rate of depolarization, and upstroke amplitude at 25 times the clinical dose with more marked effects at 50 times the clinical dose in a canine Purkinje fiber model. The decreases in action potential duration were not reverse frequency dependent. A direct effect on potassium channels is therefore not indicated; however, confirmation in HERG-transfected oocytes was not done, and major human metabolites were not tested.

Male reproductive effects: Effects on male fertility and reproductive organs were observed at 0.05 mg/kg/day (~0.04-0.11 times the steady state clinical blood levels in men) after 12 weeks of treatment in rats. Decreased weights of prostate, seminal vesicles, and epididymides were observed at all doses along with decreased secretory activity of the prostate and seminal vesicles and vacuolation of the epididymal tubular epithelium. After 14 weeks of recovery, decreases in the weight of seminal vesicles persisted even at the low dose. A low, but dose dependent, incidence of focal prostatic hyperplasia was observed after recovery. At 50 mg/kg/day and above, average sperm count was decreased during the treatment phase, but returned to normal following recovery.

Females (untreated) mated with treated males (oral gavage) showed measurable blood levels of GL198745X. Female blood levels measured 17 ng/ml after cohabitation with males with blood levels of 4417 ng/ml (~0.4%), 8.4 ng/ml after cohabitation with males with blood levels of 2088 ng/ml (~0.4%), and 0.6 ng/ml after cohabitation with males with blood levels of 649 ng/ml (~0.1%). Females were caged with males for up to 14 days, and the sponsor suggested that some of the female exposure may not have occurred through semen contact.

Although Dutasteride is not intended for use by women, it has been postulated that women may be exposed through contact with semen of treated partners, through handling of broken tablets, or through a blood transfusion from a treated man. A maximum concentration of 14 ng/ml Dutasteride has been measured in human semen. In order to estimate the risk to an unborn fetus of an exposed woman, certain assumptions were made: that a woman is exposed daily to 5 ml of semen from a Dutasteride treated partner, that all of a 70 ng dose is absorbed and crosses the placenta, and that maternal blood volume is about 4000 ml. Therefore, a fetus is potentially exposed to blood levels of .0175 ng/ml Dutasteride (not considering the potential of Dutasteride's >96% semen protein binding to reduce vaginal absorption).

Dutasteride was injected intravenously during 80 days of gestation in a study using pregnant Rhesus monkeys. Based on measured blood levels of Dutasteride at the highest dose, and assuming a linear dose relationship, the average maternal blood levels during gestation were:

Dose (ng/animal/day)	400	780	1325	2010
Average concentration predose (ng/ml)	.014	.027	.046	.07
Average concentration at 5 min post dose (ng/ml)	.056	.109	.185	.28
Multiple of human dose, predose	0.8	1.5	2.6	4
Multiple of human dose, postdose	3.2	6.2	10.6	16

No effect on anogenital distance in the fetuses of Dutasteride treated Rhesus monkeys was observed at doses resulting in blood levels ranging from 4 to 16 times estimated blood levels of women exposed through a treated partner. However, effects on adrenal, testis, ovarian, and prostate weights of fetuses were observed at those doses.

Feminization of male fetuses: No effect on feminization of male fetuses was observed in monkeys after exposure to .07 to .28 ng/ml of parent drug throughout gestation (4 to 16 fold the estimated blood levels of a partner-exposed woman). In rabbits, feminization was observed after blood levels of 5 to 15 ng/ml (>200 times) were maintained during gestation (no no-effect level was established). In rats, some evidence of feminization was observed at blood levels of about 2 ng/ml (>100 times) along with a decrease in fetal body weights. At higher doses in rats (greater than 4000 times the estimated blood levels of a partner exposed woman), fetal loss and effects on gestation length, fetal bone ossification and newborn startle response were observed. No information regarding metabolites in rabbits or monkeys is available.

Dutasteride showed no potential for genotoxicity in a standard battery of tests. In addition, several major metabolites tested negative in Ames assays. In two-year carcinogenicity studies in rats and mice, There was a significant increase in Leydig cell adenomas in male rats at 53 mg/kg/day and in hyperplasia at 7.5 and 53 mg/kg/day (52 and 135 times the clinical exposure of parent drug. Loading doses were used in the carcinogenicity studies and an integrated "average daily concentration" was calculated as an estimate of animal exposure. Average exposure levels and nominal dose levels are therefore not necessarily proportional.). There were no neoplastic effects in female rats at doses up to 15 mg/kg/day (183 times the clinical exposure of parent drug). There was a significant increase in female mouse hepatocellular adenomas at the high dose of 250 mg/kg/day (290 times the clinical dose of parent drug). There was no neoplastic effect in male mice at 500 mg/kg/day (270 times the clinical exposure of parent drug). The metabolite mixture to which humans are actually exposed was minimally tested in rats, but not in mice. The multiples of parent drug in rat carcinogenicity studies were nearly 300 times the expected drug level in humans, but analysis of known human metabolites in human and rat serum indicate that rats were not exposed to significantly more than the human dose of the known metabolites during the course of these lifetime studies. Similarly low percentages of some of the human metabolites were also present in mouse serum. In addition, the fate of possibly 55% of administered drug is not known, and no judgement of the validity of carcinogenicity testing with regard to this material can be made, except that profiles in animals appeared to be similar to humans by mass spectrometry. In addition, computerized structure function analysis indicated no known increased risk for mutagenicity or toxicity of any identified metabolite over the known characteristics of the parent drug.

Safety issues relevant to clinical use:

The effects of low metabolite coverage in animal studies, especially when metabolites may constitute the majority of drug to which humans are exposed, is to limit the information about margins of safety which might be expected for endpoints which cannot be studied in human populations. These endpoints might include carcinogenicity, reproductive toxicity, and low level chronic toxicity which are occasionally discovered by using large multiples of the human dose in animal studies. Therefore, labeling of Dutasteride should not include reassurances that the drug

has been studied in animals at many multiples of the human dose without discussion of the chemical species actually tested in those studies.

Carcinogenicity: The questionable relevance of Leydig cell tumors in man was discussed in a recent review by Cook et al[1] where it was concluded that, although Leydig cell tumorigenesis through a non-genotoxic 5-α-reductase inhibitor-induced increase in luteinizing hormone (LH) is probably relevant to humans, the no observable effect levels for the induction of these tumors in rodents is an adequate margin of safety for protection of human health. A 2 to 3 fold increase in LH was observed to correlate with tumorigenesis in rodent studies using Finasteride, which reportedly caused "no clinically relevant" increase in LH under clinical conditions. In male rats treated with Dutasteride, the tumorigenic dose level was associated with a 167% increase in LH after 80 days. The level of LH increase in men was 19% after one year of Dutasteride treatment in a phase III study. In addition, humans are reported to be less sensitive than rodents to LH levels with regard to Leydig cell tumorigenesis, although these tumors are more likely to metastasize in man than in rodents. Hepatocellular adenomas were observed in female mice only and not in rats. Both tumor types should be reported in the label.

Reproductive effects: Dutasteride effects on male reproduction in animals and men were minimal and reversible at low doses. Dutasteride is not indicated for use in women. A woman exposed to Dutasteride through transfusion or handling of broken tablets must absorb enough drug to produce steady state blood levels greater than 0.05 ng/ml to be at risk for effects on fetal adrenals or reproductive organ weights, greater than 0.07 ng/ml (no-effect level with a low-effect level at about 2 ng/ml) to be at risk for feminization of a male fetus, and greater than 74 ng/ml to be at risk for other reproductive effects. i.e. Some evidence of male fetus feminization might be expected if a woman were to absorb an average daily dose of 5% of a 0.5 mg tablet or to replace 5% of her blood volume with blood containing 40 ng/ml (average serum concentration in men taking the maximum dose). If a woman normally having 4 liters of blood is administered 0.5 liter of blood containing Dutasteride, her initial blood concentration would be about 5 ng/ml. Warnings against donation of blood from Dutasteride treated patients should be in the drug label for the protection of pregnant women. The risk of transmission of teratogenic concentrations of Dutasteride through semen is low.

Other clinically relevant issues: A pregnancy registry, if ever needed, might be difficult to establish since the patient taking the drug is not the mother of the child.

Conclusions: This drug is approvable, with changes to the label.

Communication review:

Labeling review: See communication to sponsor.

RECOMMENDATIONS:

Internal comments: The reproductive effects of this drug have been minimally assessed in animals and humans, due to low concentrations of major human metabolites in rats, no knowledge of major human metabolites in rabbits and monkeys, and few pregnancies in the course of clinical trials. Ultimately, any true risk for human reproductive effects will most likely be assessed through monitoring of human populations. It should be considered that a pregnancy registry, if ever needed, might be difficult to establish since the patient taking the drug is not the mother of the child.

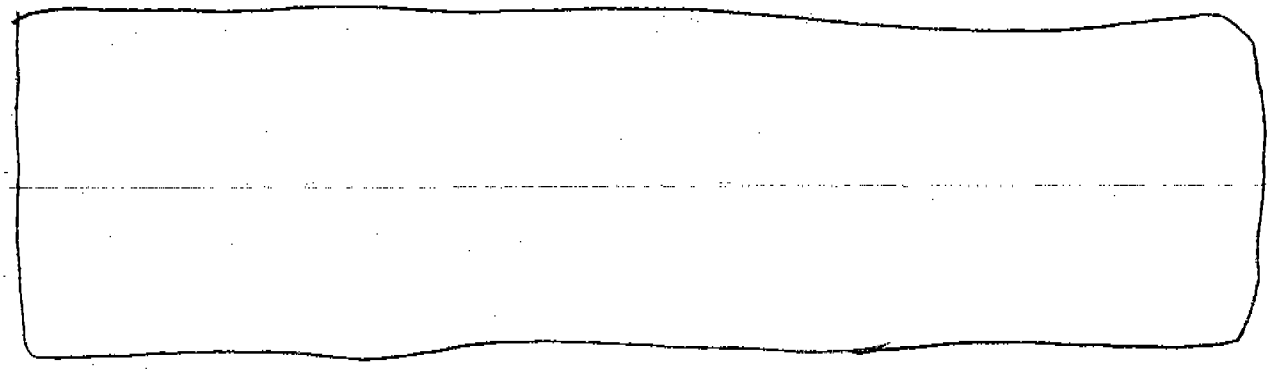
External recommendations (to sponsor): The following changes to the label are needed:

CNS Toxicity: (separate section)

In rats and dogs, rRepeated oral administration of dutasteride resulted in some animals showing signs of non-specific, reversible, centrally-mediated toxicity, without associated histopathological changes, at exposures 425 and 315-fold the expected clinical exposure (of parent drug) respectively.

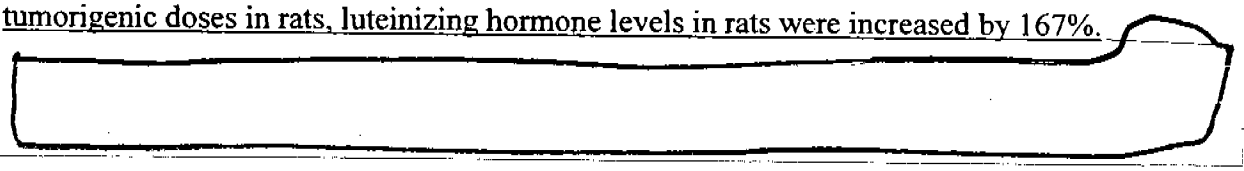
Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: In a 2-year carcinogenicity study in B6C3F1 mice, at doses of 3, 35, 250, and 500 mg/kg/ day for males and 3, 35, and 250 mg/kg/ day for females, Aan increased incidence of benign hepatocellular adenomas was noted at 250 mg/kg/ day (290-fold the expected clinical exposure to a 0.5 mg daily dose) in females only



In a 2-year carcinogenicity study in Han Wistar rats, at doses of 1.5, 7.5, and 53 mg/kg/day for males and 0.8, 6.3, and 15 mg/kg/ day for females, there was an increase in Leydig cell adenomas in the testes at 53 mg/kg/ day (135-fold the expected clinical exposure). An increased incidence of Leydig cell hyperplasia was present at 7.5 mg/kg/ day 52-fold the expected clinical exposure) and 53 mg/kg/ day in male rats. A positive

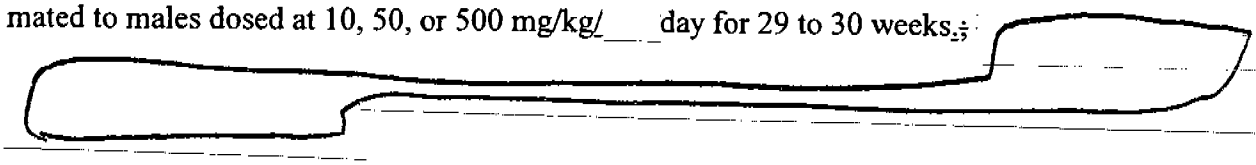
correlation between proliferative changes in the Leydig cells and an increase in circulating luteinizing hormone levels has been demonstrated with 5α-reductase inhibitors and is consistent with an effect on the hypothalamic-pituitary-testicular axis following 5α-reductase inhibition. At tumorigenic doses in rats, luteinizing hormone levels in rats were increased by 167%.



The major human metabolites, which are produced at lower concentrations in rats than in humans, were minimally tested for carcinogenicity in the rat.

Mutagenesis: Dutasteride was tested for genotoxicity in a bacterial mutagenesis assay (Ames test), a chromosomal aberration assay in CHO cells, and a micronucleus assay in rats. The results did not indicate any genotoxic potential of the parent drug. Two major human metabolites were also negative in either the Ames assay or an abbreviated Ames assay.

Impairment of Fertility: Treatment of sexually mature male rats with dutasteride at doses of 0.05, 10, 50, and 500 mg/kg/ day (0.01 to 110-fold the expected clinical exposure of parent drug) for up to 31 weeks resulted in dose- and time-dependent decreases in fertility, reduced cauda epididymal sperm counts (at 50 and 500 mg/kg/ day), reduced weights of the epididymis, prostate and seminal vesicles, and microscopic changes in the male reproductive organs. The fertility effects were reversed by recovery week 6 at all doses, and sperm counts were normal at the end of a 14-week recovery period. The 5α-reductase-related changes consisted of cytoplasmic vacuolation of tubular epithelium in the epididymides and decreased cytoplasmic content of epithelium, consistent with decreased secretory activity in the prostate and seminal vesicles. The microscopic changes were no longer present at recovery week 14 in the low-dose group and were partly recovered in the remaining treatment groups. Low levels of dutasteride (0.6 to 17 ng/mL) were detected in the serum of untreated female rats mated to males dosed at 10, 50, or 500 mg/kg/ day for 29 to 30 weeks.



In a fertility study in female rats, oral administration of dutasteride at doses of 0.05, 2.5, 12.5, and 30 mg/kg/ day resulted in reduced litter size, increased embryo resorption and feminization of male fetuses (decreased anogenital distance) at doses of ≥2.5 mg/kg/ day (1.8

to 10.1-fold the clinical exposure of parent drug in men). Fetal body weights were also reduced at ≥0.05 mg/kg/ day in rats (<0.02-fold the human exposure).

Pregnancy: Pregnancy Category **X** (see CONTRAINDICATIONS). DUAGEN is contraindicated for use in women. DUAGEN has not been studied in women because preclinical data suggest that the suppression of circulating levels of dihydrotestosterone may inhibit the development of the external genital organs in a male fetus carried by a woman exposed to dutasteride.

In an intravenous embryo-fetal development study in the rhesus monkey (12/group), administration of 400, 780, 1325, or 2010 ng/day dutasteride on gestation days 20 to 100, did not adversely affect development of male external genitalia. Based on the highest measured semen concentration of dutasteride in treated men (14 ng/mL), these doses represent 0.8 to 16 times (based on blood levels of parent drug) the potential maximum exposure of a 50-kg human female to 5 mL semen daily from a dutasteride-treated man, assuming 100% absorption. Reduction of fetal adrenal weights, reduction in fetal prostate weights, and increases in fetal ovarian and testis weights were observed in monkeys treated with the highest dose. Dutasteride is highly bound to proteins in human semen (>96%), potentially reducing the amount of dutasteride available for vaginal absorption.

In an embryo-fetal development study in female rats, oral administration of dutasteride at doses of 0.05, 2.5, 12.5, and 30 mg/kg/ day resulted in feminization of male fetuses (decreased anogenital distance) and male offspring (nipple development, hypospadias, and distended preputial glands) at all doses (0.07 to 111-fold the expected male clinical exposure. An increase in stillborn pups was observed at 30 mg/kg/ day, and reduced fetal body weight was observed at doses =2.5 mg/kg/ day (15 to 111-fold the expected clinical exposure). Increased incidences of skeletal variations considered to be delays in ossification associated with reduced body weight were observed at doses of 12.5 and 30 mg/kg/ day (56 to 111-fold the expected clinical exposure).

In an oral pre- and post natal development study in rats, dutasteride doses of 0.05, 2.5, 12.5, or 30 mg/kg/ day were administered. Unequivocal evidence of feminization of the genitalia (i.e., decreased anogenital distance, increased incidence of hypospadias, nipple

development) of F1 generation male offspring occurred at doses ≥2.5 mg/kg [redacted] 14 to [redacted] 90-fold the expected clinical exposure in men. At a daily dose of 0.05 mg/kg/[redacted] day ([redacted] 5-fold the expected clinical exposure), evidence of feminization was limited to a small, but statistically significant, decrease in anogenital distance. Doses of 2.5 to 30 mg/kg/[redacted] day resulted in prolonged gestation in the parental females, [redacted] a decrease in time to vaginal patency for female offspring, and decreased prostate and seminal vesicle weights in male offspring. Effects on newborn startle response were noted at doses greater than or equal to 12. 5 mg/kg/day. Increased stillbirths were noted at 30 mg/kg/[redacted] day.

Feminization of male fetuses is an expected physiological consequence of inhibition of the conversion of testosterone to DHT by 5α-reductase inhibitors. These results are similar to observations in male infants with genetic 5α-reductase deficiency. [redacted]

In the rabbit, embryo-fetal study doses of 30, 100, and 200 mg/kg ([redacted] 28- to [redacted] 93-fold the expected clinical exposure in men) were administered orally on days 7 to 29 of pregnancy to encompass the late period of external genitalia development. Histological evaluation of the genital papilla of fetuses revealed evidence of feminization of the male fetus at all doses. A second embryo-fetal study in rabbits at doses of 0.05, 0.4, 3.0, and 30 mg/kg/[redacted] day ([redacted] - to 53-fold the expected clinical exposure) also produced evidence of feminization of the genitalia in male fetuses at all doses. The major human metabolites, which are produced at lower concentrations in rats than in humans, were minimally tested for reproductive effects. It is not known whether rabbits or rhesus monkeys produce any of the major human metabolites.

Precautions/Warnings: Men being treated with Dutasteride should not donate blood until at least 6 months following their last dose for the protection of pregnant women.

Draft letter content for sponsor (same as above):

Future development or issues: (see internal comments):

Reviewer signature: /S/ 9/26/01

Team leader signature [concurrence/non-concurrence]:

cc: E. Farinas /S/ 9/26/01

PHARMACOLOGY:

See attached previous review.

Study: Inhibition of human 5 α-reductase by Gl198745 metabolites: (sponsor's summary)

The time-dependent inhibition of human 5α-reductase (5AR) by Gl198745X metabolites GW702541X, GW695923X, and GW695920X was investigated using the method of progress curve analysis.

The inhibition kinetics are consistent with a two-step inhibition mechanism for all three metabolites, where a fast onset of the thermodynamic equilibrium for the formation of an initial enzyme-inhibitor complex (EI) precedes a time-dependent rearrangement of the EI complex.

Comparing the values of k_3/K_i, the second order rate constant for time-dependent inhibition, the potency of GW695920X, a 6β-hydroxy derivative of Gl198745, is similar in potency to Gl198745X in inhibition of both 5AR1 and 5AR2. GW702541X, which is 4'-hydroxylated, is approximately 10-fold less potent in inhibition of both 5AR1 and 5AR2. GW695923X, the 15α-hydroxy derivative, is the least potent of the three inhibitors, with a k_3/K_i that is about 50-fold less potent than Gl198745X at the inhibition of 5AR2 and about 700-fold less potent at inhibition of 5AR1.

SAFETY PHARMACOLOGY:

See attached previous review.

PHARMACOKINETICS/TOXICOKINETICS:

(See also attached previous review)

Metabolite concentrations in preclinical studies

Mean steady state serum concentrations (±SD) of GI198745 (parent) and GW702541 in humans and animals					
Species	Study	Dose (mg/kg)	Sex	GI198745 (ng/ml)	GW702541 (ng/ml)
Human	ARIA1012	~0.01 (0.5 mg)	M	39.4±14.6	7.92±5.79 (20.1%)
	ARIB3003	~0.01 (0.5 mg)	M	36.9±18.1	6.99±4.79 (18.9%)
Mouse	M40185	250	M	8709±646	3.30±1.72 (.038%)
	M40737	0.5	M	273±37.7	0.12±0.03 (.044%)
	M40737	250	M	11969±1826	6.57±0.96 (.055%)
Rat	R40184	7.5	M	3113±2090	3.19±2.41 (.102%)
	R40184	6.3	F	3686±345	4.13±2.88 (.112%)
	R40184	53	M	6338±3623	9.10±5.98 (.144%)
	R40184	15	F	7308±1819	21.5±4.19 (.294%)
	R40783	50	M	1645±737	2.39±0.28 (.145%)
Dog	D40730	0.5	M	2380±516	0.17±0.07 (.007%)
	D40730	10	M	19488±2184	2.04±0.66 (.010%)

Mean steady state serum concentrations (±SD) of other metabolites in humans and animals					
Species	GI1201448	6-hydroxy	15-hydroxy	6,4'-hydroxy	????
Human	Similar to GW702541	?	?	?	?
Mouse	?	?	?	?	?
Rat	Estimated higher in HD rat serum than in human serum via MS*	Estimated higher in HD rat serum than in human serum via MS* (unknown stereochemistry)	Estimated higher in HD rat serum than in human serum via MS* (unknown stereochemistry)	Estimated higher in HD rat serum than in human serum via MS* (unknown stereochemistry)	?
Dog	?	?	?	?	?

Table 7.10. A Table of the Comparative Metabolism of GI198745X at Steady State Across Nonclinical Species and Humans

	Summary of Metabolism – Detection							
	Serum				Faeces			
Identity	Mice[a]	Rat[b]	Dog[c]	Human[d]	Mice[a]	Rat[b]	Dog[c]	Human[d,*]
GI198745X	✓	✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓
^{19}F-NMR Data								
Peak 1	NA	*	*	*	-	✓✓✓	-	✓✓✓*
Peak 3	NA	*	*	*	✓✓✓	✓✓✓	✓✓✓	✓✓✓*
Peak 5	NA	*	*	*	-	✓✓✓	-	✓✓✓*
Peak 8	NA	*	*	*	✓✓✓	✓✓✓	✓✓✓	✓✓✓*
Other metabolites (number)	NA	-	✓✓ (2) **	✓✓✓ (1) ✓✓ (1)	✓✓ (3)	✓✓ (5)	-	✓✓ (6) *
^{1}H-NMR, HPLC/MS data								
4'-hydroxy	-	✓*	-	✓*	NA	✓✓	NA	✓
6,4'-dihydroxy	✓	✓	✓	✓	NA	✓✓✓	NA	-
6-hydroxy	-	✓	-	-	NA	✓✓	NA	✓
1,2-dihydro (GI201448)	✓	✓	✓	✓	-	**	-	-
6,15,4'-trihydroxy	-	-	-	-	NA	**	NA	-
6,15,4'-trihydroxy 1,2-dihydro	-	-	-	-	NA	✓✓	NA	-
15,4'-dihydroxy	-	-	-	-	NA	✓✓	NA	-
15,4'-dihydroxy 1,2-dihydro	-	-	-	-	NA	✓✓	NA	-
6,4'-dihydroxy 1,2-dihydro	-	-	-	-	NA	✓✓✓	NA	-
15-hydroxy	-	✓	-	-	NA	✓✓	NA	-
15-hydroxy 1,2-dihydro	NA	NA	NA	NA	NA	✓	NA	-
4'-hydroxy 1,2-dihydro	-	-	-	-	NA	✓	NA	-
6-hydroxy 1,2-dihydro	NA	NA	NA	NA	NA	✓	NA	-
Other mono-hydroxylated	-	-	-	-	-	NA	-	NA

Key:

a = Reports RD2000/00263/00 and WD2001/00204/00
b = Reports RD2000/00262/00 and WD2001/00204/00
c = Reports RD2000/00265/00 and WD2001/00204/00
d = Reports RD1999/02818/00 and WD2001/00204/00
# = Not investigated
= These metabolites may or may not correspond to those detected in faeces by ^{19}F-NMR

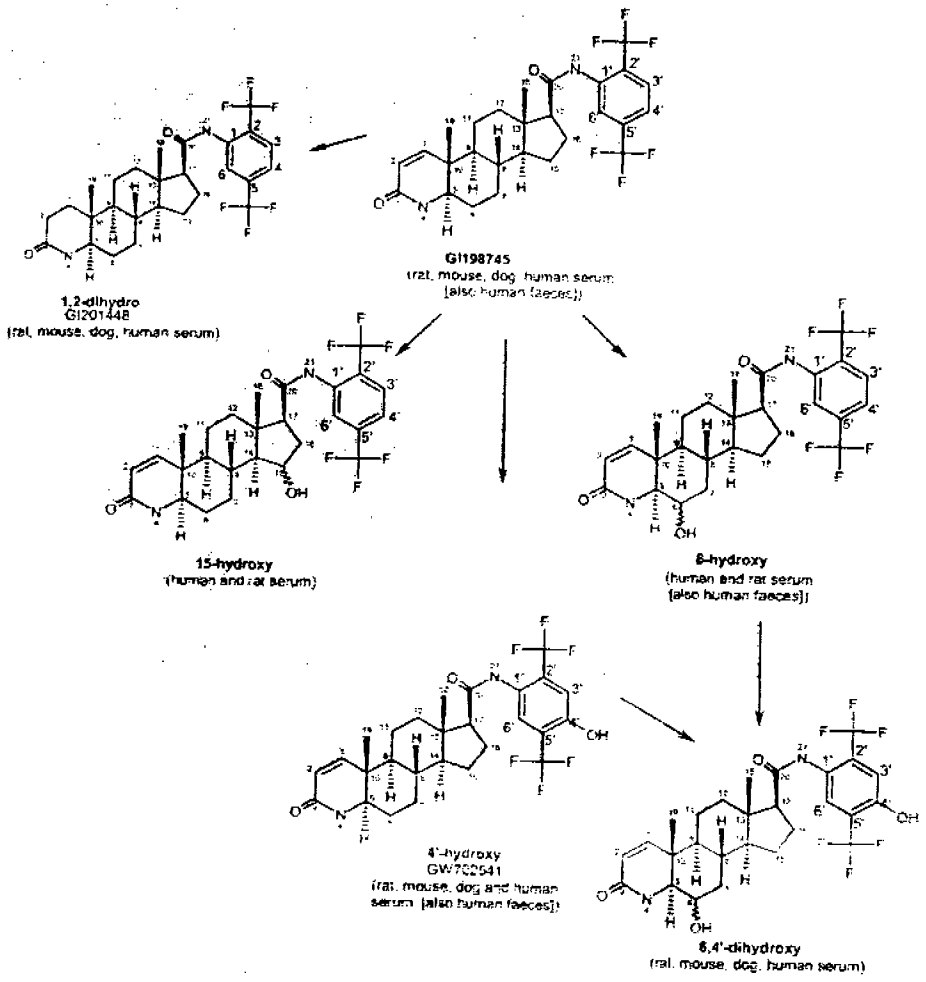
✓✓✓ = Major peak.
✓✓ = Minor peak.
✓ = Peaks detected but not quantified.
* = Work ongoing
** = Tentative evidence
NA = Not Analysed
- = Not Detected

Distribution: (also see attached previous review)

Study title: (14C)-GI198745: Quantitative Whole Body Autoradiography following Single and Repeated Oral Administration (3.3 mg [base]/kg/day) to the Mouse

Study no: 00AVV0004
120-day Safety Update, Volume #2, and page #210
Summary of individual study findings: As in the rat, the highest apparent concentrations of Dutasteride-associated radiolabel were in the adrenals at all measured times. Concentrations ranged from 5 to 7 times higher than in the prostate 8 hours following cessation of dosing and remained present in significant concentrations in the adrenals 14 days following cessation of dosing. Significant concentrations were found in the following organs 8 hours following 7 days of dosing: adrenals, gall bladder, Harderian glands, liver, > pancreas, peri-renal fat, brown fat, inguinal fat, preputial gland, kidney, > epididymis, lachrymal glands, thyroid, pituitary, brain, salivary glands, > gastrointestinal system, nasal mucosa, prostate > blood. 14 days following the cessation of dosing, concentrations were highest in adrenals >> nasal mucosa > epididymis. It was stated that visually, it was clear that concentrations were higher in the adrenal cortex than in the medulla.

Metabolism: profile



PK/TK summary/conclusions:

It was discovered relatively late in drug development that metabolism is extensive in humans and low in the toxicity species. Although human exposure levels of all known major metabolites have been shown to be present in rats at very high doses of parent drug, the metabolites, which constitute a major proportion of human exposure, have been minimally studied for carcinogenicity, genotoxicity, and reproductive effects. In addition, up to 55% of the fate of this drug in humans is still unknown. No information regarding metabolites in rabbits or monkeys is available.

Dutasteride and its metabolites are primarily eliminated in feces. Clearance values were low in all species tested and half lives were long (16, 52, and 82 hours in the rat, dog, and marmoset), resulting in accumulation. Half lives in humans were shown to be up to 5 weeks after multiple administration. The half live of the 4-OH metabolite in rats was shown to be comparable to that of the parent drug. Other metabolites might be assumed to have similar or shorter half lives than the parent drug due to their increased hydrophilicity.

The effects of low metabolite coverage in animal studies, especially when metabolites may constitute the majority of drug to which humans are exposed, is to limit the information about margins of safety which might be expected for endpoints which cannot be studied in human populations. These endpoints might include carcinogenicity, reproductive toxicity, and low level chronic toxicity which are occasionally discovered by using large multiples of the human dose in animal studies. Therefore, labeling of Dutasteride should not include reassurances that the drug has been studied in animals at many multiples of the human dose without discussion of the chemical species actually tested in those studies.

TOXICOLOGY:

(In addition to studies below, see attached previous review.)

Study Title: GI198745X: 53 week oral toxicity study in the dog

Study No: D21025

Amendment #58, Vol #1, and page #1

Conducting laboratory and location: Glaxo Wellcome Inc. Research and Development, Five Moore Drive, Research Triangle Park, NC 27709

Date of study initiation: 24 October 1995

GLP compliance: yes

QA- Report Yes (x) No ()

Dosing:

- species/strain: Beagle dogs
- age: 8-10 months
- weight: 10.04 – 16.29 kg (males) and 10.02 – 13.70 kg (females)
- dosage groups in administered units:

Group Number	Group Name	Dosage * (mg/kg/day)	Dose Concentration * (mg/ml)	Number of Dogs/Sex
1	Control #	0	0	6
2	Low	0.5 [a]	0.5	4
3	Intermediate	3 [a]	3	4
4	High	50 [a,b]	50	8
		10 [c]	10	

* Expressed as GI19845X

Control animals received vehicle alone

a On Day 0 to 6 of the study the dosage levels were doubled to 1, 6, and 100 mg/kg to attain steady state exposure drug levels.

b From Day 0 to 21 inclusive, or Day 0 to 1 inclusive (dogs 12 and 21).

c From Day 43 to end of study.

- satellite groups used for recovery: 2 control and 2 HD
- route, form, volume, and infusion rate: oral gavage at 2 ml/kg during the first week of dosing and at 1 ml/kg for the remainder of the treatment period

Drug: GI198745X (free base), lot # CD0124, 97.3% pure

Formulation/vehicle [redacted]

Results:

- Clinical signs: (expressed in animal-days, as % occurrence days 0-374)

treatment	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.5	3	50-10	0	0.5	3	50-10
Gums and/or ears pink	<1	52	76	53	<1	57	59	44
Thin	<1	1	24	34	2	<1	<1	6
Gums and/or ears pale	0	<1	<1	6	0	0	<1	2
Both ears cold	0	<1	<1	4	0	0	<1	1
Pink muzzle	0	<1	1	<1				
Salivating	<1	0	<1	<1	0	<1	<1	<1
Subdued behavior	0	0	0	1	<1	0	0	1
Unsteady gait	0	0	0	<1	0	0	0	<1
Dehydrated	0	0	0	<1				
Vocalizing	0	0	0	<1				
Lethargic	0	0	0	<1				
Shaking (both hindlimbs)	0	0	0	<1				

Convulsing	0	0	0	<1	0	0	0	<1
Lack of coordination	0	0	0	<1	0	0	0	<1
Trembling					0	0	0	<1
Splayed forelimbs					0	0	0	<1
Crouching on hindlimbs					0	0	0	<1
Appears distressed					0	0	0	<1
Reluctant to move					0	0	0	<1
Rapid breathing					0	0	0	<1
No abnormality detected	99	47	18	26	97	43	41	51
recovery								
Thin	0	---	---	13	0	---	---	0
Gums and/or ears pink	0	---	---	1	0	---	---	0
No abnormality detected	100	---	---	87	100	---	---	100

Reported figures are the percentage of animal days on which an abnormal clinical sign is observed, or on which "no abnormality detected" is the only valid sign observed, out of the total number of animals in the period for each group. Each day on which an animal was alive is counted as one animal day. Values of <1 represent a percentage of incidence of less than 0.5 but greater than 0.

- Deaths: One high dose female was sacrificed moribund on day 254, after similar clinical signs and with similar pathology to other dogs in the same group. It had also swallowed a rubber glove.

- Body weights:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.5	3	50-10	0	0.5	3	50-10
Day 0	13.918	12.070	12.425	13.434	11.220	12.473	11.593	11.576
Days 7-21, mean	13.876	12.310*	12.588	12.084	11.118	12.048	11.655	10.654
Days 24-42, mean	12.428	12.566	12.287	11.681**	12.433	11.946	12.340	11.697*
Day 42	12.676	12.748	12.558	12.139*	12.548	12.052	12.537	11.877**
Days 45-371, mean	13.100	13.201	12.727	12.616	12.876	12.512	13.073	12.530
Day 372	12.826	12.578	11.999	12.235	12.748	12.549	12.845	12.366
Day 423 (end of recovery)	14.390	na	na	13.085	12.730	na	na	12.895

* p<.05
** p<.01

- Food consumption:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.5	3	50-10	0	0.5	3	50-10
Days -1- 0	24.21	25.70	32.92	32.28	27.49	23.92	26.85	24.78
Days 0-21	31.88	33.78	32.15	25.51**	30.79	28.95	30.52	19.30**
Days 22-42	30.66	31.20	32.96	42.74**	30.91	29.96	31.40	40.27**
Days 43-371	30.53	33.23	35.27*	33.43*	29.74	31.58	31.53	29.05
Days 375- 420 (recovery)	32.30	na	na	33.62	29.22	na	na	28.94

* p<.05
** p<.01

- Ophthalmoscopy: No treatment related changes were observed.

- EKG:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.5	3	50-10	0	0.5	3	50-10
Notched P waves			1/4			1/4		
Deep Q wave	1/6	1/4		2/8		1/4		3/8
Small R waves (left axis deviation)								1/8
Deep S waves				1/8			1/4	
S-T segment depression	1/6			1/8		1/4		

Increased T wave amplitude	1/6					1/4	1/4	
Notched or biphasic T waves	1/6		1/4	6/8	2/6	2/4		4/8
Variable T wave configuration			1/4					
Total with notched, biphasic, or variable configuration T waves	4/6		2/4	6/8	2/6	2/4		4/8
Total with notched, biphasic, or variable config. T waves, day 356	3/6		2/4	3/8	2/6			2/7
Wandering pacemaker, day 356	2/6		1/4	3/8	1/6	2/4	2/4	5/7
day -8	1/6	1/4	1/4	4/8	1/6		3/4	5/8
Sinus arrest, day 356								2/7
day -8								1/8
Extended sinus (wandering pacemaker) arrhythmia				2/8, one day each				1/7, one day

- Hematology:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.5	3	50-10	0	0.5	3	50-10
MCV (fL)								
Day -15	70.23	69.20	67.95	69.28	69.67	68.80	69.63	70.08
Day 27	68.76	69.57	69.62	69.06	69.08	68.92	68.70	68.52
Day 97	69.94	71.03*	71.31*	71.14*	70.66	70.33	69.94	70.29
Day 188	70.56	70.70	70.70	70.65	69.61	69.76	69.95	70.59
Day 279	70.72	71.23	70.84	71.87	70.83	70.02	70.29	70.81
Day 363	70.78	70.90	70.59	71.19	71.35	69.51	70.70	70.91
Day 414 (recovery)	70.45	na	na	67.20	68.30	na	na	68.80
MCH (pg)								
Day -15	23.07	23.05	22.73	23.08	22.92	22.63	23.18	23.28
Day 27	23.23	23.38	23.29	23.20	23.53	23.43	23.20*	23.19*
Day 97	23.32	23.74	23.65	23.77*	23.78	23.71	23.36	23.54
Day 188	23.35	23.80	23.75	23.90	23.25	23.10	23.45	23.30
Day 279	22.92	22.98	23.14	23.12	23.34	23.11	23.11	23.01
Day 363	23.15	23.19	23.16	23.35	23.59	23.29	23.15*	23.11**
Day 414 (recovery)	23.60	na	na	22.30	23.20	na	na	23.60
MCHC (g/dL)								
Day -15	32.85	33.28	33.45	33.31	32.87	32.93	33.28	33.20
Day 27	33.70	33.67	33.58	33.63	33.99	33.98	33.79	33.82
Day 97	33.24	33.54	33.28	33.45	33.64	33.67	33.47	33.51
Day 188	32.96	33.72*	33.82*	33.38*	33.22	33.39	33.40	33.17
Day 279	32.27	32.36	32.89	32.28	32.80	32.95	32.96	32.52
Day 363	32.64	32.78	32.83	32.82	33.04	33.40	32.75	32.65
Day 414 (recovery)	33.50	na	na	33.25	33.95	na	na	34.30

* $p<.05$
** $p<.01$

- Clinical chemistry:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.5	3	50-10	0	0.5	3	50-10
Alkaline phosphatase (IU/L)								
Day -15	141.9	158.1	172.9	159.9	165.8	175.7	180.2	159.2
Day 27	218.0	219.0	287.5	275.5	183.5	222.5	226.5	231.0
Day 97	161.5	188.0	259.0	213.5	160.5	201.0	256.5	185.0
Day 188	156.9	176.0	210.1*	204.6*	136.6	186.8*	200.9*	178.0
day 231	163.0	169.8	208.2	218.1*	142.9	188.1	184.1	182.5
Day 279	162.4	215.6	283.9*	241.3*	136.2	235.8*	207.9*	200.6*
Day 363	153.9	190.0	217.8	198.8	131.6	171.3	154.2	171.2
Day 414 (recovery)	156.0	na	na	191.9	120.5	na	na	136.9

Gamma glutamyltransferase (IU/L) Day 231	3.5	4.0	5.0	4.0	3.0	5.0	6.0	5.0
Glucose (mmol/L)								
Day -15	5.392	6.170	5.908	6.081	5.360	5.988	6.048	5.863
Day 27	6.110	6.318	5.978	6.326	5.767	6.215	6.263*	6.319*
Day 97	5.973	6.283	6.205	6.315	5.610	6.005*	5.980*	6.225**
Day 188	5.285	6.323**	6.095**	6.476**	5.247	6.198**	6.380**	6.435**
Day 279	4.533	4.543	4.905	5.133	4.392	4.605	5.343	5.013
Day 363	5.882	5.985	6.128	6.181	5.383	5.623	6.085**	6.033**
Day 414 (recovery)	5.320	na	na	5.310	5.135	na	na	5.275
Cholesterol (mmol/L)								
Day -15	3.820	3.275	3.438	3.285	3.175	3.311	3.464	3.642
Day 27	3.398	3.483	3.701	3.331	3.658	3.390	3.463	3.430
Day 97	3.565	3.287	3.317	3.180	3.766	3.440	3.993	3.681
Day 188	3.350	2.980	2.770	2.485*	3.630	4.005	3.330	4.510
Day 231	2.817	2.687	2.886	2.697	3.446	3.498	2.933	3.154
Day 279	2.776	2.598	2.708	2.703	3.354	3.328	3.611	2.979
Day 363	4.079	3.767	3.873	3.456	4.465	5.002	4.849	4.293
Day 414 (recovery)	na	na	na	na	na	na	na	na
Triglycerides (mmol/L)								
Day -15	0.408	0.313	0.403	0.369	0.409	0.383	0.388	0.406
Day 27	0.366	0.312	0.335	0.306	0.353	0.355	0.365	0.312
Day 97	0.353	0.336	0.375	0.350	0.446	0.363	0.408	0.309*
Day 188	0.355	0.322	0.447	0.366	0.402	0.397	0.328	0.314
Day 279	0.433	0.378	0.356	0.361	0.558	0.524	0.422	0.355*
Day 363	0.426	0.307	0.377	0.279**	0.373	0.414	0.355	0.282
Day 414 (recovery)	0.249	na	na	0.248	0.347	na	na	0.385

* $p<.05$
** $p<.01$

- Urinalysis: No treatment related effects were observed.
- Organ weights:

	Males (mg/kg/day)				Females (mg/kg/day)			
Relative weights	0	0.5	3	50-10	0	0.5	3	50-10
Heart (g)								
treatment, based on initial BW	109.3	109.5	115.4	108.7	119.2	102.1*	107.4*	103.2*
treatment, based on final BW	108.4	108.7	118.5	118.5	116.3	101.8	104.7	103.5
recovery, based on initial BW	133.0			111.0	110.5			111.5
Liver (g)								
treatment, based on initial BW	336.5	364.7	353.7	388.5*	351.8	385.4	352.6	359.3
treatment, based on final BW	328.7	362.4	366.7	396.1**	344.4	384.1	343.1	362.4
recovery, based on initial BW	349.0			394.0	365.0			327.0
Adrenals (g)								
treatment, based on initial BW	1.895	1.697	1.742	2.065	2.101	1.824	1.918	1.699
treatment, based on final BW	1.814	1.708	1.768	2.016	2.164	1.819	1.935	1.735
recovery, based on initial BW								
Pituitary (g)								
treatment, based on initial BW	0.0805	0.0700	0.0725	0.0700	0.0690	0.0650	0.0775	0.0810
treatment, based on final BW	0.0821	0.0720	0.0703	0.0813	0.0696	0.0696	0.0835	0.0796
recovery, based on initial BW	0.0795			0.0705	0.0755			0.1005
Thymus (g)								
treatment, based on initial BW	6.68	5.90	5.61	7.00	7.39	8.15	6.73	8.14
treatment, based on final BW	5.96	5.86	6.29	7.08	7.38	8.07	6.41	8.45
recovery, based on initial BW								
Thyroid (g)								
treatment, based on initial BW	0.857	1.009	1.020	0.982	0.872	0.993	1.016	1.127*

__treatment, based on final BW	0.867	1.002	1.033	1.007	0.843	0.992	0.996	1.122*
__recovery, based on initial BW	1.210			1.015*	0.935			1.035
Prostate (g)								
__treatment, based on initial BW	7.677	2.715**	2.454**	2.006**				
__treatment, based on final BW	7.325	2.602**	2.555**	2.073**				
__recovery, based on initial BW	12.625			4.145				
Testes (g)								
__treatment, based on initial BW	27.73	26.60	29.11	27.35				
__treatment, based on final BW	27.03	25.99	29.72	27.82				
__recovery, based on initial BW								
Ovaries (g)								
__treatment, based on initial BW					2.055	2.106	1.421	1.497
__treatment, based on final BW					2.172	2.006	1.408	1.500
__recovery, based on initial BW					1.032			1.004
Uterus (g)								
__treatment, based on initial BW					15.611	20.413	7.7984	14.563
__treatment, based on final BW					17.069	19.112	7.7174	14.502
__recovery, based on initial BW								

* $p<.05$
** $p<.01$

- Gross pathology:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.5	3	50-10	0	0.5	3	50-10
Prostate								
__reduction in size, after treatment	0/4	4/4	2/4	4/6				
__reduction in size, after recovery	0/2			2/2				

- Histopathology:

	Males (mg/kg/day)				Females (mg/kg/day)			
treatment	0	0.5	3	50-10	0	0.5	3	50-10
Brain								
__choroid plexus fat cells, very slight	1/4							1/5
__choroid plexus fat cells, marked								1/5
Spinal cord								
__focal perineural mineral deposits, very slight				1/6		1/4	1/4	1/5
__focal meningeal mineral deposits, very slight			1/4				1/4	
__focal meningeal hyperplasia, slight			1/4					1/5
Peripheral nerve, focal axonal degen., very slight				2/6				
Kidney								
__cortical tubular pigmentation, very slight	2/4	3/4	1/4		1/4	2/4	3/4	2/5
__cortical tubular pigmentation, slight				3/4	1/4			2/5
Liver								
__centrilobular leukocyte infiltrate, very slight	3/4	3/4	3/4	1/6	3/4	3/4	2/4	
__centrilobular leukocyte infiltrate, slight	1/4		1/4	3/6	1/4		1/4	2/5
__centrilobular leukocyte infiltrate, moderate								1/5
__centrilobular leukocyte infiltrate, marked								1/5
__hepatocellular hypertrophy, very slight	2/4	2/4	1/4	2/6	3/4	3/4	2/4	2/5
__hepatocellular hypertrophy, slight			2/4	4/6	1/4	1/4	2/4	3/5
Stomach								
__fundic glandular mineral deposits, very slight	1/4	3/4		1/6		1/4	2/4	3/6
__fundic glandular mineral deposits, slight	1/4		2/4	1/6		1/4		
__fundic glandular mineral deposits, moderate				1/6				
__fundic glandular mineral deposits, marked								1/6
__increased mucus secretory activity, very slight	2/4			2/6	1/4	3/4		2/6

__increased mucus secretory activity, slight	2/4	4/4	3/4	3/6	3/4	1/4	4/4	1/6
__increased mucus secretory activity, moderate								2/6
__increased mucus secretory activity, marked								1/6
__leukocyte infiltrate, very slight			2/4	2/6		1/4	1/4	2/6
__leukocyte infiltrate, slight	2/4	2/4						1/6
__leukocyte infiltrate, moderate	1/4	1/4	1/4	2/6	2/4	1/4	2/4	2/6
__leukocyte infiltrate, marked	1/4	1/4	1/4	2/6	2/4	2/4	1/4	
Gall bladder								
__proliferative cholecystitis, very slight	1/4	1/4					1/4	
__proliferative cholecystitis, slight								
__proliferative cholecystitis, moderate				1/6		1/4		
__secretion inspissated, very slight	1/4				1/4		1/4	2/6
__secretion inspissated, slight				1/6	1/4	1/4	2/4	2/6
__secretion inspissated, moderate				1/6				
__secretion inspissated, marked								1/6
Pancreas								
__acinar cell apoptosis, very slight	1/4	2/4			2/4	2/4	2/4	3/5
__acinar cell apoptosis, slight	3/4	2/4	4/4	4/6		2/4	2/4	1/5
__acinar cell apoptosis, moderate				2/6	2/4			1/5
Spleen								
__focal siderosis, slight							1/4	
__focal siderosis, moderate							1/4	1/5
Pituitary								
__chromophobe enlargement, very slight		3/4	4/4	5/6			1/4	2/5
__pars distalis cyst, slight				1/6				
__pars distalis cyst, moderate	1/4			1/6		1/4	1/4	1/5
__focal pars nervosa pig. macrophages, very slight	1/4			2/6		2/4	1/4	
__focal pars distalis pig. macrophages, very slight				1/6				
__focal pars intermed. lymphocytic infilt., very slight	1/4		1/4	1/6				
__focal pars intermed. lymphocytic infilt., slight				1/6	1/4		1/4	2/5
Thyroid								
__focal vacuolated follicular cells, very slight			1/4	2/6		1/4	2/4	1/6
__focal vacuolated follicular cells, slight		2/4	1/4	1/6		1/4		
__focal vacuolated follicular cells, moderate				1/6				
__colloid reduced, very slight	2/4	1/4		2/6		2/4		1/6
__colloid reduced, slight	1/4	2/4	3/4	3/6		1/4	2/4	3/6
__colloid reduced, moderate	1/4	1/4			4/4	1/4	2/4	2/6
__lymphocyte infiltrate, very slight			1/4					
__lymphocyte infiltrate, slight	2/4		1/4	1/6	2/4			
__lymphocyte infiltrate, moderate				2/6				
Adrenals								
__zona glomerulosa hypertrophy, very slight		3/4	1/4		2/4	1/4	1/4	
__zona glomerulosa hypertrophy, slight		1/4		3/6			2/4	2/6
__zona glomerulosa hypertrophy, mod.			2/4					1/6
__zona glomer. incr'd cytoplasm. vac.,very slight	2/4	2/4		2/6				2/6
__zona glomerulosa increased cytoplasm. vac., slight			2/4	3/6			1/4	1/6
__zona glomerulosa increased cytoplasm. vac., mod.			1/4			1/4		
__zona reticularis hypertrophy, very slight							1/4	1/6
__zona reticularis hypertrophy, slight			3/4	2/6	1/4			1/6
__zona reticularis hypertrophy, moderate				3/6				
__zona reticularis incr'd cytoplasm. vac., very slight	1/4		1/4	2/6	1/4	2/4		2/6
__zona reticularis increased cytoplasm. vac., slight				1/6	2/4		4/4	
__zona reticularis increased cytoplasm. vac., mod.				1/6	1/4	1/4		2/6
__zona fasciculata hypertrophy, very slight	2/4	2/4			1/4	2/4	2/4	3/6
__zona fasciculata hypertrophy, slight		2/4	2/4	3/6	1/4	1/4	2/4	3/6
__zona fasciculata hypertrophy, moderate			2/4	3/6				

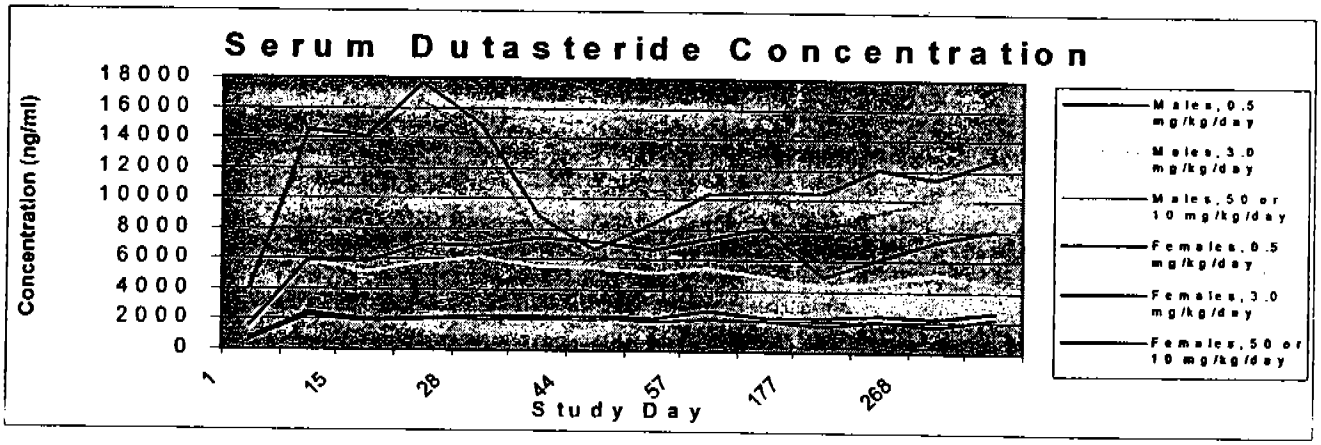
__increased pigment macrophages, very slight				2/6			2/4	
__increased pigment macrophages, slight			2/4					3/6
__increased pigment macrophages, moderate				3/6	1/4			1/6
__cortical cell inflammatory cell infiltrate, very slight				3/6			1/4	3/6
__cortical cell inflammatory cell infiltrate, slight			1/4	2/6	1/4			1/6
__cortical cell inflammatory cell infiltrate, moderate			1/4				1/4	
Epididymides								
__ductal vacuolation, very slight		1/4	1/4					
__ductal vacuolation, slight		1/4	1/4	1/6				
__ductal vacuolation, moderate			1/4	1/6				
__sperm stasis, very slight				1/4				
__epithelial atrophy, very slight				1/6				
__epithelial atrophy, slight			1/4	1/6				
__epithelial atrophy, moderate		1/4	1/4					
__lymphocytic/histiocytic infiltration, very slight		1/4	1/4					
__lymphocytic/histiocytic infiltration, slight		1/4		1/6				
__lymphocytic/histiocytic infiltration, moderate			1/4					
__germinal centers present, slight			1/4					
Ovaries								
__corpora lutea prominent, slight						1/4	1/4	1/5
__corpora lutea prominent, moderate					1/4	2/4	2/4	2/5
__corpora lutea prominent, very marked					1/4			
__corpora lutea involution, very slight					1/4			
__corpora lutea involution, slight						1/4		1/5
__corpora lutea involution, moderate							1/4	
__corpora lutea involution, marked								1/5
Mammary glands								
__glandular development, very slight					1/4	1/4		
__glandular development, slight						1/4	2/4	1/6
__glandular development, moderate					2/4		1/4	2/6
__glandular development, marked						1/4	1/4	3/6
__secretory activity, very slight							1/4	1/6
__secretory activity, slight					1/4	1/4	3/4	1/6
__secretory activity, moderate						1/4		2/6
__eosinophil infiltration, very slight							1/4	1/6
__eosinophil infiltration, moderate								1/6
__hemorrhage, very slight								
__hemorrhage, slight						2/4	1/4	1/6
__hemorrhage, moderate								
__hemorrhage, marked						1/4		
Uterus								
__epithelial cytoplasmic vacuolation, very slight					1/4		1/4	1/6
__epithelial cytoplasmic vacuolation, slight						1/4	1/4	2/6
__epithelial cytoplasmic vacuolation, moderate							1/4	2/6
__cyst, very slight					1/4	1/4		1/5
__cyst, slight							2/4	
__cyst, moderate								1/5
__endometrial proliferation, very slight						1/4	2/4	
__endometrial proliferation, slight					2/4	2/4	1/4	1/5
__endometrial proliferation, moderate								2/5
__late metestrus					1/4		3/4	4/6
__early metestrus						3/4		
__estrus/early metestrus					1/4			
__early proestrus					1/4	1/4		1/6
__estrus					1/4			
__early anoestrus							1/4	

Vagina								
__late metestrus					1/4		3/4	5/6
__early metestrus						3/4		
__estrus/early metestrus					1/4			1/6
__early proestrus					1/4	1/4		
__estrus					1/4			
__anestrus							1/4	
Prostate								
__increased mitotic cells, slight				1/6				
__increased apoptosis, very slight				1/6				
__increased apoptosis, slight		4/4	4/4	2/6				
__epithelial sloughing, very slight			2/4	2/6				
__epithelial sloughing, slight			1/4					
__increased pigment macrophages, very slight		1/4		2/4				
__increased pigment macrophages, slight			1/4					
__secretion reduced, slight		1/4		1/6				
__secretion reduced, moderate			1/4					
__secretion reduced, marked		3/4	2/4					
__secretion reduced, very marked			1/4	5/6				
__epithelial atrophy, very slight				1/6				
__epithelial atrophy, slight		1/4						
__epithelial atrophy, moderate			1/4					
__epithelial atrophy, marked		3/4	2/4					
__epithelial atrophy, very marked			1/4	5/6				
__mineralized secretion, very slight				2/6				
__mineralized secretion, slight		1/4						
Testes								
__bilateral tubular degeneration, marked			1/4					
__bilateral tubular degeneration, very marked		1/4						
__multinucleate giant spermatids, very slight	3/4	2/4	1/4	3/6				
__multinucleate giant spermatids, slight				3/6				
__multinucleate giant spermatids, moderate		1/4	1/4					
__lymphocytic/histiocytic infiltration, moderate		1/4	1/4					
recovery								
Pituitary								
__chromophobe enlargement, very slight	1/2	ne	ne	1/2	1/2	ne	ne	1/2
Thyroid								
__focal vacuolated follicular cells, very slight		ne	ne		1/2	ne	ne	1/2
__focal vacuolated follicular cells, slight	0/2			1/2				
__colloid reduced, very slight	1/2							
__colloid reduced, slight		ne	ne	2/2	1/2	ne	ne	1/2
__colloid reduced, moderate	1/2				1/2			1/2
Adrenals		ne	ne			ne	ne	
__zona glomerulosa hypertrophy, very slight				1/2	1/2			
__zona glomerulosa hypertrophy, slight	0/2			1/2				1/2
__zona glomer. incr'd cytoplasm. vac.,very slight	1/2				2/2			
__zona glomerulosa increased cytoplasm. vac., slight				2/2				
__zona glomerulosa increased cytoplasm. vac., mod.								1/2
__zona reticularis hypertrophy, moderate	0/2			1/2	0/2			0/2
__zona reticularis incr'd cytoplasm. vac., very slight								1/2
__zona reticularis increased cytoplasm. vac., slight				1/2	1/2			1/2
__zona reticularis increased cytoplasm. vac.n, mod.	0/2				1/2			
__zona fasciculata hypertrophy, slight	0/2			1/2	0/2			0/2
__cortical cell inflammatory cell infiltrate, very slight	0/2			1/2	1/2			0/2
__increased pigment macrophages, very slight				1/2				
__increased pigment macrophages, slight	0/2			1/2	0/2			1/2

Testes		ne	ne					
__focal tubular degeneration, slight				1/2				
__focal tubular degeneration, moderate	1/2							
__lymphocytic/histiocytic infiltration, slight	0/2			1/2				
__multinucleate giant spermatids, very slight	2/2			1/2				
__multinucleate giant spermatids, slight				1/2				
Epididymides		ne	ne					
__lymphocytic histiocytic infiltration, slight	1/2							
__lymphocytic histiocytic infiltration, moderate				1/2				
__ductal vacuolation, slight	0/2			2/2				
__germinal centers present, slight	1/2			0/2				
Prostate		ne	ne					
__increased mitotic cells, very slight	0/2			1/2				
__increased apoptosis, very slight	0/2			1/2				
__secretion reduced, slight				1/2				
__secretion reduced, moderate	0/2			1/2				
__epithelial atrophy, slight				1/2				
__epithelial atrophy, moderate	0/2			1/2				
Mammary glands								
__glandular development, very slight					1/1	ne	ne	2/2
Uterus								
__early proestrus					2/2	ne	ne	2/2
Vagina								
__early proestrus					2/2	ne	ne	2/2
Stomach		ne	ne			ne	ne	
__fundic glandular mineral deposits, slight	0/2			2/2	0/2			0/2
__increased mucus secretory activity, very slight	2/2				2/2			1/2
__increased mucus secretory activity, slight				1/2				1/2
__leukocyte infiltrate, very slight				1/2	1/2			2/2
__leukocyte infiltrate, moderate	1/2							
__leukocyte infiltrate, marked				1/2	1/2			

- Toxicokinetics:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.5	3	50-10	0	0.5	3	50-10
$AUC_{0\text{-}24hr}$, day 370 (ng hr/ml)	---	52025	107540	236083	---	61770	201565	300263



Key Study Findings:

At the low dose of 0.5 mg/kg/day (~50 times the Css of the clinical dose), atrophy and reduced secretions of the prostate and epididymis were observed. Very slight to slight focal vacuolation of thyroid follicular cells and very slight pituitary chromophobe enlargement (M) were also observed. Thyroid weights appeared to increase during treatment (although not significantly at this dose) and to decrease again upon recovery. A slight increase in blood glucose at day 188 was reversed by day 363. Slight increases in alkaline phosphatase and glutamyl transferase were observed. Clinical signs included pink gums and ears.

At the high dose of 10 mg/kg/day (>200 times the Css of the clinical dose, with loading blood concentrations of nearly 400 times), effects on the adrenals were observed, including increased severity of hypertrophy, vacuolation, and inflammation. Focal vacuolation of thyroid follicular cells and pituitary chromophobe enlargement were observed in both males and females. Increased severity of inspissated gall bladder secretions, focal apoptosis of pancreatic acinar cells (M) and focal siderosis of the spleen (F) were noted. Increased hepatocellular hypertrophy, centrilobular leukocyte infiltration, and effects on stomach secretion were observed. Slightly increased kidney cortical tubular pigmentation and peripheral cell axonal cell degeneration were observed in males. Very slight focal spinal mineral deposits and slight meningeal hyperplasia were observed in a few animals. Cholesterol and triglycerides decreased while blood glucose levels increased. Alkaline phosphatase and glutamyl transferase increased along with liver weights (M). Female reproductive organs showed an increased incidence of late metestrus. Slight effects on red blood cell parameters were observed. Clinical signs included neurological signs (unsteady gait, subdued behavior, lack of coordination, convulsions), thinness, salivation, and cold ears. Cardiology measurements were inconclusive since 4/8 high dose males and 5/8 females exhibited wandering pacemaker and 1 of 8 high dose females experienced an incidence of sinus arrest before the initiation of dosing. Although extended sinus (wandering pacemaker) arrhythmia was later observed in 2/8 males and 1/7 females, the effect could not be definitively attributed to the drug. No treatment related effects were observed in the low or mid dose groups. (Note: A human QT study at the maximally tolerated dose was conducted.)

No effects were observed following the recovery period except decreases in prostate size and secretion and thinness of some high dose males.

Histopathology Inventory for NDA #21319

Study	R40184		D21025	
Species	Rat	Mouse	Dog	
Adrenals	X	X	X	
Aorta	X	X	X	
Bone Marrow smear	X	X	X	
Bone (femur)	X	X	X	
Brain	X	X	X	
Cecum	X	X	X	
Cervix	X	X		
Colon	X	X	X	
Duodenum	X	X	X	
Epididymis	X	X	X	
Esophagus	X	X	X	
Eye	X	X		
Gall bladder		X	X	
Gross lesions	X	X	X	
Harderian gland	X	X		
Heart	X	X	X	
Ileum	X	X	X	
Jejunum	X	X	X	
Kidneys	X	X	X	
Lachrymal gland			X	
Larynx	X	X	X	
Liver	X	X	X	
Lungs	X	X	X	
Lymph nodes	X	X		
Lymph nodes, cervical			X	
Lymph nodes, mesenteric			X	
Mammary Gland	X	X	X	
Nasal cavity	X	X		
Optic nerves	X	X		
Ovaries	X	X	X	
Pancreas	X	X	X	
Parathyroid	X	X	X	
Peripheral nerve	X	X	X	
Pharynx	X	X		
Pituitary	X	X	X	
Prostate	X	X	X	
Rectum	X	X	X	
Salivary gland	X	X	X	
Sciatic nerve	X	X		
Seminal vesicles	X	X		
Skeletal muscle	X	X	X	
Skin	X	X	X	
Spinal cord	X	X	X	
Spleen	X	X	X	
Sternum	X	X		
Stomach	X	X	X	
Testes	X	X	X	
Thymus	X	X	X	
Thyroid	X	X	X	
Tongue	X	X	X	
Trachea	X	X	X	
Urinary bladder	X	X	X	
Uterus	X	X	X	
Vagina	X	X	X	
Zymbal gland	X	X		

GENETIC TOXICOLOGY: (also see attached previous review).

Summary: Dutasteride was shown to be non-genotoxic in the following assays:

Species tested	Assay	Results
Gl198745X (parent drug)	Ames assay	negative
Gl198745X (parent drug)	Chromosome aberration assay (CHO cells)	negative
Gl198745X (parent drug)	Micronucleus assay (Wistar rats)	negative
Gl201448X (dihydro metabolite)	Mini-well Ames assay	negative
GW702541X (4-OH metabolite)	Ames assay	negative

Study title: Gl201448X: (non-GLP Screening Assay) Salmonella E.Coli/Microsome Reverse Mutation Miniscreen Assay
Study no: V40957
Study type: Ames test (mini-well)
NDA amendment, Volume #1, and page #74
Conducting laboratory and location: **not reported**
Date of study initiation: 22 June 2001
GLP compliance: no
QA reports: yes ( ) no (x)
Drug: Batch/lot# U3819/84/1, 97.8% pure
Formulation/vehicle: [redacted]

Methods:

Strains/species/cell line: *S.typhimurium* strains TA98, TA 100, TA 1535, TA 1537 and *E.coli* WP2*uvr*A (pKM101) (TA 1535 and TA 1537 were tested in 6 well plates and others in 12 well plates)
Dose selection criteria:

Precipitation was observed in 12 well plates at 400 µg/well and in 6 well plates at 800 µg/well (presumably at twice the volume, although assay volume was not reported)

Metabolic activation system: rat liver S9, inducer not reported
Controls:

Vehicle: [redacted]
Negative controls: DMSO (20 µl in 12 well plates and 40 µl in 6 well plates
Positive controls: (-S9) 0.4 µg/well 2-nitrofluoriene in TA98, 0.5 µg/well sodium azide in TA100, 1.0 µg/well sodium azide in TA1535, 40 µg/well 9-aminoacridine in TA1537, 0.5 µg/well 1-ethyl-3-nitro-1-nitroguanidine in WP2*uvr*A (pKM101) and (+S9) 0.5 µg/well benzo[a]pyrene in TA98, 0.5 µg/well 2-aminoanthracene in TA100 and WP2*uvr*A (pKM101), 1.0 µg/well 2-aminoanthracene in TA1535 and TA1537

Exposure conditions: not reported
Analysis:

No. of replicates: 2 wells

Summary of individual study findings:

Study validity: Positive and negative controls responded as expected. However, no protocol was given and no study facility was identified.

Study outcome: No increase in the number of revertants over controls was observed at any dose of Gl201448, and therefore it was concluded to be non-mutagenic under the conditions of this assay.

Study title: GW702541X: *Salmonella* and *E.coli* / Microsome Standard Plate Incorporation Assay
Study no: V40926
NDA Amendment, Volume #1, and page #76
Conducting laboratory and location: Glaxo Wellcome Inc., Medicines Safety Evaluation Division and Bioanalysis and Drug Metabolism Division, 5 Moore Drive, Research Triangle Park, NC 27709 USA
Date of study initiation: 25 April 2001
GLP compliance: yes
QA reports: yes (x) no ( )
Drug: batch # R7094/6/3, purity not reported
Formulation/vehicle: [redacted]

Methods:

Strains/species/cell line: *S.typhimurium* strains TA98, TA 100, TA 1535, TA 1537 and *E.coli* WP2*uvr*A (pKM101)
Dose selection criteria:
A maximum of 5000 µg/plate was tested.
Metabolic activation system: S9 liver fraction from [redacted] treated S.D. rats
Controls:
Vehicle: [redacted]
Negative controls: DMSO, 100 µl/plate
Positive controls: (-S9) 20 µg/plate 2-nitrofluoriene in TA98, 2.5 µg/plate sodium azide in TA100 and TA 1535, 100 µg/plate 9-aminoacridine in TA1537, 2.5 µg/plate 1-ethyl-3-nitro-1-nitroguanidine in WP2*uvr*A (pKM101) and (+S9) 2.5 µg/plate benzo[a]pyrene in TA98, 2.5 µg/plate 2-aminoanthracene in TA100, TA1535, and TA1537, 5.0 µg/plate 2-aminoanthracene in WP2*uvr*A (pKM101)
Exposure conditions:
Incubation and sampling times: Cultures were incubated for 72 hours in a standard plate incorporation assay.
Doses used in definitive study: 0, 100, 500, 1000, 2500, and 5000 µg/plate, with precipitation observed at concentrations of test material $\geq$ 500 µg/plate.
Analysis:
No. of replicates: 2 replicates in one assay and 3 replicates in a second assay.

Summary of individual study findings:

Study validity: Positive and negative controls responded as expected.
Study outcome: No increase in the number of revertants over controls was observed at any dose of GW702541X, and therefore it was concluded to be non-mutagenic under the conditions of this assay.

Structural analyses of Gl198745X metabolites: Computerized structural analyses of Gl198735X and its metabolites did not identify any metabolite functional groups that was known to confer any new toxicity beyond that of the parent drug.

Genetic toxicology summary/conclusions:

Dutasteride parent drug Gla98745X was negative in a common battery of genotoxicity tests. In addition, it 1,2 dihydro and 4-OH metabolites were negative in the Ames or abbreviated Ames assay. Computerized structural analyses of Gl198735X and its metabolites did not identify any metabolite functional group that was known to confer any new toxicity beyond that of the parent drug.

Labeling recommendations:

Mutagenesis: [redacted] Dutasteride was tested for genotoxicity in a bacterial mutagenesis assay (Ames test), a chromosomal aberration assay in CHO cells, and a micronucleus assay in rats. The results did not indicate any genotoxic potential of the parent drug. Two major human metabolites were also negative in either the Ames assay or an abbreviated Ames assay.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CARCINOGENICITY:

Study title: GI198745X: 2 year oral gavage oncogenicity study in rats

Key study findings: There was a significant increase in Leydig cell tumors in male rats at 53 mg/kg/day (135 times the clinical exposure).

Study number: R40184
Volume #32, and page #1
Conducting laboratory and location: [redacted]
Date of study initiation: 17 April 1996
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: GI198745X (free base equivalents), lot #s CD0124 and MBR/019/01/01, both 97 % pure
CAC concurrence: yes

Study Type: 2-year bioassay
Species/strain: Han Wistar (Glx: Han: WIfBR) rats
Number/sex/group; age at start of study: 60/sex/group, 131-208 g (males) and 115-166 g (females), age approximately 7 weeks
Animal housing: 5/cage or individually during poor health
Formulation/vehicle: [redacted]

Doses: doses based on C_{24} rather than on nominal dose

Time table	Male (mg/kg/day)				Female (mg/kg/day)			
Week 1	begin 0	begin 10	begin 50	begin 500	begin 0	begin 2.5	begin 12.5	begin 30
Week 37	--	--	--	begin 0	--	--	--	--
Week 39	--	--	--	begin 350	--	--	--	--
Week 45	--	begin 5	begin 25	begin 175	--	begin 1.3	begin 6.3	begin 15
Week 61	--	begin 3	begin 15	begin 105	--	begin 0.8	begin 6.3	begin 15
Week 85	--	begin 1.5	begin 7.5	begin 53	--	begin 0.8	begin 6.3	begin 15

Basis of dose selection: The doses were based on a maximally tolerated blood level of 17000 ng/ml, at which non-specific, centrally mediated toxicity was observed in Han Wistar rats after 500 mg/kg/day (males) or 20000 ng/ml, 30 mg/kg/day (females) for 6 months (oral gavage).
Route of administration: oral gavage at 10 ml/kg/day
Frequency of drug administration: once daily
Dual controls employed: two identical
Satellite PK or special study group(s): 16/sex/group
Deviations from original study protocol: none significant

Results:

Mortality:

	Males (group #)					Females (group #)				
	1	2	3	4	5	1	2	3	4	5
Survival at week 104 (%)	78	82	90	82	78	70	82	82	78	70

Clinical signs: days 1-738

	Males (group #)					Females (group #)				
Oncogenicity animals	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Thin	5	7	3	8	10	10	10	6	7	10
Hunched	1	3	3	3	7	9	6	9	9	8
Head tilt	1	1	0	4	2	6	1	4	4	6
Convulsions	0	0	0	1	2	1	0	0	2	3
Alopecia	4	7	4	8	11	6	19	10	17	21
Rough hair coat	3	2	3	6	6	9	6	9	13	15
Scabs on back	0	3	2	4	7	3	5	2	4	5
Dilated pupils	1	3	0	2	4	0	0	2	2	5
Incoordination	1	3	0	6	3	7	2	4	5	7
Excess salivation	1	1	0	3	4	0	0	2	2	5
Toxicokinetic animals		**6**	**7**	**8**	**9**		**6**	**7**	**8**	**9**
Convulsions		0	1	0	0		0	1	1	0
Thin		1	4	0	0		0	2	4	2

Body weights:

	Males (group #)					Females (group #)				
g	1	2	3	4	5	1	2	3	4	5
Week 1	170	170	169	168	169	137	135	135	136	134
Week 5	303	304	297	301	299	195	195	197	202*	199
Week 13	395	402	386	395	388	230	231	235	242*	239
Week 26	465	475	454	462	454 (-3.4%)	257	260	264	272*	267
Week 35	509	519	491*	500	481* (-6.4%)	271	277	289*	294*	284
Week 36	514	524	496*	504	478* (-7.9%)	274	278	292*	293*	286
Week 37	518	530	500*	507	477* (-9.0%)	275	281	295*	296*	284
Week 38	523	533	503*	509	478* (-9.5%)	277	284	297*	296*	284
Week 39	526	538	508*	513	487* (-8.5%)	280	284	298*	297*	285
Week 40	530	542	511*	516*	494* (-7.8%)	282	287	301*	300*	287
Week 43	544	555	522*	527*	500* (-9.0%)	289	290	310*	303*	291
Week 44	546	559	523*	529*	500* (-9.5%)	291	293	312*	305*	291
Week 45	549	560	525*	530*	500* (-9.8%)	289	293	313*	306*	292
Week 52	571	581	544*	551*	524* (-9.0%)	303	307	323*	320	306
Week 60	597	605	569*	572*	542* (-9.8%)	322	326	337	335	317 (-2.2%)
Week 61	598	607	570*	572*	544* (-9.7%)	324	327	338	335	317 (-2.6%)
Week 67	615	623	585*	585*	559* (-9.7%)	335	340	351	346	323 (-4.3%)
Week 78	640	641	607*	604*	562* (-12.3%)	349	363	367	361	340 (-4.5%)
Week 84	651	648	618*	613*	569* (-12.4%)	364	383	379	373	350* (-6.3%)
Week 85	650	652	613*	610*	565* (-13.2%)	366	387	382	375	353* (-6.2%)
Week 89	660	653	626	616*	571* (-13.0%)	375	387	380	374	350* (-8.1%)
Week 104	658	641	615	606*	554* (-14.7%)	387	400	402	377	353* (-10.3%)
Week 105	655	644	614	602*	550* (-15.3%)	385	400	401	376	352* (-10.3%)
Week 106	656	648	631	598	547* (-16.1%)	386	394	389	372	358 (-8.2%)

	Males (group #)					Females (group #)				
g	1	2	3	4	5	1	2	3	4	5
Body weight gain (weeks 1-105)	484	473	445	435* (-9.1%)	380* (-20.6%)	247	266	265	240	218* (-15.0%)

Food consumption:

	Males (group #)					Females (group #)				
g	1	2	3	4	5	1	2	3	4	5
Week 1	746	763	755	744	751	551	558	559	557	559
Week 5	831	860	832	836	859	601	615	607	619	602
Week 13	794	822	783	809	819	591	620	588	607	589
Week 26	789	814	774	781	810	594	616	586	616	587
Week 35	807	820	788	776	697*	567	576	568	590	556
Week 36	795	816	787	775	699*	566	590	585	584	534*
Week 37	804	818	788	771	744*	573	607	598	592	545*
Week 38	795	813	773	755*	790	573	593	573	573	545
Week 39	796	819	779	764*	829	581	611	589	590	557
Week 40	792	820	782	771	774	586	608	593	575	566
Week 43	813	841	806	796	790	602	616	612	615	591
Week 44	803	838	803	787	782	579	606	592	604	576
Week 45	825	847	811	807	801	589	614	595	613	581
Week 52	846	878	845	821	841	640	665	653	658	645
Week 60	827	883	838	817	795	679	669	645	646	609
Week 61	830	891	843	830	803	671	687	643	654	620
Week 67	863	912	885	855	841	666	711	661	673	617*
Week 78	842	855	856	771*	736*	618	689	645	616	537*
Week 84	790	777	780	693*	663*	575	633	600	595	503*
Week 85	814	825	815	704*	676*	603	623	566	560	468*
Week 89	773	753	798	713	713	544	615	597	586	519
Week 104	659	623	738	636	588	494	575	535	511	457
Total	83037	81864	83678	81714	79481	--	64171	63405	67065	56567
Total %	--	--	101	99.1	96.4	--	--	98.8	105	88.1

Hematology: No significant treatment related changes were observed.

Gross pathology:

	Males (group #)					Females (group #)				
	1	2	3	4	5	1	2	3	4	5
Small prostate	2	1	45	46	37	--	--	--	--	--
Small seminal vesicles	6	15	57	57	54	--	--	--	--	--
Testes										
__small	4	5	3	6	14	--	--	--	--	--
__large	3	2	1	3	8	--	--	--	--	--
__red/yellow focus(i)	1	2	1	3	8	--	--	--	--	--
__contain fluid	1	2	0	2	10	--	--	--	--	--
Small epididymides	0	2	4	13	16	--	--	--	--	--

Histopathology:

Non-neoplastic:

	Males (group #)					Females (group #)				
	1	2	3	4	5	1	2	3	4	5
Prostate										
__atrophy	7	3	59	59	56	--	--	--	--	--
Seminal vesicles										
__atrophy	10	15	58	60	56	--	--	--	--	--

19 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.