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NDA20498
CASODEX

1 OF 3

NDIA 20498

CHOCODEX

NDA 20-498

OCT 4 1995

Zeneca Pharmaceuticals, Inc.
Attention: Frances M. Kelleher, Ph.D.
Manager, Drug Registration
Drug Regulatory Affairs Department
P.O. Box 15437
Wilmington, DE 19850-5437

Dear Dr. Kelleher:

Please refer to your September 14, 1994, New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Casodex® (bicalutamide) Tablets, 50 mg.

We also acknowledge receipt of your amendments dated September 19 and 20 and your revised package insert dated October 4 (telefacsimile), as amended October 4 (telefacsimile), 1995, submitted in response to our approvable letter dated September 14, 1995.

This application provides for the use of Casodex® (bicalutamide) Tablets in combination therapy with an LHRH analogue in the treatment of advanced prostate cancer.

We have completed our review of this application under the policies and procedures reflected in the accelerated approval regulations published in Title 21 of the Code of Federal Regulations (CFR), part 314, subpart H, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated October 4, 1995. Accordingly, the application is approved effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations. In particular, we remind you that all promotional materials must be submitted at least 30 days prior to the intended time of initial dissemination of the labeling or the initial publication of the advertisement. Please submit one copy to NDA 20-498 and a second copy directly to the Division of Drug Marketing, Advertising, and Communications. Such submissions should be prominently labeled "Accelerated Approval Materials."

Products approved under the accelerated approval regulations (§314.510) require further adequate and well-controlled studies to verify and describe clinical benefit. The study underway that could provide such verification is study 7054US/0001. We acknowledge and concur with your accelerated approval post-marketing commitments as stated in the telephone conversation on September 14, 1995, between Mr. Anthony Rogers and others of your office and me. Your commitments are as follows:

1. For study 7054US/0001:
 - a. Within 3 to 6 months of completion of the study, defined as the achievement of a 50% mortality rate in all arms (to ascertain median survival time of the treatment in the various arms), you will provide FDA with a study report of the key analyses of effectiveness and safety, along with corresponding data sets. In advance of the completion of the study, you will seek FDA agreement on the specific efficacy and safety analyses to be conducted.
 - b. Quarterly updates on the progress of the study will be submitted to the FDA that include total number of deaths, patients lost-to-follow-up, and patients discontinuing drug. Safety reporting should continue under the usual IND clinical practice requirements as provided for by 21 CFR 312.32 and 312.33.
2. If study 7054/US0001 does not provide verification of clinical benefit to conclude that the drug is safe and effective for an intended use, you will comply with the accelerated approval withdrawal procedures described in 21 CFR 314.530. Additional studies, including treatment IND protocols, could proceed after such a withdrawal if the data supported continued trials.
3. It is the understanding of Zeneca and the FDA that at the completion of study US0001 and following the presentation of data to the FDA and the appropriate FDA advisory committee, the decision whether to grant full approval or to continue accelerated approval status will be evaluated based on efficacy and safety from this trial.

Interim and final reports should be submitted to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

The final printed labeling (FPI) must be identical to the October 4, 1995, draft labeling. Marketing the product with FPI that is not identical to this draft labeling may render the product misbranded and an unapproved new drug. Please submit 16 copies of the FPI as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-498. Approval of this labeling by FDA is not required before it is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions concerning this application, please contact:

Lana L. Pauls, M.P.H.
Consumer Safety Officer
301-443-3510.

Sincerely yours,

A handwritten signature in cursive script, followed by the date "10/14/95".

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

PROFESSIONAL INFORMATION BROCHURE

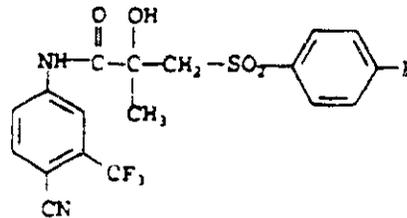
CASODEX®

(bicalutamide) TABLETS

FOR
AT
10/4/95

DESCRIPTION

CASODEX® (bicalutamide) Tablets for oral administration contain 50 mg of bicalutamide, a non-steroidal antiandrogen with no other known endocrine activity. The chemical name is propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (+). The structural and empirical formulas are:



Bicalutamide has a molecular weight of 430.37. The pKa is approximately 12. Bicalutamide is a fine white to off-white powder which is practically insoluble in water at 37°C (5 mg per 1000 mL), slightly soluble in chloroform and absolute ethanol, sparingly soluble in methanol, and soluble in acetone and tetrahydrofuran.

CASODEX is a racemate with its antiandrogenic activity being almost exclusively exhibited by the R-enantiomer of bicalutamide; the S-enantiomer is essentially inactive.

The inactive ingredients of CASODEX Tablets are lactose, magnesium stearate, methylhydroxypropylcellulose, polyethylene glycol, polyvidone, sodium starch glycolate, and titanium dioxide.

CASODEX®
(bicalutamide) TABLETS

Page 2

CLINICAL PHARMACOLOGY

Mechanism of Action: CASODEX is a non-steroidal antiandrogen. It competitively inhibits the action of androgens by binding to cytosol androgen receptors in the target tissue. Prostatic carcinoma is known to be androgen sensitive and responds to treatment that counteracts the effect of androgen and/or removes the source of androgen.

In clinical trials with CASODEX as a single agent for prostate cancer, rises in serum testosterone and estradiol have been noted. When CASODEX is combined with luteinizing hormone-releasing hormone (LHRH) analogue therapy, CASODEX does not affect the suppression of serum testosterone induced by the LHRH analogue.

Pharmacokinetics

Absorption: Bicalutamide is well-absorbed following oral administration, although the absolute bioavailability is unknown. Co-administration of bicalutamide with food has no clinically significant effect on rate or extent of absorption.

Distribution: Bicalutamide is highly protein-bound (96%). See Drug-Drug Interactions below.

Metabolism/Elimination: Bicalutamide undergoes stereospecific metabolism. The S (inactive) isomer is metabolized primarily by glucuronidation. The R (active) isomer also undergoes glucuronidation but is predominantly oxidized to an inactive metabolite followed by glucuronidation. Both the parent and metabolite glucuronides are eliminated in the urine and feces. The S-enantiomer is rapidly cleared relative to the R-enantiomer, with the R-enantiomer accounting for about 99% of total steady-state plasma levels.

Special Populations

Geriatric: In two studies in patients given 50 or 150 mg daily, no significant relationship between age and steady-state levels of total bicalutamide or the active R-enantiomer has been shown.

Hepatic Insufficiency: No clinically significant difference in the pharmacokinetics of either enantiomer of bicalutamide was noted in patients with mild-to-moderate hepatic disease as compared to healthy controls. Patients with severe liver disease have significantly longer half-life values for the R-enantiomer.

Renal Insufficiency: Renal impairment (as measured by creatinine clearance) had no significant effect on the elimination of total bicalutamide or the active R-enantiomer.

CASODEX®

(bicalutamide) TABLETS

Page 3

Women, Pediatrics. Because of the mechanism of action and the indication, bicalutamide has not been studied in women or pediatric subjects.

Drug-Drug Interactions: Clinical studies have not shown any drug interactions between bicalutamide and LHRH analogues (goserelin or leuprolide). There is no evidence that bicalutamide induces hepatic enzymes. *in vitro* protein-binding studies have shown that bicalutamide can displace coumarin anticoagulants from binding sites. Prothrombin times should be closely monitored in patients already receiving coumarin anticoagulants who are started on CASODEX.

Pharmacokinetics of the active enantiomer of CASODEX in normal males and patients with prostate cancer are presented in Table 1.

Table 1

Parameter	Mean	CV%	95% Confidence Interval
Normal Males (n=30)			
Apparent Oral Clearance (L/hr)	0.320	32.1	0.281 - 0.358
Single Dose Peak Concentration (µg/mL)	0.768	23.2	0.702 - 0.835
Single Dose Time to Peak Concentration (hours)	31.3	46.5	25.9 - 36.7
Half-Life (days)	5.8	39.5	4.9 - 6.7
Patients with Prostate Cancer (n=40)			
CSS (µg/mL)	8.939	39.2	7.817 - 10.06

CV = Coefficient of Variation

CSS = Mean Steady State Concentration

Clinical Studies

In a large multicenter, double-blind, controlled clinical trial, 813 patients with previously untreated advanced prostate cancer were randomized to receive CASODEX 50 mg once daily (404 patients) or flutamide 250 mg (409 patients) three times a day, each in combination with LHRH analogues (either

CASODEX® (bicalutamide) TABLETS

Page 4

goserelin acetate implant or leuprolide acetate depot). At a median follow-up of 95 weeks, time to treatment failure with CASODEX-LHRH analogue therapy was not dissimilar when compared to flutamide-LHRH analogue therapy.

At the same timepoint, 130 (32%) patients treated with CASODEX-LHRH analogue therapy and 145 (35%) patients treated with flutamide-LHRH analogue therapy had died.

Quality of life was assessed with self-administered patient questionnaires on pain, social functioning, emotional well-being, vitality, activity limitation, bed disability, overall health, physical capacity, general symptoms, and treatment related symptoms. Assessment of the Quality of Life questionnaires did not indicate consistent significant differences between the two treatment groups.

INDICATIONS AND USAGE

CASODEX is indicated for use in combination therapy with a luteinizing hormone-releasing hormone (LHRH) analogue for the treatment of advanced prostate cancer.

CONTRAINDICATIONS

CASODEX is contraindicated in any patient who has shown a hypersensitivity reaction to the drug or any of the tablet's components.

CASODEX may cause fetal harm when administered to pregnant women. The male offspring of rats receiving doses of 10 mg/kg/day (plasma drug concentrations in rats equal to approximately 2/3 human therapeutic concentrations*) and above were observed to have reduced anogenital distance and hypospadias in reproductive toxicology studies. These pharmacological effects have been observed with other antiandrogens. No other teratogenic effects were observed in rabbits receiving doses up to 200 mg/kg/day (approximately 1/3 human therapeutic concentrations*) or rats receiving doses up to 250 mg/kg/day (approximately 2 times human therapeutic concentrations*). CASODEX is contraindicated in women who are, or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

WARNINGS

In clinical trials with CASODEX as a single agent for prostate cancer, gynecomastia and breast pain have been reported in up to 38% and 39% of patients, respectively.

CASODEX®
(bicalutamide) TABLETS

Page 6

human therapeutic concentrations*). There is no evidence of Leydig cell hyperplasia in patients; uterine tumors are not relevant to the indicated patient population.

A small increase in the incidence of hepatocellular carcinoma in male mice given 75 mg/kg/day of bicalutamide (approximately 4 times human therapeutic concentrations*) and an increased incidence of benign thyroid follicular cell adenomas in rats given 5 mg/kg/day (approximately 2/3 human therapeutic concentrations*) and above were recorded. These neoplastic changes were progressions of non-neoplastic changes related to hepatic enzyme induction observed in animal toxicity studies. Enzyme induction has not been observed following bicalutamide administration in man. There were no tumorigenic effects suggestive of genotoxic carcinogenesis.

A comprehensive battery of both in vitro and in vivo genotoxicity tests (yeast gene conversion, Ames, *E. coli*, CHO/HGPRT, human lymphocyte cytogenetic, mouse micronucleus, and rat bone marrow cytogenetic tests) has demonstrated that CASODEX does not have genotoxic activity.

Administration of CASODEX may lead to inhibition of spermatogenesis. The long-term effects of CASODEX on male fertility have not been studied.

In male rats dosed at 250 mg/kg/day (approximately 2 times human therapeutic concentrations*), the precoital interval and time to successful mating were increased in the first pairing but no effects on fertility following successful mating were seen. These effects were reversed by 7 weeks after the end of an 11-week period of dosing.

No effects on female rats dosed at 10, 50 and 250 mg/kg/day (approximately 2/3, 1 and 2 times human therapeutic concentrations, respectively*) or their female offspring were observed. Administration of bicalutamide to pregnant females resulted in feminization of the male offspring leading to hypospadias at all dose levels. Affected male offspring were also impotent.

*Based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient.

Pregnancy: Pregnancy Category X (see CONTRAINDICATIONS)

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CASODEX is administered to a nursing woman.

CASODEX®
(bicalutamide) TABLETS

Page 7

Pediatric Use: Safety and effectiveness of CASODEX in pediatric patients have not been established.

ADVERSE REACTIONS

In patients with advanced prostate cancer treated with CASODEX in combination with an LHRH analogue, the most frequent adverse experience was hot flashes (49%).

Diarrhea was the adverse event most frequently leading to treatment withdrawal: 6% of the patients treated with flutamide-LHRH analogue and 0.5% of the patients treated with CASODEX-LHRH analogue.

In the multicenter, double-blind, controlled clinical trial comparing CASODEX 50 mg once daily with flutamide 250 mg three times a day, each in combination with an LHRH analogue, the following adverse experiences with an incidence of 5% or greater, regardless of causality, have been reported.

Table 2
Incidence of Adverse Events
(≥ 5% in Either Treatment Group)
Regardless of Causality

Adverse Event	Treatment Group	
	Number of Patients (%)	
	CASODEX Plus LHRH Analogue (n = 401)	Flutamide Plus LHRH Analogue (n = 407)
Body as a Whole		
Pain (General)	109 (27)	93 (23)
Back Pain	62 (15)	68 (17)
Asthenia	60 (15)	69 (17)
Pelvic Pain	52 (13)	46 (11)
Infection	41 (10)	35 (9)
Abdominal Pain	33 (8)	31 (8)
Chest Pain	24 (6)	20 (5)
Headache	17 (4)	20 (5)
Flu Syndrome	16 (4)	20 (5)

CASODEX®
(bicalutamide) TABLETS

Page 9

Other less frequent (greater than or equal to 2%, but less than 5%) adverse experiences reported in the CASODEX-LHRH analogue treatment group are listed below by body system and are in order of decreasing frequency within each body system regardless of causality. Some of these are commonly reported in elderly patients.

Body as a Whole: Edema; Neoplasm; Fever; Neck pain; Chills; Sepsis

Cardiovascular: Angina pectoris; Congestive heart failure

Digestive: Anorexia; Dyspepsia; Rectal hemorrhage; Dry mouth; Melena

Endocrine: Breast pain; Diabetes mellitus

Metabolic and Nutritional: Alkaline phosphatase increased; Weight gain; Creatinine increased; Dehydration; Gout

Musculoskeletal: Myasthenia; Arthritis; Myalgia; Leg cramps; Pathological fracture

Nervous: Anxiety; Depression; Libido decreased; Hypertonia; Confusion; Neuropathy; Somnolence; Nervousness

Respiratory: Cough increased; Pharyngitis; Bronchitis; Pneumonia; Rhinitis; Lung disorder

Skin and Appendages: Dry skin; Pruritus; Alopecia; Injection site reaction

Urogenital: Urinary frequency; Urination impaired; Dysuria; Urinary retention; Urinary urgency

Abnormal Laboratory Test Values: Laboratory abnormalities including elevated AST, ALT, bilirubin, BUN, and creatinine and decreased hemoglobin and white cell count have been reported in both CASODEX-LHRH analogue treated and flutamide-LHRH analogue treated patients. Increased liver enzyme tests and decreases in hemoglobin were reported less frequently with CASODEX-LHRH analogue therapy. Other changes were reported with similar incidences in both treatment groups.

SENT BY ZENECA PHARMS DRUG REG. TO ...

CASODEX®
(bicalutamide) TABLETS

Page 11

Store at controlled room temperature, 20°-25°C (68°-77°F).

Manufactured for
Zeneca Pharmaceuticals
A business unit of Zeneca Inc.
Wilmington, DE 19850-5437 USA
by Zeneca GmbH, Plankstadt, Germany

T\CASNO8.DOC

Rev C-9 10/95 SIC XXXXX-XX

ZENECA

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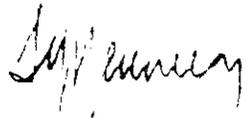
William J. Kennedy, Ph.D.
Vice President
Drug Regulatory Affairs Department

SEP 14 1994

Re: CASODEX[®] (bicalutamide)
NDA 20-498

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of Zeneca Pharmaceuticals Group, a Business Unit of Zeneca Inc., that we did not and will not use in connection with this application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,



William J. Kennedy, Ph.D.

WJK/jr 19795

August 22, 1995

Memorandum

To: NDA 20498 Casodex (bicalutamide)

From: Solomon Sobel M.D. Director DMEDP

Subject: Approvability of the NDA

AS 8/22/95

There are a number of issues to be addressed

1. The reason why this application was filed despite the submission of only one pivotal study.

On October 20, 1994 a 45-day meeting was held to determine the filability of this application. The medical officer argued that the toxicity data promised to be much better than flutamide in regard to hepatotoxicity.

The potential public health benefits were such that it was acceptable to allow the sponsor to submit one study. It was understood that the benefit of bicalcutamide over flutamide would have to be clearly demonstrated. The study also was substantial in numbers --over 800 patients.

2. The acceptability of a surrogate endpoint to enable an accelerated approval.

An objective endpoint of progression and treatment failure would serve as the surrogate endpoint. An extension of the investigation into phase 4 would serve to corroborate at least equivalent mortality benefits.

This use of a surrogate endpoint in a serious disease is consistent withn the stipulations of the accelerated approval regulation.

3. The applicability of a not yet mature endpoint in respect to mortality.

Only about 33% of the patients have died. The estimated hazard ratio at this point is 0.88 favoring Casodex (over flutamide) with a 95% confidence interval of 0.69, 1.11.

A 50% mortality endpoint would be more robust. However, it is very unlikely that the trends would reverse in favor of flutamide at a greater than 25% level(that is, to upper bound confidence interval of 1.25)-the prospectively defined clinically significant difference.

Conclusion: I recommend that this NDA be considered for approval under the accelerated approval regulation.

A statistical analysis of the data in respect to treatment failure indicates that the casodex-LHRH arms are superior to the flutamide-LHRH arms.

solomon sobel
Solomon Sobel

cc. NDA 40011

HFD-510

HFD-510/JT OWS/COOM/AP/COM/CL/PAUL

HFD-500/LA/PA/BJ/BUSTAN

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-498 Trade (generic) names ASODEX (DIPALUTAMIDE)

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&W studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

1 Casodex (bicalutamide review)

1.1 Medical Officer's Review

1.1.1 NDA #20-498

1.1.2 M.O. Review

1.1.3 Submission : September 14, 1994

1.1.4 Review completed: June 22, 1995

1.2 Drug name

1.2.1 Generic name

bicalutamide (176,334)

1.2.2 Proposed trade name

Casodex®

1.2.3 Chemical name

propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (+-).

Bicalutamide has a molecular weight of 430.37. Bicalutamide is a fine white to off white powder which is practically insoluble in water at 37°C (5 mg per 1000 mL), slightly soluble in chloroform and absolute ethanol, sparingly soluble in methanol, and soluble in acetone and tetrahydrofuran.

Casodex has two enantiomers, the R form is thought to be primarily responsible for the antiandrogenic activity. At steady state, the active R-enantiomer accounts for 99% of the circulating plasma bicalutamide concentration. Bicalutamide is highly protein bound (96%). On daily administration, the R-enantiomer accumulates about 10-fold in plasma, consistent with an elimination half-life of approximately 1 week. The S-enantiomer is very rapidly cleared relative to the R-enantiomer. The long half-life of the R-enantiomer makes CASODEX suitable for once-daily dosing. At the 50 mg/day dose, the pharmacokinetics of the R-enantiomer are unaffected by age, renal impairment, or mild to moderate hepatic impairment. Patients with severe hepatic impairment eliminate the R-enantiomer from plasma more slowly. Bicalutamide is extensively metabolized via both oxidation and glucuronidation with renal and biliary elimination of the metabolites.

1.3 Sponsor - Zeneca Pharmaceuticals Group

1.4 Pharmacologic Category - Nonsteroidal Antiandrogen

1.5 Proposed Indication:

The sponsors believes that the proposed indication is for the treatment of Prostate Cancer in combination therapy with either an LHRH analog or surgical castration for the treatment of advanced prostate cancer. However the pivotal trial demonstrates efficacy only for use with medical castration.

1.6 Dosage Form and Route of Administration:

oral 50 mg per day

1.7 NDA Drug Classification - P

1.8 Important Related Drugs: nonsteroidal antiandrogens, e.g., flutamide) an

2 Table of Contents (use decimal system to number pages)

Page	
1	1 Title and General Information
	1.4 Pharmacologic Category:
	1.5 Proposed Indication:
	1.6 Dosage form
	1.7 NDA Drug Classification
	1.8 Important Related Drugs
2	2 Table of Contents
2	3 Material Reviewed
3	4 Chemistry
3	5 Animal Pharmacology Toxicology
4	6 Clinical Background
14	7 Description of Clinical Data Sources
15	8 Clinical Studies
16	8.1 Trial # 7045US/0001
29	8.2 Trial # 176334/0301
36	8.3 Misc. Studies
36	9 Overview of Efficacy
	10 Overview of Safety
41	12 Conclusions
42	13 Recommendations

3 Material Reviewed:

Integrated Summary of Safety Information Volume 1.100 1.105
 Integrated Summary of Benefits and Risks of the Drug Volume 1.105
 Clinical Trial Reports for the following trials:

Report	Volume	Date*
0001	1.64 1.77 and 1.10 1.121	9/24/93#
0002/0003/0005	1.78 1.87	3/4/93#
0006	1.88	7/25/90
0007	1.89	12/21/90
0010	1.90	5/24/90
0201/0202/0203	1.99+	9/10/90
0204/0205	1.93 1.96	11/21/93
0301	1.122 1.125	9/13/91#
0302	1.126 1.129	6/1/93
0303	1.130 1.136	10/7/91
0306	1.138 1.143	6/30/93
0307	1.144 1.155	6/30/93
0308	1.92	7/9/93
7054US/0002	1.60	12/21/91
7054IL/0003	1.61 1.62	6/7/94
7054IL/0005	1.57 1.58	9/25/93

*Date refers to when trial was completed, except where trial recruitment completion date is given.

#Date refers to when trial recruitment was completed.

+Summary only; report was submitted to the IND.

Refer also to INDs

- 4 Chemistry
see chemistry review
- 5 Animal Pharmacology
see Pharmacology review

The sponsor states that Casodex binds to rat prostate and pituitary androgen receptors with an affinity of approximately 1/50th of the naturally occurring 5- α dihydrotestosterone. It is reported to have an affinity for the prostate androgen receptor of around 4-fold higher and for the pituitary androgen receptor of 10-fold higher than hydroxyflutamide.

Inhibition of the growth of seminal vesicles and ventral prostate gland have been demonstrated in immature castrated rats with a minimum effective dose of about 0.5 mg/kg of CASODEX. This appears to be at least as effective as flutamide.

Prostate and seminal vesicle atrophy were observed in intact pubertal and mature rats. Prostate atrophy was observed in the dog with no effect on testicular weight. In the rat, CASODEX was approximately 5 times more potent than flutamide which also caused significant rises in serum LH and testosterone, not observed with CASODEX. Studies with tritium-labeled CASODEX showed that the drug accumulates in the target organs (ventral prostate and seminal vesicles) and organs of

excretion (liver and kidney) but is excluded, relative to serum concentrations, from the hypothalamus and cerebral cortex. Since the hypothalamus is the major site of the negative feedback effect of androgens, the relative exclusion of CASODEX from this tissue may explain the peripheral selectivity seen in rats.

The liver profile of antiandrogens is a very important safety consideration. Casodex is known to cause liver tumors in the mouse at high dose in the males; and induces hepatic enzymes in the rat and dog. The sponsor believes that this is a much lower dose than to treatment patients (approximately 1 mg/kg/day).

6 Clinical Background

- Incidence and prevalence of prostate cancer today

The incidence of cancer of the prostate has reached an estimated rate of 22% of all malignancies in men (1991). By the age of 50 up to 30% of men are found to have cancer of the prostate. The incidence for white males is estimated to be 88/100,000 white men and 132/100,000 for black men. The mortality rate in the black population is almost double that for white males. In the year 1992 there were 34,999 deaths from prostate cancer and 46,300 deaths for Breast cancer (American Cancer Society). Although geographic differences in prostate cancer are known to exist no clear cause for this difference is known. Androgens and age are the only important risk factors. Family of origin, e.g. father, brother or cousin with prostate cancer, are also strong risk factors. This is why guidelines for prostate cancer screening suggest a Digital Rectal Exam (DRE) and Prostate Specific Antigen (PSA) starting at the age of 50 for white males, 45 for black men and those with a positive family history for cancer. Familial prostate cancer may account for 9% of prostate cancer with an earlier age of onset of disease, and multiple affected family members (Carter, 1992)

- Staging of Prostate Cancer

In the U.S. the usual stage system for prostate cancer is the Whitmore-Jewett classification. World-wide the more common classification is the American Joint Committee for Cancer (AJCC) system. Stage A is not identified on examination but depends on biopsy or a post-surgery finding; Stage B is palpable and confined to the prostate; Stage C is locally advanced to contiguous structures: bladder, seminal vesicles, and prostatic capsule; and Stage D is outside the adnexal area. It is estimated that 25% of patients with newly diagnosed prostate cancer will present with Stage D₂ disease. This submission concerns clinical studies for palliative treatment in men with Stage D₂ prostatic cancer. This is

disease defined as outside the pelvis in distant lymph nodes, bone or other organs.

Most patients presenting with symptomatic disease generally have cancer spread outside of the prostate gland and are incurable. The responses to androgen deprivation therapy are not durable and the cancers become hormone-refractory (Garnick, 1993). 75% of patients diagnosed with prostate cancer have clinical stage C or D disease at the time of initial diagnosis. The five year survival rate with treatment is approximately 72% for stage C disease. Stage D₁ have a 5 year survival rate of 58% and Stage D₂ disease have a median survival rate of 2.5 years. (J Urol 1991. 146: 96-98.)

- Treatment of prostate cancer:

Metastatic PCA must still be considered to be incurable. The purpose of treatment is to improve quality of life, time to progression and perhaps survival. 70% of men with metastatic diseases treated with androgen deprivation will experience a symptomatic and often a clinical regression with androgen deprivation - but most will relapse within 18 to 24 months. Median life expectancy at time of progression is 6 months or less. It is not clear whether the quality of life is extended by any of these treatments. There have been no advances in the treatment of Stage D since 1940 and the first hormone deprivation by bilateral orchiectomy. Subsequently diethylstilbesterol (DES) was used. In 1984 Leuprolide was first approved for medical castration but orchiectomy has remained the gold standard and the most economical approach. Labrie and the European community were the first proponents of blockade of the adrenal androgens; this concept was the basis of the NCI 0036 studies comparing leuprolide with flutamide (the first nonsteroidal antiandrogen) to leuprolide with placebo. This combination therapy for total androgen blockade was approved in 1988. There is a continuing dialogue regarding the adrenal androgen contribution, the necessity of total androgen blockade and it's possible advantages and resulted in an international meta-analysis pooling comparable studies. The 1992 preliminary results of this meta-analysis included 5,353 patients from randomized studies that had at least one arm using total androgen blockade. At 5 years there was an overall reduction of 3 percent. This has probably not drastically changed since that analysis (Schroeder, 1995 - Advisory Committee)

Today there are two gonadotropins approved for medical castration: leuprolide (LUPRON - TAP) and goserelin (Zoladex - Zeneca-19-726). Leuprolide (Lupron - 19-732), with a substitution at the 6th position of GnRH, is thought to be 20

times as potent as the natural molecule. There is only one antiandrogen approved for use with a gonadotropin: flutamide (Schering). Two antiandrogens have been studied: (Zeneca) The subject of this submission is flutamide.

The **Efficacy Endpoints in Stage D prostate cancer** used in most clinical studies are:

- Regression + stabilization
- Time to progression
- Survival time

Some of the current terms and abbreviations:

PCA - prostate cancer

CAT - combined androgen treatment or

MAB - maximal androgen blockade or **TAB** Total androgen blockade - primarily aimed to prevent the effect of metabolized adrenal androgens that may be present.

PSA - prostate specific antigen

PSAD - Prostate specific antigen density

ALP - alkaline phosphatase

PAP - Prostatic acid phosphatase

Prostate specific antigen

Prostate specific antigen (PSA) has become an important marker in the management of prostate cancer patients.

- first identified 1970 - prostate tissue
- seminal plasma 1971 - rape marker - P-30 serine protease - may play a role in semen liquefaction.
- approved first for predicting relapse.
- significant overlap between BPH AND PCA; may be more specific with identification of complexed vs free forms.

PSA was first approved by FDA for the diagnosis of recurrence of prostate cancer. Not until 1994 was PSA approved for the screening of prostate cancer in previously undiagnosed patients in conjunction with digital rectal examination. Prostate specific antigen is an androgen sensitive glycoprotein and may be increased independently by androgen stimulation. In addition it appears that the prolonged exposure to a nonsteroidal antiandrogen, e.g. flutamide, results in the selective proliferation of cancer cells containing a mutant

androgen receptor that aberrantly recognizes flutamide metabolites and nonandrogenic steroids as androgenic stimuli (Sartor et al, 1994).

PSA has been developed by several methods:

Hybritech*	Tandem E Tandem R Tandem ERA
Abbott*	IMX
Ciba Corning*	ACS
Toschmedix*	AIA pack

* FDA approved

It is important to remember that there are differing forms of the PSA molecule - both free and complexed. Further elucidation of these forms may increase the sensitivity and specificity of PSA in the future. The percentage of free versus complexed may be different between benign and malignant prostate tissue. It is also expected that newer monoclonal antibodies will be more specific and sensitive. However, to date there is no definitive test separating BPH from OCA.

The major forms of PSA circulating in serum are:

- Free PSA found in much lower concentrations in serum than complexed PSA is enzymatically nonactive..
- Complexed PSA - found in serum - irreversibly and covalently bound to alpha 1 antichymotrypsin and enzymatically nonactive
- smaller quantities complexed to alpha₂ macroglobulin

These differences are important in comparing PSA assay results. One major assay may overestimate the free PSA and underestimate the complexed PSA.

ABLE AGE-RELATED PSA LEVELS (Hybritech)

PSA	AGE
0 - 2.5	40 - 49
0 - 3.5	50 - 59
0.0 - 4.5	60 - 69
0.0 - 6.5	70 - 79

PSA is not a perfect screening test for prostate cancer with up to 10% false positives. An ideal marker should have high sensitivity and specificity for distinguishing benign from malignant prostatic disease and provide prognostic information as well as improve treatment outcomes. The positive predictive value for PSA as a screening assay was only 47% . . . The margin of difference between benign and malignant is dependent on volume of tissue, grade of tissue and secretion into the plasma. Early detection has not yet been demonstrated to improve survival for men with prostate cancer. (for further information see Assessment, Office of Technology, Costs and Effectiveness of Prostate Cancer Screening Elderly Men. Congress of the U.S., 1995. OTAA-BP-H-145.)

PSA REDUCTION (RESPONSE) AND PSA PROGRESSION (RELAPSE)

Castration, medical or surgical, initiates extensive apoptosis of the secretory epithelial cells lining the ducts of the rat ventral prostate resulting in the striking reduction of male sexual accessory tissue.

Since PSA expression is influenced predominantly by androgens, the mutation of the androgen receptor appears to occur as prostate cancer cells less differentiated and may affect the expression of the PSA gene. Therefore, the elevation of PSA may not only signal relapse and progression of prostate cancer but also signal receptor mutation and an agonist effect of the antiandrogen.

FACTORS THAT DETERMINE SERUM PSA IN MEN WITH PROSTATE CANCER;

- Number of viable normal prostatic epithelial cells and the extent of differentiation of neoplastic Prostatic epithelial cells
- hormonal milieu
- architectural integrity of the prostate gland location of malignant prostatic epithelium -intraprostatic or metastatic.
- Rate of marker clearance.

A PSA increase is the first sign of progression after treatment in those patients with prostate cancer that secrete prostate specific antigen and a reduction in PSA is an indication of an apoptotic response by the prostate cancer cells. Elevation of PSA allows for identification of relapse at an earlier time than otherwise clinically evident. It is important to remember that poorly differentiated prostate cells may lose this ability to manufacture and secrete PSA. There appears to be an inverse relationship between

histologic grade of the tumor and PSA production (Partin). It has been suggested that if the PSA decreases to less than 10 ng/ml at 6 months, the time to progression was 22.7 months and survival was 33.2 months; if the 6 month PSA exceeded 10 ng/ml time to progression was 12.5 and survival 18.8 months (Stamey). This work still needs to be confirmed.

The decline of PSA > 90% is thought to predict a prolonged progression free survival. A rise in PSA within the limits defined in the criteria for progression may be an indication for a change in therapy. It has recently been estimated by Soloway (1994 - preliminary report) that responders after treatment with the lowest PSA (< 4) and a decrease in maximum PSA level by 95% or greater from baseline will have the best progression free intervals.

An example of this is seen in the percent reduction of PSA after 3 months of different doses of bicalutamide compared with surgical castration or flutamide as monotherapy (Dennis, Cancer supplement Dec 15, 1993 - 3890).

TABLE - PSA LEVELS NOTED WITH ANDROGEN DEPLETION
From Cancer 1993

Bicalutamide monotherapy	10 mg	30 mg	50 mg	100 mg	150 mg
% PSA decline	57%	73%	90%	97%	97%
	Surgical castration	97%			
	Flutamide monotherapy	73%			

PERCENTAGE OF PSA AFTER THREE MONTHS CASODEX MONOTHERAPY
(sponsor's data)

Bicalutamide monotherapy DOSE	%PSA DECLINE	%PSA REMAIN	N=	study
10 MG	55.3	45.7	14	02
30 MG	72.1	27.9	10	02
50 MG	84.4	15.6	780	02, 201, 202, 203, 204, 203, 301, 302, 303
100 MG	91.8	8.2	202	305, 306, 307
150 MG	93.2	6.8	792	305, 306, 307
200 MG	94.8	5.2	29	5
300 MG	93.8	6.2	4	9

FROM Zeneca Presentation Summary TABLE I APRIL 28, 1995

150 MG CASODEX

Bicalutamide monotherapy VS Castration	%PSA DECLINE	%PSA REMAIN	N=	PROTOCOL 306 AND 307
150 MG	92.7	7.3	747	
CASTRATION	94.9	5.1	360	

The role of Androgens and PCA

The advantage of antiandrogen therapy is the ability to block the action of androgens both from the testes and the adrenal glands. In 1982, Labrie et al first reported the concept of combination therapy for the treatment of prostate cancer, which involves combining antiandrogen therapy with castration to achieve MAB. This was the first therapeutic approach possibly improving progression and survival of advanced prostate cancer since the initial description of hormone manipulation in 1941 (Huggins and Hodges 1941; Huggins et al 1941).

When given as monotherapy, antiandrogens compete with relatively high concentrations of testosterone for binding to the androgen receptor. Castration removes testicular androgens (approximately 90% of circulating androgens), and combining castration with an antiandrogen permits only low levels of androgen produced by the adrenal glands to compete with the antiandrogen for receptor binding.

Androgen withdrawal and sequelae:

Androgen withdrawal and subsequent cellular apoptosis ultimately results in the relative enrichment of tumors with cells that are more undifferentiated and less responsive to hormonal therapy. Testosterone serum levels have been the gold standard of monitoring castration. Approximately 5 - 7% of the circulating androgens are of adrenal source. If one assumes that castration removes all androgens to the prepubertal status a level of 20 ng/dL (Tanner 1-2) should be attained. If one considers the contribution of the adult adrenal it is reasonable to consider a circulating testosterone level up to 40 ng/dL reflecting the metabolism of DHEA to T and DHT. Antiandrogens, unlike the downregulation of gonadotropins, do not decrease androgen levels but rather increase the serum testosterone by approximately 80% (seen in clinical monotherapy bicalutamide trials). The effects of this elevated testosterone on prostate cancer are not understood. Several investigators believe that intermittent therapy is more appropriate using PSA normalization as a marker both for response and

progression. This possible benefit has not yet been evaluated in clinical studies (Bruchovsky)

Monotherapy antiandrogen is always associated with elevated estrogens and breast changes, e.g. gynecomastia, or breast pain. This is probably a reflection of the increased aromatization of testosterone. One case of breast cancer with flutamide has been reported.

Antiandrogens appear to be associated with changes in liver profile. Hepatitis or marked increases in liver enzymes leading to discontinuation occurred in 1% of nilutamide patients in controlled clinical trials with one death related to liver disease. The sponsor notes that in study 908 Between 7 and 11% versus 4% placebo patients had SGOT and SGPT values more than twice the upper limit of normal and in study 606 there were SGOT and SGPT values elevated 20% versus 15%. Flutamide is also associated with fatal liver toxicity.

6.1 relevant human experience

- Review of nonsteroidal antiandrogens

- FLUTAMIDE - Eulexin

The active form is hydroxyflutamide which is thought to be twice as potent as Cyproterone acetate (CPA). It has a short half life of 5 - 6 hours. The dose is 250 mg tid for a total of 750 mg per day. The safety profile has been disappointing. There have been 20 reported deaths from hepatotoxicity and 26 patients who were hospitalized with serious hepatotoxicity. Other adverse events associated with flutamide are diarrhea and "flutamide-withdrawal syndrome". The latter defined first by Sher reflects the agonist effect of flutamide on the androgen receptors that are perhaps mutated. Flutamide is marketed under many names around the world and at least two forms which are not bioequivalent.
Drogenil, Euflex, Eulexin, Eulexine, and Fugerel

	BICALUTAMIDE	FLUTAMIDE
Status	-----	approved NDA 1989 0306
Active metabolite	R-enantiomer S- inactive	Hydroxyflutamide
relative potency		
half life	1 week	5 - 6 hours max 2 hours
Dose/day	1 per day 50 mg	750 mg 6 capsules
T levels	increase 88%	
Agonist * activity	documented	documented
safety profile	-----	hepatotoxic diarrhea/gi sx
	NDA 20-498 pending	NDA 18-854
Trade name	Casodex	Eulexin

6.2 Important information from related INDs and NDAs

INDs and
Two Open Phase II Studies to determine the safety efficacy
and long-term endocrine effects of Casodex .

volume 1.93

Volume 1.99 - combination therapy with CASODEX 50 mg
Volume 1.108 - randomized with medical castration
Volume 1.100 - integrated summary of effectiveness data

6.3 Foreign experience - approved in several countries and
pending in others.

6.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics
see pharmacology review

Study	N =
0001	22
0006	5
0007	23
0008	16
0010	28
0012	28
7045L/ 0005	35

The pharmacokinetics and metabolism of CASODEX and its two enantiomers were investigated after administration of single doses of 10 to 150 mg to healthy volunteers and patients with prostate cancer; data from daily administration of 10 mg to 200 mg bicalutamide (Casodex) were obtained from patients with prostate cancer. (R) bicalutamide was slowly absorbed and very slowly eliminated, whereas (S) bicalutamide was much more rapidly absorbed and eliminated. During daily dosing, (R) bicalutamide accumulates about 10 fold in plasma, whereas (S) bicalutamide accumulates only slightly.

Bicalutamide is excreted almost equally in urine (36%) and feces (43%) over a 9 day collection period (Trial 0006); the incomplete recovery is a consequence of the slow elimination of (R) bicalutamide from plasma. There is little evidence for the presence of metabolites of bicalutamide in the circulation; but in urine, metabolites predominate. The major urinary metabolites are the glucuronide conjugates of CASODEX and hydroxy bicalutamide. Bicalutamide and the hydroxy form are recovered in feces, probably as a result of enzyme cleavage of the corresponding glucuronide conjugates by gut flora.

6.6 Directions for Use

Bicalutamide (Casodex) is indicated for the treatment of prostate cancer in conjunction with medical castration. There is no data demonstrating efficacy with surgical castration nor is it to be used as monotherapy.

- 7 Description of Clinical Data Sources (both IND and non-IND)
 CASODEX has been investigated extensively over a 7 year period under INDS. In the CASODEX clinical trial program, worldwide, 3,521 men were exposed to CASODEX, of whom 2,938 had advanced prostate cancer.

7.1 Study Type and Design/Patient Enumeration, Demographics, Extent of Exposure

DOSE RANGING STUDIES

Study	N	DOSES
0002/3/5	350	
	45	10 MG
	54	30 MG
	140	50 MG
	45	100 MG
	66	150 MG
	29	200 MG

Patients were exposed to doses ranging from 10 mg through to 200 mg. The majority of exposures were at either 50 mg daily or 150 mg daily. At the CASODEX 50 mg dose, which is the proposed dose of The total number of patients treated in the combination therapy and monotherapy prostate cancer trials was 1478, and the total exposure at the 50 mg dose was 1270 patient years. The total number of prostate cancer patients (combination therapy and monotherapy trials, including the ongoing trials) treated with 50 mg CASODEX in the clinical program was 1557 patients

The following prostate cancer studies have been ongoing or completed:

Study	N	Dose
301**	305	50 mg#
302	245	50 mg#
303	486	50 mg#
306	468	100/150 mg#
307	985	100/150 mg#
7054/0001*	813	50 mg
ongoing studies:		
102	31	
101	231	
c-15-11	16	
c-15-21	121	
c-15-24	49	

- pivotal trial
- supporting trial
- # versus castration
- ## versus LHRH analog

The dose ranging studies were conducted only in the monotherapy trials. The data establishing the validity of PSA as an end point have been collected almost entirely in monotherapy trials. The action of bicalutamide in a combination trial is presumed the same but competing with lower concentrations of androgen due to the down regulation of androgen by the gonadotropin analog. 211 patients received bicalutamide daily in a dose-ranging study. 45 received 10 mg daily, 54 received 30 mg daily and 112 patients received a 50 mg daily dose. (see chart above)

7.2 Post-Marketing Experience - none

7.3 Literature - see appendix

8 Clinical Studies

The sponsor has submitted one pivotal trial and one supporting trial. The first trial to be started was a monotherapy trial comparing a 50 mg daily dose of bicalutamide to castration, either medical, with goserelin (Zoladex), or surgical. Early in the study it was determined that the prostate specific antigen normalization was not adequate with bicalutamide and did not match the PSA response after orchiectomy. It is not clear if the lack of equivalence to the gold standard of castration was due to the dose or the weakness of the antiandrogens. These monotherapy trials are important in providing important antiandrogen data. The pivotal trial planned by the sponsor was a combination trial with a 2 x 2 factorial design (see appendix) comparing bicalutamide/goserelin to flutamide leuprolide. The monotherapy trial (301), compared bicalutamide 50 mg to castration and is considered adequate supporting data in

addition to the pivotal trial and provides important data both as to safety and efficacy not available before.

The aim of the combination therapy trial was to demonstrate equivalence with the marketed and approved dose of flutamide to be used in conjunction with leuprolide.

- US0001 - Randomized comparative trial of Casodex versus flutamide used in combination with medical castration (ICI 176,334) in the treatment of metastatic carcinoma of the prostate (Study number 7054US/0001))

Monotherapy comparative trials: evenly distributed between drug and castration.

50 mg trials:

- 0301 - An open, multicenter, randomized study to compare the effect of orchiectomy with Casodex (ICI 176,334) in the treatment of metastatic carcinoma of the prostate (Study number 176,334/0301) (Supporting study) n= 306
- 0302 - An open multicenter, randomized study to compare the effect of castration (Medical or surgical ICI176,334) in the treatment of metastatic carcinoma of the PROSTATE (STUDY NUMBER 176,334/0302) n= 245
- 0303 - same as above n= 485

Doses > 50 mg

- 0306 - 100 mg
- 0307 - 150 mg

5 uncontrolled studies including 418 patients

- 0002, 0003, 0005, 0201, 0204, 0205 - monotherapy non-comparative
- 0401,0402,0403 - benign prostate hyperplasia
- 0002,0006,0007, 0008, 0010, 0012, IL0005 - Clinical Pharmacology studies

Mean serum testosterone concentrations increased while on bicalutamide - 50 mg increased 88% at 3 month, and 89% on 150 mg.

8.1 Trial # 001

This protocol was a 2 x 2 factorial design (four-group study). Patients were randomized to goserelin or leuprolide in a 2:1 ratio and to bicalutamide or flutamide in a 1:1 ratio. It was a double-blind study; patients were randomized

to goserelin or leuprolide in a 2: 1 ratio and to bicalutamide 50 mg oral dose once a day or flutamide 250 mg three times a day in a 1: 1 ratio. Both the antiandrogen and analog were begun on the same day. **The primary endpoint was time from randomization to treatment failure. The goal was to demonstrate equivalence of the two antiandrogen therapies in terms of time to treatment failure with a least 80% power and a one-sided alpha level of 5%.**

	CASODEX + GOSERELIN N=266	CASODEX + LEUPROLIDE N=135	FLUTAMIDE + GOSERELIN N=269	FLUTAMIDE + LEUPROLIDE N=138
N=813	N = 404 CASODEX+LHRH		N= 409 FLUTAMIDE +LHRH	
60 centers North America				
Primary investigator Shellhammer Virginia				

In order to maintain this double blind trial, the sponsor reformulated US marketed capsules of flutamide. The bioavailability of the unmarked flutamide capsule used in the clinical trials was compared with the marketed capsule by measuring 2 hydroxy-flutamide (Trial US0002). This is discussed in summary of efficacy and comparison.

8.1.1 Objective

Efficacy was analyzed on an intention to treat basis (analyzed by randomized treatment) and included all randomized patients who have documented histologic or cytologic prostate cancer and informed consent.

The endpoints on which efficacy assessed were:

- a) time to treatment failure
- b) quality of life
- c) survival time
- d) subjective response

The survival time **was** determined from the date of randomization to the date of death, or if death had not occurred at the time of analysis, to the date last known to be alive. The treatment comparison of interest is bicalutamide combination therapy versus flutamide combination therapy. The analysis will be performed using the Cox regression model, adjusting for LHRH

analog, baseline ECOG performance status, and baseline extent of disease (Soloway et al., 1988). Confidence intervals were reported for the ratio of hazard rates.

8.1.2 Design

This was a randomized, comparative, multicenter trial designed to include at least 800 evaluable patients. The study employed a 2 x 2 factorial design or four-arm study. Patients were randomized to goserelin implant or leuprolide acetate depot in a 2:1 ratio and between the two antiandrogens, bicalutamide or flutamide, in a 1:1 ratio. It was planned that there would be approximately 267 patients in each of the goserelin arms of the study and 133 patients in each of the leuprolide acetate depot arms. The two antiandrogens in this trial were blinded. Patients randomized to bicalutamide received a once daily 50 mg. dose.

Patients randomized to flutamide received 250 mg three times daily. All patients were randomized centrally at
Pre-treatment
assessments were completed and the patient evaluated as being eligible prior to randomization.

8.1.3 Protocol

Any patient entered into the study patients had to have histologically confirmed, previously untreated stage D2 prostate cancer, an Eastern Cooperative Oncology Group (ECOG) performance score of 2 or less, and a life expectancy of more than 3 months. Patients were excluded from enrollment if they had previous systemic therapy for prostate cancer, history or presence of another malignancy within the last 5 years other than prostate cancer or treated squamous (or basal) cell carcinoma of the skin. Patients were also excluded if they had any severe concomitant medical condition that would make it undesirable for them to participate in the trial or that would jeopardize compliance with the trial protocol.

Patients did not receive any concomitant medication for the treatment of prostate cancer or any medication that could affect testosterone status, except for LHRH analog therapy.

It was anticipated that there would be no interaction between the antiandrogens and the LHRH analogs, so that data may be combined to test the comparison of interest, which is bicalutamide versus flutamide in combination with an LHRH analog. The Zeneca product flutamide was tested against the marketed flutamide which included both the United States capsule and the Canadian tablet.

Measurement of outcomes:

Objective Progression

Any of the following were considered sufficient evidence for progression of disease.

--Appearance of one or more new bone metastasis on bone scan considered by the investigator to be due to metastatic disease.

--Evidence of worsening of any existing bone metastases on bone scan considered by the investigator to be due to metastatic disease.

--Appearance of one or more new extraskkeletal metastasis or increase by 25% or more (compared to the minimum dimensions recorded during the study) of any existing measurable extraskkeletal metastasis.

Stable Disease

Lack of objective progression and insufficient evidence for partial objective regression will be classified as stable disease.

Criteria for subjective response

The following criteria were identified to represent a satisfactory subjective response:

a) No increase from baseline in performance status, bone pain SCORE or analgesic score.

b) Any of the following:

--decrease from baseline in total subjective score by 3 or more (The total subjective score equals the sum of the performance status, bone pain score and analgesic scores).

--decrease from baseline in any performance score, bone pain score or analgesic score by 2 or more.

8.1.3.1 Population

The population of patients included men between the ages of 42 and 91; 71-72 % Caucasian; 23-24% Black; and 3 - 5% Hispanic. They had a mean PSA concentration of 642.16 and 715.14 and similar ranges. There appeared no differences between the patients randomized to each arm of the study. See appendix for demographics of this study.

8.1.3.2 Endpoints

The sponsor defined treatment failure as any one of the following events:

- (a) death
- (b) adverse event leading to withdrawal of trial therapy
- (c) objective progression
- (d) patient unable to continue therapy

- (e) addition of systemic or radiation therapy
- (e) investigator decision

This definition was not modified during the conduct of the trial or the analysis of trial data. Although the sponsor used multiple end points (ie, time to treatment failure, survival, quality of life, subjective response, and tolerability), the weight was appropriately placed on the primary end point of time to treatment failure. Data were also collected to evaluate the interaction of LHRH analog therapy on bicalutamide plasma levels and the interaction of bicalutamide dosing on LHRH analog efficacy, as measured by serum testosterone levels.

The sponsor notes that defining time to progression in clinical trials that evaluate initial hormonal therapies among metastatic prostate cancer patients is problematic. Patients can be withdrawn from trials for reasons other than documented progression. Reasons such as toxicity and concomitant disease exacerbation are not uncommon reasons for patients to be removed from active follow-up. As a consequence, defining an end point that captures these types of events as well as disease progression is important for the ability to provide unbiased assessments of treatment differences. The definition of treatment failure included all events that could potentially occur in the follow-up of patients under treatment. By defining time to treatment failure (TTF) as the duration of follow-up until the first event occurs allows for unbiased assessments. TTF is an appropriate end point for the assessment of the worth of therapy in stage D2 prostate cancer. Therefore, this trial was designed to demonstrate equivalence of the two antiandrogens with regard to time to treatment failure.

8.1.3.3 Statistical considerations

8.1.4 Results

8.1.4.1 Patient Disposition, comparability

A total of 813 patients, from 60 North American investigation sites, entered the trial. The distribution of patients across this large number of sites was as expected for a multicenter trial. Of these, 404 patients were randomized to bicalutamide-LHRH (268 to bicalutamide-goserelin and 136 to bicalutamide-leuprolide) and 409 were randomized to flutamide-LHRH (272 to flutamide-goserelin and 137 to flutamide-leuprolide). Three patients randomized to bicalutamide-LHRH and two to flutamide-LHRH refused their assigned therapy. Ten patients (8 bicalutamide-LHRH, 2 flutamide-LHRH) with prostate cancer did not have stage D2

disease and an additional 7 patients (2 bicalutamide-LHRH, 5 flutamide-LHRH) had previous systemic therapy; however, these patients were included in all analyses of efficacy

8.1.4.2 Efficacy endpoint outcomes

According to sponsor:

"The results, therefore, demonstrated a benefit for patients treated with bicalutamide-LHRH compared with those patients who received flutamide-LHRH therapy with regard to time to treatment failure, which was the primary end point of this study. Examination of the difference in time to treatment failure indicated both a greater number of withdrawals due to adverse events and a greater number of progression events for the flutamide-LHRH group compared with the bicalutamide-LHRH group.

The survival data is considered still too immature for any comparative conclusions.

In both treatment groups, patients improved subjectively (52 bicalutamide-LHRH, 54% flutamide-LHRH), and quality of life improved from baseline with a reduction in pain, improved physical activity, better emotional well-being, and more vitality.

Bicalutamide-LHRH therapy was associated with an improvement in time to treatment failure compared with flutamide-LHRH therapy ($p=0.005$).

Tumor flare is an important consideration in the treatment of patients with advanced prostate cancer, but an endpoint poorly documented with the initiation of therapy. In this study the sponsor states that tumor flare was infrequently reported. Tumor flare or flare was reported as an adverse event in less than 0.2% in the bicalutamide-LHRH-treated group and in 1.2% in the flutamide LHRH-treated group (1 bicalutamide-LHRH, 5 flutamide-LHRH). Cord compression, as a possible symptom of a tumor flare reaction, was reported during the first month of therapy for one patient in each treatment group. The incidence of pain, bone pain, or back pain reported during the first 35 days of study therapy, regardless of whether the event was attributed to tumor flare, was similar for both treatment groups (7% bicalutamide-LHRH, 8% flutamide-LHRH).
(Identify these patients....)

Neoplasm

Forty-two patients (21 bicalutamide-LHRH, 21 flutamide-LHRH) had either a growth of any type or, on initiation of therapy, tumor flare of their prostate cancer reported as an adverse

event, although neither event had an incidence of 5% or greater in any of the four treatment groups.

47% of 813 patients had reached a treatment failure endpoint

Bicalutamide-LHRH therapy was thought to be superior to flutamide LHRH therapy with regard to time to treatment failure. No definitive conclusions regarding survival were possible because too few patients (17%) had died.

	CASODEX + GOSERELIN	CASODEX + LEUP	FLUTAMIDE +GOSERELIN	FLUTAMIDE + LEUP
	N = 404		N= 409	
Reached treatment failure	168 (42%)		218 (53%)	
Median % PSA fall	99%		99%	
Month 3 685 pts analyzed	N=349 248 (71%)		N=336 236 (70%)	

(from Sections 4.4.1 and 4.4.2 of Integrated Summary of Effectiveness Data.)

Subjective response

ECOG performance status; assessment of pain and analgesic use
(see page 40)

Quality of life

self-administered quality of life questionnaire.

8.1.4.3 Safety comparisons

Table noting the incidence of adverse events > 5% in either treatment group regardless of causality. Incidence of Adverse Events (> 5% in Either Treatment Group) Regardless of Causality

Adverse Event

Treatment Group

Adverse Event	Number of Patients (%)		Treatment Group	
	CASODEX Plus LHRH Analogue (N = 401)		Flutamide Plus LHRH Analogue (N = 407)	
Hot Flashes	196	(49)	202	(50)
Pain (General)	109	(27)	93	(23)
Constipation	67	(17)	50	(12)
Back Pain	62	(15)	68	(17)
Asthenia	60	(15)	69	(17)
Pelvic Pain	52	(13)	46	(11)
Nausea	44	(11)	45	(11)
Infection	41	(10)	35	(9)
Diarrhea	40	(10)	98	(24)
Nocturia	35	(9)	43	(11)
Peripheral Edema	34	(8)	28	(7)
Abdominal Pain	33	(8)	31	(8)
Dizziness	30	(7)	27	(7)
Dyspnea	30	(7)	24	(6)
Hematuria	30	(7)	20	(5)
Anemia*	29	(7)	35	(9)
Urinary Tract Inf	26	(6)	24	(6)
Incr Liver Enz	25	(6)	40	(10)
Rash	25	(6)	20	(5)
Paresthesia	24	(6)	27	(7)
Chest Pain	24	(6)	20	(5)
Sweating	23	(6)	18	(4)
Flatulence	22	(5)	16	(4)
Hypertension	21	(5)	18	(4)
Impotence	20	(5)	29	(7)
Hyperglycemia	20	(5)	16	(4)
Insomnia	19	(5)	30	(7)
Gynecomastia	19	(5)	23	(6)
Bone Pain	18	(4)	26	(6)
Headache	17	(4)	20	(5)
Flu Syndrome	16	(4)	20	(5)
Weight Loss	16	(4)	20	(5)
Vomiting	12	(3)	20	(5)
Urinary Inc	9	(2)	20	(5)

- Assessment of liver function

Liver function abnormalities were thought to be reported less frequently for bicalutamide-LHRH-treated patients. 77 patients had changes in liver function tests (LFT) at least one liver enzyme test result i.e. SGOT or SGPT,

exceeding twice the upper limit of normal (28 in bicalutamide-LHRH arm and 49 flutamide-LHRH arm) exceeding twice the upper limit of normal on more than one occasion

25 patients - 8 CASODEX-LHRH and 17 flutamide-LHRH had LFT changes. Of the 25 patients 10 patients, 2 on bicalutamide-LHRH and 8 on flutamide-LHRH had liver enzymes levels which decreased while therapy continued and 3 returned to normal limits (2 on bicalutamide and 1 on flutamide).

A clinically relevant change was defined as an increase from the pretreatment value of at least 100% of the ULN for bilirubin and of at least 300% of the ULN for AST and ALT.

Six patients (Patients 013/008, 021/008, 031/006, 039/008, 040/001, and 057/007) had clinically relevant changes in liver function tests on more than one occasion and are described in more detail below (if the changes have been reported as adverse events leading to withdrawal, individual patient summaries are presented in Appendix A).

Patient 013/008 (flutamide-goserelin) had increased liver enzyme test results after approximately 6 months of study therapy and at the Month 12 visit (no assessment in between), without evidence of cholelithiasis or gross hepatic mass; however, the results for tests for hepatitis were positive. The investigator considered the increased liver enzyme test results to be possibly related to therapy while the patient's hepatitis was considered unlikely to be related to study therapy.

Patient summaries from sponsor:

Patient 021/008 (flutamide-goserelin) had increased liver enzyme test results reported as adverse events, in the absence of clinical symptoms of abnormal liver function; CT scan results indicated a normal liver. One of this patient's concomitant medications was glipizide, which occasionally causes mild to moderate increases in AST levels (Physicians' Desk Reference 1994). Clinically relevant changes were reported during the first 3 months of therapy. Glipizide therapy was discontinued at Month 2. After approximately 3 months of study therapy, liver enzyme test results decreased, although they remained above the ULN after 6 months of therapy. The investigator considered these increased test results to be probably related to study therapy, which was continued.

Patient 031/006 (flutamide-goserelin) had clinically relevant increased liver enzyme test results 2 and 3 months after the initiation of study therapy, including increased levels of AST, ALT, and bilirubin (at month 3) and a slightly increased level of alkaline phosphatase (at month 3). These test results were reported by the investigator as adverse events, in the absence of clinical symptoms of abnormal liver

function. CAT scan results indicated a normal liver, and tests for hepatitis were negative. The patient appeared jaundiced, and study therapy was withdrawn. One of this patient's concomitant medications was hydrochlorothiazide and triamterene, which occasionally causes jaundice and liver enzyme abnormalities (Physicians' Desk Reference 1994). Six months after withdrawal of study therapy, liver enzyme test results were reported to be normal (local laboratory). The investigator considered this event to be probably related to study therapy.

Patient 039/008 (bicalutamide-goserelin) had increased liver enzyme test results after his first month of study therapy. His physician was unable to find a cause and suggested mild drug induced hepatitis. The investigator considered these liver enzyme test results to be possibly related to study therapy and withdrew bicalutamide therapy after 1 month. Patient 040/001 (flutamide leuprolide) had increased liver enzyme test results 3 months after initiating study therapy (results were confirmed 1 week later). The investigator considered these results to be adverse events, without clinical symptoms of abnormal liver function. Of the medications the patient received before entering the study, the following are known to have the potential to affect liver function (Physicians' Desk Reference 1994): hydrochlorothiazide (jaundice and liver enzyme abnormalities) and verapamil (increased transaminases, without increased bilirubin). The investigator considered the increased liver enzyme test results to be related to study therapy and withdrew flutamide therapy after 3 months.

Patient 057/007 (flutamide leuprolide) had increased liver enzyme test results at Month 3. However, at visits 1 and 2 weeks after the withdrawal of flutamide, this patient still had increased liver enzyme test results. For 20 of these 26 patients, clinically relevant liver enzyme test results were reported at only one visit (although some patients had results outside the normal range, before or after these visits, with clinically relevant changes). For Patients 002/009, 016/057, and 019/030, the investigator considered the values to be the result of laboratory error because the clinically relevant changes were not consistent with other liver enzyme test results for these patients.

A total of 67 patients (16 bicalutamide-goserelin, 9 bicalutamide-leuprolide, 29 flutamide-goserelin, 13 flutamide leuprolide) had abnormal liver enzyme test results (outside the normal range or with a clinically relevant change) or abnormal liver function reported as an adverse event.

For 19 patients (3 bicalutamide-goserelin, 3 bicalutamide-leuprolide, 9 flutamide-goserelin, 4 flutamide-leuprolide),

the investigator reported the clinically relevant changes in liver enzyme test results as adverse events. For 48 patients (13 bicalutamide-goserelin, 6 bicalutamide-leuprolide, 20 flutamide-goserelin, and 9 flutamide-leuprolide), although not clinically relevant (as defined in Section 2.9.2), abnormal values (outside the normal range) for liver enzyme tests were reported by the investigator as adverse events. Note that not all values that were outside the normal ranges for liver enzyme tests (AST normal range < 1.08 mkat/l, ALT normal range < 0.92 mkat/l, and bilirubin normal range 3.4 to 23.9 mmol/l) were considered adverse events by the investigators.

Summary of liver function

In summary, approximately twice as many patients treated with flutamide LHRH (16 patients) had clinically relevant changes in liver function tests when compared with patients treated with bicalutamide-LHRH (9 patients). Also, the increases reported for these flutamide LHRH-treated patients were frequently higher (e.g., more than 5 times ULN) than those reported for bicalutamide-LHRH-treated patients. Five of the 6 patients with clinically relevant changes on more than one occasion were treated with flutamide LHRH therapy.

More adverse events related to liver function were reported for patients treated with flutamide LHRH (42 patients), compared with bicalutamide-LHRH (25 patients). Although approximately the same number of patients was withdrawn from study therapy in both treatment groups because of liver enzyme test abnormalities, flutamide LHRH-treated patients had more events judged to be severe (3) or moderate (12) compared with bicalutamide LHRH-treated patients (2 severe and 5 moderate). The number of events that were reported to be mild was approximately the same in both treatment groups. Jaundice was reported for two patients in each treatment group (bicalutamide-LHRH and flutamide LHRH).

- Gastrointestinal profile:

Diarrhea was the adverse event most frequently leading to treatment withdrawal: 6% of the patients treated with flutamide-LHRH analog and 0.5% of the patients treated with bicalutamide-LHRH analog. The lack of diarrhea with bicalutamide is a clear advantage to the patient.

- Lung disorders

No investigator reported interstitial lung disease as an adverse event for any patient. A total of 54 patients (30 bicalutamide-LHRH, 24 flutamide-LHRH) had dyspnea. Increased

cough was reported for 32 patients (17 bicalutamide-LHRH, 15 flutamide-LHRH). Nineteen patients (13 bicalutamide-LHRH, 6 flutamide-LHRH) had bronchitis reported as an adverse event. Unlike nilutamide there does not appear to be an associated pulmonary problem.

- Special senses

No investigator reported any patients who had difficulty with light-dark adaptation, although Patient 020/003 (flutamide-goserelin) had photophobia reported as an adverse event. Eleven patients did have the following vision related adverse events: amblyopia (4 bicalutamide-LHRH, 2 flutamide-LHRH), abnormal vision (2 bicalutamide-LHRH), temporary blindness (2 bicalutamide-LHRH), and visual field defect (1 bicalutamide-LHRH).

The sponsor noted that one patient reported alcohol intolerance.

- Hematuria and bleeding

A small difference in the treatment groups in the incidence of hematuria was observed (7.4% bicalutamide-LHRH, 4.9% flutamide LHRH). Because hematuria is frequently reported for patients with advanced prostate cancer, ZENECA stated that they evaluated urological symptoms to determine if these types of adverse events occurred more frequently in one of the treatment groups. The number of patients is similar in both treatment groups when the following adverse events are combined: impaired urination, urinary retention, urinary incontinence, urinary frequency, nocturia, pyuria, hydronephrosis, hematuria, cystitis, and dysuria. A total of 99 (24.6%) bicalutamide-LHRH-treated patients and 99 (24.3%) flutamide-LHRH-treated patients had urological symptoms.

For 51 patients (25 bicalutamide-LHRH, 26 flutamide-LHRH), the investigator reported bleeding as an adverse event (patients could have more than one event), which included the following COSTART terms: epistaxis, ecchymosis, hemorrhage (including rectal, gastrointestinal, cerebral, duodenal ulcer, eye, and retinal), coagulation disorder, and hemoptysis. For those patients who had bleeding or hematuria, 7 patients (5 bicalutamide-LHRH, 2 flutamide-LHRH) were receiving concomitant warfarin therapy at the time of the reported event. For all of these patients, the investigator considered the adverse event (bleeding or hematuria) unlikely to be related to study therapy.

- other neoplasms

Quality-of-life questionnaires were completed at baseline and at Months 1, 3, and 6 only and reflected the patients experience over the previous month. Although 85% of the patients completed a questionnaire at baseline, patients who withdrew from treatment because of diarrhea would have only completed a questionnaire if withdrawal occurred at one of these time points.

Although the planned analysis did not specifically address the two questions directly related to diarrhea, further evaluation of these data revealed that after 3 and 6 months of treatment, the proportion of patients treated with flutamide-LHRH who reported mild or severe diarrhea more than once per week was greater than of patients treated with bicalutamide-LHRH. For example, at Month 3, 26 (9.5%) of 274 flutamide-LHRH-treated patients reported severe diarrhea more than once per week during the previous month compared with 2 (0.7%) of 270 bicalutamide-LHRH treated patients (see above).

The sponsor states that the bicalutamide combination therapy study in 813 patients comparing bicalutamide 50 mg/day with flutamide 750 mg/day, each in combination with a luteinising hormone releasing hormone (LHRH) analog, was designed to show equivalent efficacy between the two treatments. However, the results clearly show that bicalutamide LHRH analog therapy is superior to flutamide LHRH analog therapy in time to treatment failure ($p=0.005$). They attributed this difference to a greater number of patients who withdrew from flutamide LHRH therapy both because of adverse events (particularly diarrhea) and because of objective progression of prostate cancer.

If leuprolide and flutamide combination have a comparable effect on circulating androgen concentrations and treatment outcome as the sponsor suggests than the data does suggest that bicalutamide and goserelin are a comparable and acceptable combination.

8.1.5 Reviewer's Comments and Conclusions:

The approval is based on the assumption that a total androgen blockade is important for both progression and survival and this benefit exceeds the possible risks.

Progression data demonstrated in this pivotal trial is consistent and comparable to that with treatment of the approved combination of flutamide-leuprolide for the palliative treatment of prostate cancer. There is no survival data demonstrated in this pivotal trial.

The safety Profile demonstrated in this pivotal trial is excellent.:

Because of the increased diarrhea with flutamide, which is well known, bicalutamide had a clear advantage. Increased number of patients withdrew from the flutamide/LHRH treated arm because of diarrhea (98) versus 40 in the bicalutamide/LHRH arm. 6.1% patients withdrew from the flutamide arm because of diarrhea and 0.5% from the bicalutamide arm.

The incidence of liver profile adverse events was 6.2 % for the bicalutamide treated patients compared to 10.3% in the flutamide arm. The same number of patients were withdrawn from therapy. The sponsor would suggested that more of the patients in the flutamide arm had more severe or moderate disease. This is possible.

	Bicalutamide/LHRH N= 401	Flutamide/LHRH
LIVER FX ABN N (%)	25 (6%)	42 (10%)

BICALUTAMIDE N=401	ALL ADVERSE EVENTS	NON-FATAL WITHDRAWALS
SGOT INC	6	2
SGPT INC	11	2
ABN LFT	13	4
BILIRUBINEMIA	1	0
HEPATIC NEO	1	0
HEPATOMEGALY	1	11
JAUNDICE	2	

The sponsor states that tumor flare was seen in 0.2% of bicalutamide LHRH treated patients and in 1.2% of flutamide-LHRH treated patients in study 0001. A tumor flare would suggest inadequate therapy and suggest an advantage of bicalutamide over flutamide.

8.2 Trial # Study 301

306 patients were included in this analysis. Recruitment began on 15 June 1990. This was an open multicenter randomized study to compare the effect of orchiectomy versus Casodex 50 mg once daily .

8.2.1 Objective/Rationale

This was one of several monotherapy trials.

Study 301	Casodex 50 mg	Castration
N=306	153	153
25 European sites in Denmark, Norway and Sweden		

8.2.2 Design

This was an open, randomized, multicenter study in which antiandrogen therapy with bicalutamide was compared with castration in patients with previously untreated metastatic prostate cancer. Up to 450 patients were to be recruited and patients were allocated, on a 1:1 basis, either to long-term treatment with a 50 mg once daily oral dose of CASODEX or to castration (either bilateral orchidectomy or Zoladex).

8.2.3 Protocol (ECOG)

	Casodex 50 mg	Castration
N=306 randomized	153	153
D2		
Duration RX weeks	36.6	40.2
Mean Age	71.5	70.3
		3 patients refused therapy

8.2.3.1.

Study population

The patients in this study were recruited from study centers located in Denmark, Norway and Sweden. Eligible patients were numbered sequentially for each participating center; thus Patient 006/004 was the fourth patient to be recruited at center number six.

The principal investigator for this study was responsible for the overall administrative aspects of the study. A Steering Committee was formed comprising two investigators in addition to the principal investigator, such that there was a representative from each of the three participating countries. The purpose of the committee was to act in a consultative, advisory and decision-making capacity on occasions when it was not possible to convene meetings for these purposes with all the investigators participating in the study.

Size of the study and patient recruitment period

A total of 306 patients were included in this analysis. Recruitment began on 15 June 1990. There was no restriction on the number of patients recruited at each study center. For the purpose of this analysis, the last patient was recruited on 13 September 1991; although recruitment into the study was not completed until 26 February 1992. For this analysis, all visits were completed on or before 31 December 1991, which can be regarded as the study cutoff date for this study report.

Inclusion criteria

Patients had to satisfy all of the following criteria before entry into the study:

- (a) histologically or cytologically diagnosed prostate carcinoma;
- (b) metastatic prostate carcinoma (patients with metastases in local lymph nodes only were not eligible);
- (c) either evaluable bone metastases or at least one measurable metastatic lesion (lesions that had been previously irradiated were not considered measurable/evaluable);
- (d) fitness for orchidectomy;
- (e) provision of informed consent to participate in the study,

Exclusion criteria

Any one of the following was a criterion for exclusion:

- (a) previous or concurrent systemic therapy for prostate cancer including either orchidectomy, or antiandrogen, estrogen, LHRH analog, ketoconazole or cytotoxic therapy;
- (b) previous radiotherapy to the prostate within the 3 months before entry into the study;
- (c) previous history or presence of an invasive malignancy other than prostate cancer or squamous/basal cell carcinoma of the skin within the last 5 years;
- (d) an Eastern Cooperative Oncology Group (ECOG) performance score of 3 or 4
- (e) a bilirubin value above 1.26×2 the upper limit of the reference range;
- (f) any severe concomitant medical condition that would either make it undesirable, in the investigator's opinion, for the patient to participate in the study, or that would jeopardize compliance with the study protocol.

All patients were seen every 4 weeks for the first 12 weeks and every 12 weeks thereafter until either:

(a) evidence of objective progression of disease regardless of whether or not the patient had a change to his randomized therapy for prostate cancer;
or

(b) death before evidence of objective progression.

Having reached the point of objective progression of disease, patients who were alive thereafter were contacted every 12 weeks to assess survival status and safety.

For administrative purposes (e.g., scheduling of visits), Day 1 was regarded as the day the patient first received randomized treatment with bicalutamide or underwent an orchidectomy. However, times to treatment failure, progression, and death were measured from the date of randomization.

8.2.3.2 End points

The following end points were used to assess the efficacy of bicalutamide as monotherapy for the treatment of advanced prostate cancer:

- (a) subjective response
- (b) quality of life
- (c) objective tumor response
- (d) time to treatment failure, time to progression and survival
- (e) PSA and endocrine response

All pre-treatment assessments were performed where practical on Day 1. Where this was not feasible, they were performed as near as possible to Day 1 and within the month before randomization. These assessments included measuring/recording age, past medical history, tumor category (as defined in the study protocol shown in Appendix D), plasma testosterone level, and the extent of bone disease

Subjective and objective assessments

Subjective parameters were assessed before treatment, at 4, 8 and 12 weeks, and every 12 weeks thereafter during treatment; QOL questionnaires were completed before treatment, and at 4, 12, 24, and 48 weeks only.

Objective assessments were performed as follows:

- (a) patients' weight, prostate dimensions, and sites and dimensions of clinically measurable metastases were recorded before treatment and every 12 weeks during treatment; in cases where assessment was performed by X-ray or CT scan, and

it was not possible to repeat these at 12 weekly intervals, 24 weekly intervals were acceptable;

(b) bone scan and/or Xray assessment of bone metastases were performed before treatment and every 24 weeks thereafter;

(c) concurrent disease and concomitant medication were recorded before treatment, at 4, 8 and 12 weeks, and every 12 weeks thereafter.

In general, any tumor assessment found to be positive at baseline (i.e., before randomized therapy began), was reassessed at intervals no greater than 24 weeks thereafter. NB Subjective and objective assessments were no longer performed after objective progression of disease, but patients were monitored for adverse events and survival. Haematological and biochemical assessments These assessments were performed on Day 1 before treatment, and during the study at 12 weekly intervals up to the point of objective progression of disease.

8.2.4 Results

8.2.4.1 Populations enrolled and analyzed

The demographics of the patients in the monotherapy trials are comparable between trials and between bicalutamide and comparison treatments (see appendix)

Concomitant medications and illnesses were those commonly seen in this patient population and were assessed in the evaluation of safety. Protocol violations observed and reported for these trials did not influence the analysis of efficacy. The number of patients refusing randomized therapy was minimal and this did not influence the analysis of efficacy.

8.2.4.1 Efficacy

	CASODEX 50 MG	CASTRATION
N=306 randomized	153	153
PSA X % fall	86.48*	96.48%
% pts fell into nl range	23.3%	35.8%
Treatment Failure	86	51
Objective disease progression	63	36

Subjective Assessment:

Social functioning evaluation suggested a statistical significant difference in score change at 6 months. The patients randomized to castration were thought by the sponsor to experience a greater increase in score indicative of an improvement in their social function, when compared with patients randomized to bicalutamide. Castration was associated with greater emotional well-being and social functioning. There was also improvement in bed disability after castration.

This was consistent with the greater incidence of progression of disease with bicalutamide in this study. However the quality-of-life assessments indicated a statistically significant benefit after bicalutamide therapy. This is thought to reflect the maintenance of sexual interest while on bicalutamide rather than castration.

8.2.4.3 Safety outcomes

The safety evaluation showed that bicalutamide was well tolerated. No single adverse event category led to withdrawal in more than 1% of the bicalutamide treated patients. The most frequently reported adverse events were the expected pharmacological events of hot flashes gynecomastia (25% to 26%) and breast tenderness (31% to 36%).

	CASODEX 50 MG	CASTRATION
N=306 randomized	153	153
gynecomastia	16.3%	-
some breast pain or tenderness	24.2%	-
hot flushes	5.2%	41.3*

8.2.5 Sponsor's Conclusions regarding efficacy of bicalutamide as monotherapy

The comparative bicalutamide monotherapy trials were designed to demonstrate equivalence with castration in regard to time to treatment failure or time to progression. Considering the 50 mg dose as monotherapy, the data do not justify an equivalence claim; in fact, bicalutamide was significantly worse compared with castration. Considering the 150 mg dose, the data are not mature enough to draw final conclusions. Data from these trials,

however, demonstrate that bicalutamide is an active oral agent with regard to the secondary end point PSA.

The open, non-comparative trials confirmed that bicalutamide therapy was associated with an objective response in patients with advanced prostate cancer and gave symptomatic improvement. Response was assessed using internationally accepted endpoints and based on the modified NPCP criteria. These trials have shown that bicalutamide can be administered long term without undue loss of activity.

The consistency of activity is also observed in the comparative monotherapy trials with regard to changes in tumor markers, and subjective and objective response. Furthermore the sponsor believes that the trials with bicalutamide 150 mg provide supportive safety data at doses of up to three times that recommended for use in combination therapy.

The overall conclusion of these trials and the implication of PSA changes are that bicalutamide has intrinsic activity in advanced prostate cancer and the dose response, which is related to clinical outcome, confirms this activity. The sponsor believes that the decreased PSA response is a reflection of the low dose of bicalutamide.

Reviewers remarks:

This study is important in demonstrating the problems of treating prostate cancer with an antiandrogen as a monotherapy agent. No sponsor to date has provided placebo-controlled clinical monotherapy data using a nonsteroidal antiandrogen and demonstrating efficacy or equivalence to castration. Either the dose chosen by the sponsor is ineffective because it is too low or the concept of monotherapy treatment is inappropriate with weak nonsteroidal antiandrogens. Surgical castration still remains the gold standard of androgen control to which other therapies are compared.

Prostate specific antigen provides a fairly accurate accounting for lack of efficacy for the 50 mg dose in a randomized study. For all patients who had a PSA value recorded both at entry and at 3 months, the median percent fall in PSA after 3 months of therapy was calculated. If PSA was elevated outside the normal range at entry, the sponsor calculated the number and percentage of patients whose PSA subsequently fell into the normal range at 3 months:

PSA CHANGES 3 MONTHS	CASODEX	CASTRATION
Median percent decrease	86.48	96.48
Number of men with PSA in normal range	20/150 (13.3%)	54/151 (35.8%)

The median percent fall in PSA and the percentage of patients whose PSA had fallen into the normal range were greater in the castration group of patients consistent with inadequate suppression of androgen. (Need to identify how many patients did not have PSA values recorded and if this is distributed in both arms evenly.)

8.3.1. Summary of additional studies:

Additional controlled studies with 50 mg Casodex dose included: protocols 302, and 303. The design, eligibility criteria, efficacy and safety profile were similar and not reviewed in depth. The median percent fall in PSA levels at Month 3 are included for 302.

PSA Med % decrease	CASODEX	CASTRATION
Study 302	84.6 n=119	96.3 n=126
Study 303	88% n=243	97% n=243
Obj Progression		
Study 302	42/119	45/128
Study 303	92/243	59/243
Treatment failure		
Study 302	59/119	61/126
Study 303	129/243	101/243

Treatment failure and objective disease progression for study 302 and 303 is consistent with the changes in PSA. For some men with advanced prostate cancer the antiandrogen blockade is not sufficient. No studies were done to demonstrate if any of the of lack of efficacy was secondary to an agonist effect of the drug.

9 Overview of Efficacy

Total androgen blockade has thought by some to provide an advantage for the palliative treatment of prostate cancer in areas of progression free survival and total survival time. It may be that for the treatment of advanced prostate cancer the best that

can be hoped for is improved quality of life and progression free survival. The pivotal study provided by the sponsor (001) was designed to compare time to treatment failure with a known approved androgen blockade - flutamide and leuprolide. The second study does not provide any additional efficacy but underscores the weakness of antiandrogens in singly blocking androgen and it's effects. The second study (301) provides important supporting evidence when compared to castration and improves our understanding of PSA.

Although monotherapy antiandrogen therapy is clearly not as good as the gold standard of therapy, castration, the study provides important information on the use of nonsteroidal alone. Although the sponsor and others believe that the dose simply was not sufficient it is more likely that the nonsteroidal antiandrogens are weak and although they are helpful in conjunction with castration they are not sufficient by themselves. Higher doses may provoke additional safety problems, e.g gynecomastia and liver profile abnormalities. The benefits of a monotherapy treatment could be very important because of the maintenance of sexual function during this period.

The two gonadotropins used in study 001 trials have been independently approved for medical castration, leuprolide and goserelin.

The studies with bicalutamide are extensive within the last 7 years. A total of 3,521 men were exposed to bicalutamide, of whom 2,938 had advanced prostate cancer. It is an orally active antiandrogen which when used results in predictable reductions in objective tumor markers and symptom improvement. The drug has the added advantage of being oral and a once daily dosing of 50 mg.

EXAMPLES OF TIME TO TREATMENT FAILURE FOR BICALUTAMIDE AS MONOTHERAPY

Trial number	dose (mg)	CASODEX No. of patients	monotherapy	Median time to treatment failure (weeks)
0201	50	263		36
0204	50	150		34
Overview of 0301, 0302 and 0303	50	515		38
0306	150	288	data immature	
0307	150	574	data immature	

From Table 2 in the Integrated Summary of Effectiveness Data.

For the overview of comparative trials, median time to progression for CASODEX 50 mg was 38 weeks, and median time of survival was 109 weeks. The latter included also patients entered after the cutoff point for the first analysis. Median time to progression and survival were not calculated for Trials 0201 and 0204. The data for Trials 0306 and 0307 are still immature.

10 Overview of Safety

The overall safety profile of bicalutamide appears excellent. It is far superior to other antiandrogens. The most important safety issue concerns the liver profile. There are no pulmonary, gastrointestinal or ocular changes.

Liver profile

The studies submitted suggest that the liver profile when compared to flutamide is improved. The following chart compares the adverse events.

ALL ADVERSE EVENTS

	BICALUTAMIDE N=401	FLUTAMIDE n= 407
Incidence of ABN LFT #	25 (6%)	41 (10%)

From table 12 Hepatic adverse events during therapy with CASODEX/LHRH .

Casodex-LHRH Therapy (US0001)			
	All adverse events %	non-fatal withdrawals %	
SGOT INC	6	2	
SGPT INC	11	2	
ABN LFT	13	4	
BILIRUBINEMIA	1	0	
HEPATIC NEO	1	0	
HEPATOMEGALY	1	11	
JAUNDICE	2	1	

Abnormal LFT including increases in SGPT, SGOT, or both.

monotherapy trials			
	ALL ADVERSE EVENTS	NON-FATAL WITHDRAWALS	
SGOT INC	16	2	
SGPT INC	9	1	
Alk Phos inc	9	0	
GGT inc	8	1	
LFT abn	11	3	
Bilirubinemia	4	0	
Cholestatic jaundice	2		
jaundice	5	2	
Hepatitis	1	0	
Hepatomegaly	2	0	
Hepatic neoplasm	1	1	
Cirrhosis	1	0	
Total	69	10	

Casodex-LHRH Therapy (US0001)		
PERCENTAGE OF PATIENTS WITH HEPATIC ADVERSE EVENTS ON CASODEX-LHRH THERAPY WITH FLUTAMIDE-LHRH THERAPY IN THE COMBINATION STUDY. (001) (TREATMENT RELATED EVENT %)		
	CASODEX-LHRH	FLUTAMIDE-LHRH
SGOT INC	1.2	3.9
SGPT INC	2.5	5.7
ABN LFT	3.0	3.4
BILIRUBINEMIA	0.2	0
HEPATIC NEO	0	0
HEPATOMEGALY	0.2	0
JAUNDICE	0.5	0

1.5% of the patients had adverse events related to hepatic function compared with 1.1% of the patients who had castration. The sponsor claims no dose related increase in the hepatic adverse events.

Of 77 patients had at least one liver enzyme test either SGOT or SGPT exceeding twice the upper limit. (28 bicalutamide arm, 49 flutamide arm). 25 patients had changes exceeding twice the upper limit of normal on more than one occasion. - 8 bicalutamide and 17 flutamide. Of these 25 patients had 10 had liver enzymes levels which decreased while therapy continued - 2 bicalutamide and 8

flutamide and for 3 patients - 2 bicalutamide and 1 flutamide the levels returned to within the normal limits. 52 of the 77 patients (20 bicalutamide and 32 flutamide - had changes in liver function tests exceeding twice the upper limit of normal on only one occasion.

Like all antiandrogens bicalutamide is capable of causing drug related increases in liver function tests; however the incidence in the clinical trials related to bicalutamide appears to be better and the changes appeared to be less severe.

• Testosterone rise with antiandrogen therapy:

Detailed endocrinological assessments provided by the sponsor during bicalutamide monotherapy (Trials 0002/0003/0005, 0202, 0205, and 0307) demonstrated consistent rises in serum LH, testosterone and estradiol. For the majority of patients (about 90%), testosterone levels remained within the normal range at all times measured. Testosterone levels do not increase progressively with time. If the antiandrogen was to be used as monotherapy compliance would need careful monitoring.

	CASODEX DAILY DOSE 50 MG (# 202)		CASODEX DAILY DOSE 150 MG (# 307)	
	N	Mean T nmol/l	N	Mean T nmol/l
Baseline	17	13.1	23	10.9
Month 3	16	24.6	20	20.6
% increase		87.8%		89%
Month 6	11	20.5	20	18.1
% increase		56.5%		66.1%

% percent increase from baseline concentration.

Tumor flare is thought to be the result of the initial stimulation of the gonadotropins by the analogs. The addition of an antiandrogen presumably should block the action of increased androgens. Tumor flare was reported as an adverse event in less than 0.2% in the bicalutamide-LHRH-treated group and in 1.2% in the flutamide LHRH-treated group (1 bicalutamide-LHRH, 5 flutamide-LHRH - study 001). Cord compression, as a possible symptom of a tumor flare reaction, was reported during the first month of therapy for one patient in each treatment group. The incidence of pain, bone pain, or back pain reported during the first 35 days of study therapy, regardless of whether the event was attributed to tumor flare, was similar for both treatment groups (7% bicalutamide-LHRH, 8% flutamide-LHRH). It does not appear that total androgen blockade is able to block the initial stimulatory androgen response.

10.1 Significant/Potentially Significant Events

10.1.1 Deaths

There were no deaths attributable to the drug; nor were there increased deaths from any single cause that could be drug related. As expected the most important factor was the prostate cancer.

There was no data suggesting other exposure, drug demographic interactions or drug-drug interactions. Data is needed regarding the agonist effect on the androgen receptor with chronic use. Bicalutamide is not indicated for treatment other than prostate cancer and could be expected to have adverse reproductive effects other than maintenance of libido.

11 Labeling Review

The label will be review in full subsequently.

- 11.1 Description]
- 11.2 Clinical Pharmacology
- 11.3 Indications and Usage

label:

Clinical Studies

In a large multicenter, double-blind, controlled, clinical trial, 813 patients with previously untreated advanced prostate cancer were randomized to receive CASODEX 50 mg once daily (404 patients) or flutamide 250 mg (409 patients) three times a day, each in combination with LHRH analogs (either goserelin acetate implant or leuprolide acetate depot). At the time of analysis, the median time of follow-up was 49 weeks. CASODEX-LHRH analog therapy is associated with a significant ($p=0.005$) improvement in time to treatment failure compared to flutamide-LHRH analog treatment. The hazard ratio of CASODEX-LHRH analog to flutamide-LHRH analog is 0.749. The two-sided 95% confidence interval (CI) for the hazard ratio is 0.61 to 0.92.

The label should include identification of prostate specific antigen monitoring and indications from stopping therapy whether from objective progression or antiandrogen agonist effect. Laboratory tests must include monitoring of liver function tests particularly at initiation of therapy. It should clearly note that it is not indicated for women or children.

12 Conclusions

Sponsor's conclusions:

The benefits and the reduced risks associated with CASODEX 50 mg once daily in combination therapy for patients with advanced

prostate cancer over treatment with flutamide in combination therapy are the following:

- (a) CASODEX is an active oral agent in the treatment of advanced prostate cancer.
- (b) CASODEX in combination therapy has superior efficacy in terms of time to treatment failure over flutamide in combination therapy-a clear clinical benefit for patients with advanced prostate cancer.
- (c) CASODEX is well tolerated. CASODEX in combination therapy is better tolerated than flutamide in combination therapy, especially with regard to diarrhea, and therefore has a reduced safety risk for patients. This aspect is also a benefit, since fewer CASODEX-LHRH-treated patients than flutamide-LHRH-treated patients are withdrawn on account of diarrhea. Thus, more patients can benefit from antiandrogen therapy when CASODEX-LHRH is given instead of flutamide LHRH. Furthermore, abnormalities in results of liver function tests were less frequently reported with CASODEX in combination therapy than with flutamide in combination therapy.
- (d) The once daily dosing of CASODEX 50 mg is a benefit for patient convenience and compliance.
- (e) CASODEX can be combined with either an LHRH analog or surgical castration. The benefits and risks of CASODEX in combination with an LHRH analog are similar to those of CASODEX in combination with surgical castration, since the two forms of castration are considered equivalent.

In summary, the benefits and risks of CASODEX in combination therapy demonstrate that CASODEX is a more efficacious and better-tolerated alternative to flutamide in combination with LHRH analog therapy for the treatment of advanced prostate cancer.

13 Recommendations

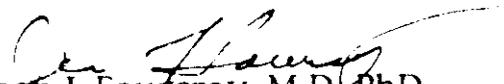
The sponsor has submitted one pivotal and one supporting study in support of the use of bicalutamide for the palliative treatment of prostate cancer (stage D) in conjunction with medical castration. Additional safety data is derived from both uncontrolled and controlled Phase II and Phase III monotherapy trials comparing bicalutamide with castration. The sponsor should be commended for providing the medical officer with an excellent review and accessible computerized data.

The efficacy profile is comparable to the approved flutamide-leuprolide combination for the palliative treatment of prostate cancer. The drug appears to have a better profile regarding gastrointestinal adverse events, in particular diarrhea which has been so troublesome with flutamide. It is not clear if the liver profile will be superior to other antiandrogens but the clinical trials suggest that it may well be better. Although survival data is lacking the time to treatment failure and objective progression is similar between the two treatments. Although monotherapy (bicalutamide 50 mg) is safe and effective treatment in the

majority of men as well as maintaining a better quality of life, it falls short of equally the cancer benefits of castration - either medical or surgical.

The pivotal trial compared CASODEX and zoladex to the approved combination therapy. There was no comparison to therapy with surgical castration; therefore approval can not encompass that indication. The use of bicalutamide in conjunction with gonadotropin analogs, either, goserelin or leuprolide is approvable.

- Phase IV commitments must continue to monitor the survival profile of total androgen blockade comparing the treatments and this should be included in future labeling.
- The sponsor should identify the incidence of changes of responsiveness to antiandrogen with androgen receptor changes, e.g. withdrawal syndromes with antiandrogens.
- The sponsor should be aware that many practicing physicians may use monotherapy treatment, although not approved, to preserve the sexual function in patients. The risks and benefits must be clearly be available to all physicians and patients.


Jean L Fourcroy, M.D, PhD
Medical Officer

See group header memo

Copy to File
Fleming
El Hage
Hoberman
Hunt

AD Lemj
9/10/95

TABLE I ESTIMATES FROM COMPARABLE STUDIES

	Response Rate	Progression Free Survival	Disease Progression	Survival
Leuprolide Study Group LEU vs DES	Obj Res 86% Leu 85% DES	Surv 1 yr 87% Leu 78% DES		146 Weeks Leu 136 Weeks DES no difference
0036 N=603 L+F vs L+Pbo		Months 16.5 Flut 13.9 Pbo (p 0.039)		Months 35.6 Flut 28.3 Pbo (p = 0.035)
001				
301				
Eortc 30853 Zoladex/Flut (Z/F) Vs Orch N=327			Difference in median progression 35 weeks for Zol/flu	7 month ext of survival - p=0.05 *
Daproca-86 Orch vs Zol/F N=264	No difference in time to progression or median survival.		Time To Progression Months 16.Orchiectomy 16.Zol/F	Median Survival Months 27.6 Orch 22.7 Zol/F
908 # Anandron/ Orchiectomy Placebo/ Orchiectomy 66 Inv.	41% Nil 24% Pbo		Time To Obj Prog./ Months 19 Nil/orch 14.9 Pbo/orch	Median Survival months Nil 28.3 Pbo 23.2 Not Significant
606# Anandron/ Lhrh 38 Inv. U.S.			Median Time To Prog Months 25 Leu/Pbo 24.5 Leu/Fbo	Not Reached
Inter PCA Study Grp Zolodex vs Zol + Flut N=571	Obj Response 67% Zol 65% Zol/F		No Difference In Time To Progression Or Time To Failure	Time To Treatment Failure not significant 37.7 M Zol 42.4 M Zol/F

current submission

* patients with minimal disease and good performance status received the greatest benefit in 0036 and EORTC 30853.
based on data from Cancer Supplement, December 1993.

NDA #20-498 Addition:

11 Labeling Review for Casodex (bicalutamide)

11.1 Description

This is satisfactory

11.2 Clinical Pharmacology

"This inhibition results in regression of Prostatic tumors" - This statement is too enthusiastic

Flutamide label states that Prostatic carcinoma is known to be androgen sensitive and responds to treatment that counteracts the effect of androgen and/or removes the source of androgen (this is a better statement.)

The sponsor states that the dose and pharmacokinetics are unaffected by age, renal impairment or mild to moderate hepatic impairment. (It is not clear that there is sufficient evidence to include patients with mild to moderate impairment.

A statement regarding testosterone and estradiol changes should be included.

11.3 Indications and Usage

Clinical Studies

"In a large multicenter, double-blind, controlled, clinical trial, 813 patients with previously untreated advanced prostate cancer were randomized to receive CASODEX 50 mg once daily (404 patients) or flutamide 250 mg (409 patients) three times a day, each in combination with LHRH analogs (either goserelin acetate implant or leuprolide acetate depot). At the time of analysis, the median time of follow-up was 49 weeks. CASODEX-LHRH analog therapy is associated with a

significant ($p=0.005$) improvement in time to treatment failure compared to flutamide-LHRH analog treatment. The hazard ratio of CASODEX-LHRH analog to flutamide-LHRH analog is 0.749. The two-sided 95% confidence interval (CI) for the hazard ratio is 0.61 to 0.92.

This statement appears to be satisfactory.

The statements regarding subjective responses and quality of life are satisfactory and suggests no differences between the two antiandrogens.

In keeping with flutamide label the sponsor should include all of the analyzed endpoints. Therefore, in addition to time to treatment failure, subjective responses and quality of life the **label should include the current survival time.**

11.2 Clinical Pharmacology

11.3 Indications and Usage

There is insufficient evidence that Casodex is indicated for use in conjunction with surgical castration therefore the surgical castration references must be removed.

Both the antiandrogen, Casodex, and the gonadotropin were started simultaneously; this should be included in the dosage section. Both drugs should be started at the same time.

1.4 Contraindications

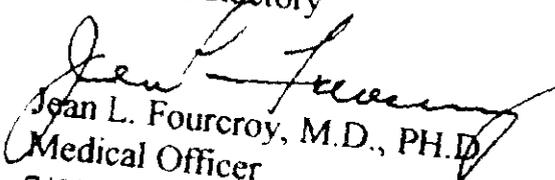
This section is satisfactory and includes the contraindication for female use. There is no statement regarding pediatric use

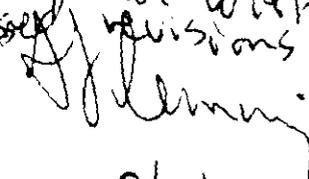
11.5 Warnings - there should be a statement regarding gynecomastia if drug used with surgical castration or without gonadotropin suppression. Should a liver disclaimer be included under precautions?

The suggested nilutamide labeling states " In case of jaundice, or in case of abdominal pain or unexplained gastrointestinal symptoms, together with a rise

We should not be encouraging the use of any antiandrogen in mild to moderate hepatic impairment.

11.11 How Supplied
This is satisfactory


Jean L. Fourcroy, M.D., PH.D.
Medical Officer
7/6/95

Concur,
Communicate to sponsor by
fax so that they may
respond with a revised
draft. Also concur with
attached proposed revisions.

8/11/95

SEP 11 1995

Safety Update

Medical Officer Review
Casodex (bicalutamide) review
Submission: August 25, 1995
September 7, 1995

NDA #20-498

bicalutamide 176,334
Proposed trade name
Casodex

This summary safety updates the previous 4 month safety update. The cutoff date for this report is March 3, 1995 and includes data from the pivotal combination trial, 0001 - LHRH/Antiandrogen as well as all other studies ongoing. The differences between this update and the previous 4 month safety update are minimal.

The changes include:

- Increased patient exposure - n=3983. This represents an increase of 280 patients or 8% over the 4 month safety report.
- Exposure time to Casodex treatment is increased from 11.9 to 46.7 patient years in the pivotal combination study.

The adverse event profile is unchanged and similar to previous review.

The following is noted:

- No change in the profile of cases of death. There are no deaths due to cerebral hemorrhage previously not related to drug.
- The withdrawal profile reported in the bicalutamide arm is consistent with previous reports.
- The liver disease by liver effect included in a previous report.

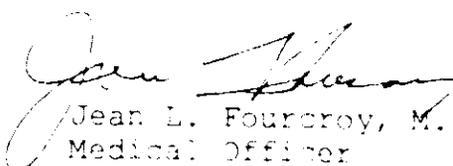
Hepatic Adverse Events

	Casodex	Placebo
SAE	1/17	1/17
AE	1/17	1/17

PAAM - preapproval safety update
4MUC - 4 month safety update

There were 3 cases of jaundice reported in which Casodex, three of which were in monotherapy trials at higher doses, and an additional 3 cases in the 4 month safety update. All of these patients were on monotherapy trials at doses higher than the pivotal trial (150 mg). Drug induced hepatotoxicity could not be excluded in these cases all it appears that many of the cases were associated with metastatic cancer progression. There have been no new cases reported in the latest safety update.

In summary this safety update does not demonstrate any changes in the safety profile that are drug related. The 150 mg dose appears to be a well-tolerated dose.


Jean L. Fourcroy, M.D., PhD
Medical Officer
HFI-510/September 6, 1995

There were more ^{probable CR-related} deaths in the Casodex-treated group than in the placebo group (11 vs 4) during this update interval. There are still fewer overall ^{probable CR-related} deaths in the Casodex group (130) vs placebo (114).


9/11/95

BICALUTAMIDE/CASODEX - ZENECA PHARMACEUTICALS GROUP

4 MONTH SAFETY REPORT - January 13, 1995

August 2, 1995

The Safety Update report review of January 13, 1995 was included in the NDA review; however, several points will be reviewed.

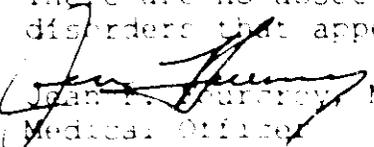
There were a total of 267 new patients exposed to Casodex subsequent to the submission of the NDA including more data on the 150 mg comparative monotherapy studies. The bulk of the patients were exposed to 150 mg monotherapy.

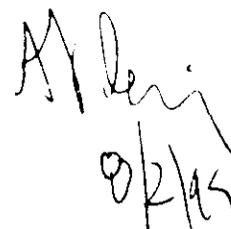
The monotherapy trials were associated with gynecomastia and breast pain. Patients receiving 150 mg monotherapy doses had a 39% incidence gynecomastia and breast pain. In the LhRH therapy trials there was an incidence of 5.7% in the bicalutamide-LhRH therapy arm versus 4% in the flutamide-LhRH arm.

The hepatic profile in the update report is consistent with that seen in the NDA submission. The hepatic profile update was included the NDA review. There was only one patient with a serious hepatic adverse event considered to be treatment related. - one case of chronic aggressive hepatitis - 4.5 years after starting

During combination therapy, the incidence of hepatic adverse events was lower in the bicalutamide treated patients than in the flutamide arms (6.7% versus 12% respectively). The corresponding incidence reported prior, in the ISS, were 6.7% (bicalutamide) and 10.3% (flutamide) respectively. The incidence of hepatic adverse events during monotherapy was 1.8% in the 150 mg bicalutamide treated patients and 0.9% in castration patients, while the previous report was 0.8% and 1.2% respectively. In the entire monotherapy program the incidence of hepatic adverse events was 1.7% in the bicalutamide patients and 1.3% in castration patients, the corresponding incidence in the ISS were 1.0% and 1.0% respectively

There are no associated problems with ophthalmic or pulmonary disorders that appear to be drug related.


JEAN P. GARVEY, M.D., PhD
Medical Officer
NDA 20-498 - Safety Update


AT
02/15

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 3, 1995

From: David Hoberman, Ph.D., HFD-713

Thru: Satya Dubey, Ph.D. *SD*
Chief, Statistical Evaluation and Research Branch (HFD-713)

Subject: Mortality in Casodex trial 7045US/0001

To: File (NDA 20-498)

The sponsor has provided an update on survival in the US trial. Median follow up is now twice what it was in the first report (95 vs 49 weeks). The current cutoff date is March 3, 1995 (18 months after the last patient was recruited). Only 1/3 of the randomized patients have died. The estimated hazard ratio is now .88 (Casodex/flutamide) with a 95% confidence interval of (.69, 1.11), indicating that Casodex is not more than 10% worse than flutamide. See **Figure 1**. Casodex's slightly more favorable result is due to a somewhat higher death rate among flutamide patients taking leuprolide vs Casodex patients taking leuprolide. See **Figure 2**. The previous confidence interval was (.70, 1.35).



David Hoberman, Ph.D.

Concur: Dr. Nevius *HN 7-3-95*

cc: Arch NDA 20-498

HFD-510

HFD-510/Dr. Fourcroy

~~HFD-510~~/Ms. Pauls

HFD-713/Dr. Nevius

HFD-713/Dr. Hoberman

HFD-713/Dr. Dubey [File 1.3.2 DRU]

HFD-344/Dr. Lisook

This review contains 1 page of text and 2 figures.

Figure 1 Kaplan-Meier probability of death by antiandrogen

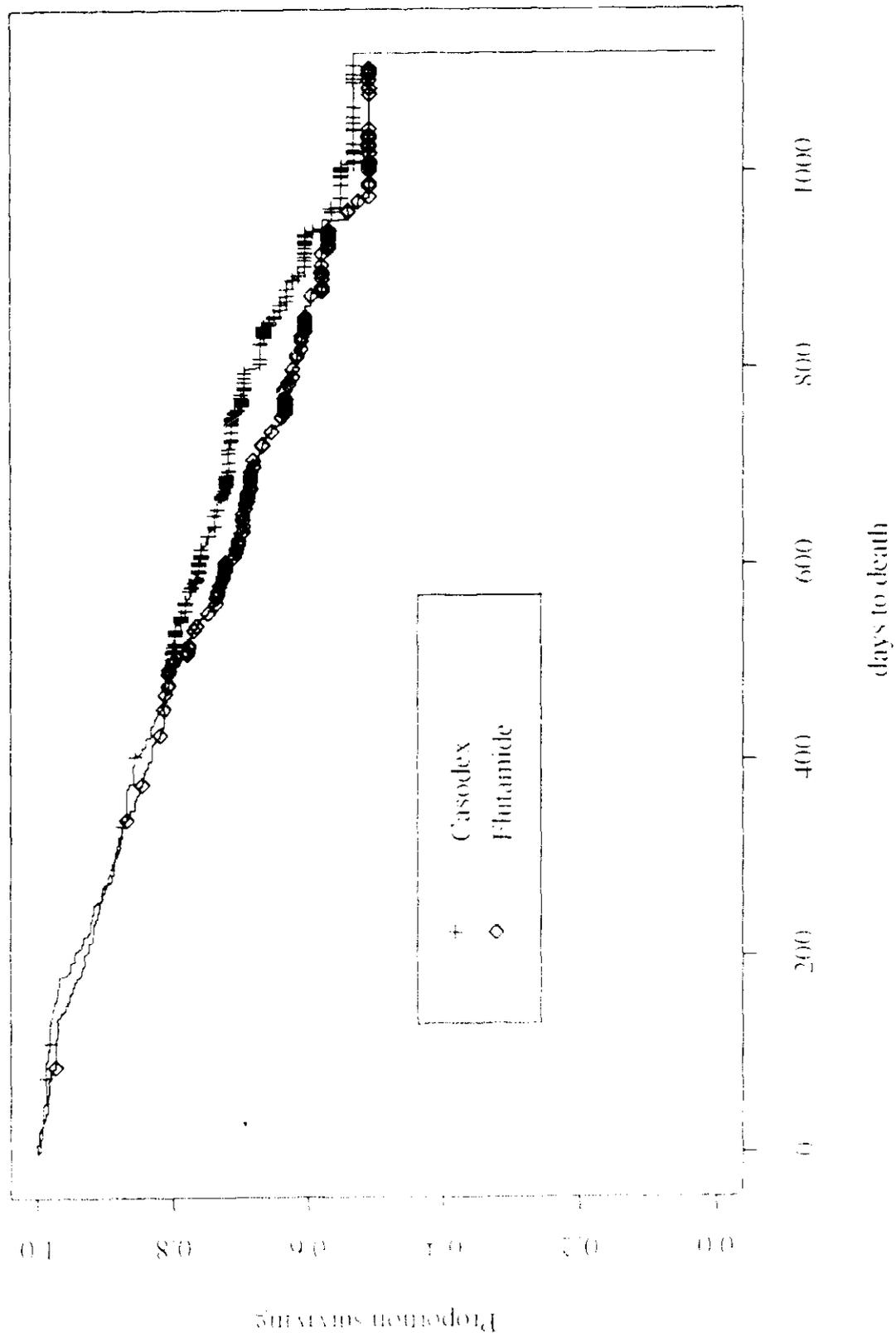
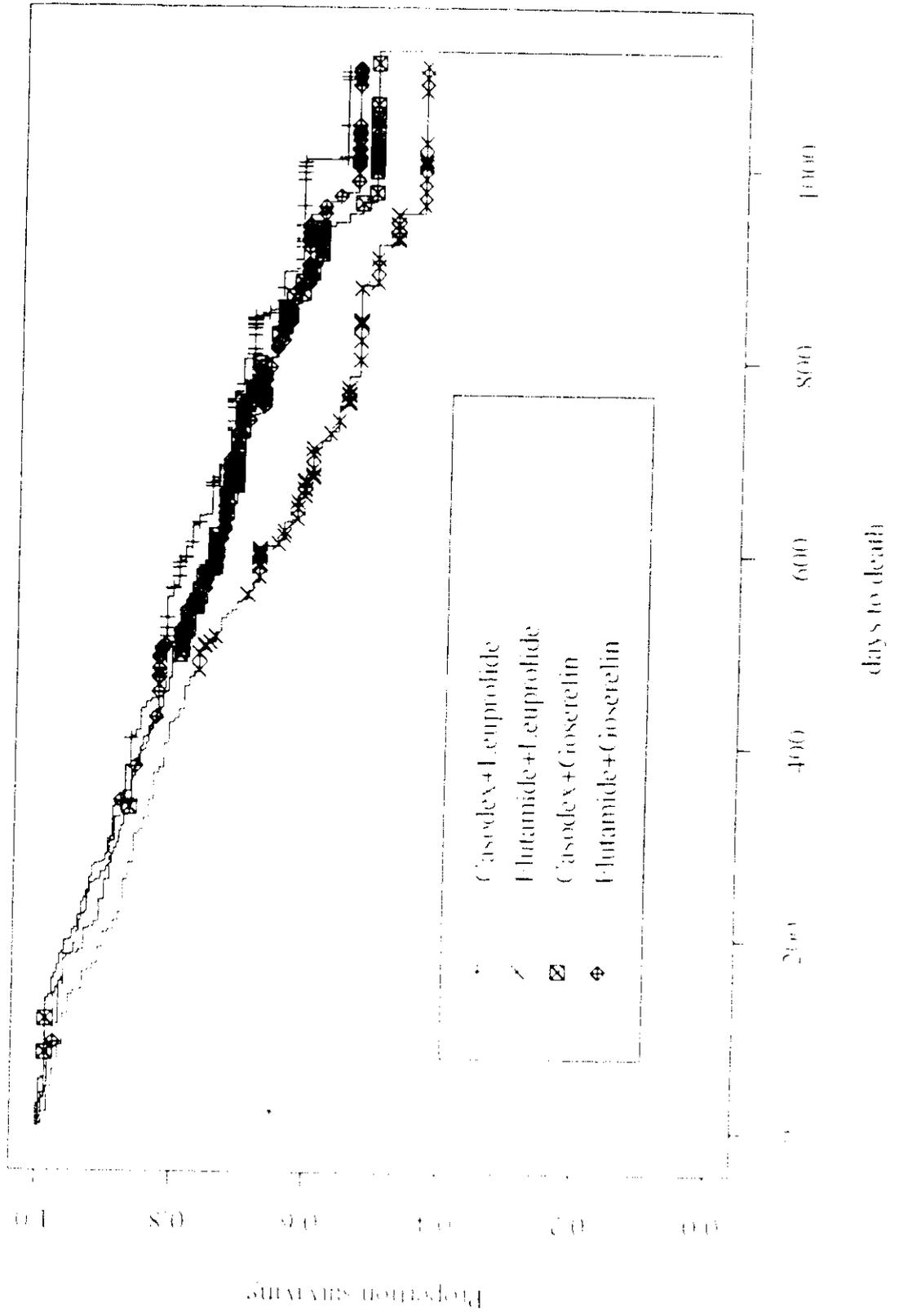


Figure 2 Kaplan-Meier probability of death by combination



Statistical Review and Evaluation

NDA#: 207498

Applicant: Zeneca Pharmaceuticals Group

Name of Drug: Casodex

Document Reviewed: Vol 1.108

Medical Input: Jean Fourcroy, M.D., HFD-510

Background

Dr. Fourcroy regards Study 7054US/0001 to be the substantial trial for this application. This review focuses on the question of whether Casodex and flutamide are 'equivalent' with respect to 'objective progression' and 'treatment failure'. Survival data is not very mature at this time but shows no evidence of a difference between groups. **A request for more recent follow up has been communicated to the firm.**

Trial 7045US

This trial **centrally** randomized 813 previously untreated patients with metastatic prostate carcinoma from the US and Canada to one of 4 groups: Casodex-Zoladex, Casodex Leuprolide, flutamide-Zoladex, flutamide-Leuprolide, where the second drug is an LHRH analogue. There were 404 in the Casodex regimens and 409 in the Flutamide regimens. Five (5) patients refused randomized therapy and were assigned an event time of '0' in the analyses. Randomization occurred in 60 centers between 1/30/92 and 9/24/93. The report included analyses based on a data cutoff of 3/11/94 at which time all patients had been followed for at least six months.

Subjective assessments included bone pain, ECOG performance status and a quality of life questionnaire. Objective assessments were objective progression and treatment failure. The latter was defined by any of the following: death, severe adverse event, objective progression, unwillingness to continue, radiation therapy at least 4 weeks after study therapy, or investigator judgement. The protocol also lists 'administration of an additional systemic therapy...'

The trial size was designed to demonstrate that Casodex is not more than 25% less effective than flutamide (hazard ratio \leq 1.25: Casodex/flutamide), power = 80%, Type I error = 5%.

Table 1 illustrates that baseline variables were well balanced between the groups. **Table 2** displays the numbers and reasons for early withdrawal. Note the greater frequency of objective progression and adverse events on flutamide.

Efficacy Results

Figure 1 displays the Kaplan-Meier plots of the two groups for treatment failure. **Figure 2** displays the treatment failure plots broken out by LHRH analogue. There is no obvious evidence of antiandrogen-LHRH interaction. A Cox regression with LHRH analogue, extent of disease at entry, and ECOG performance at entry as covariates (stated in protocol) produced a 95% confidence interval of (.61 to .92) indicating that the Casodex arm was statistically significantly superior to the flutamide arm. Dr. Fourcroy wished to confirm that the comparison was not driven by the excess adverse event experience on flutamide. Censoring all adverse events results in **Figure 3** which indicates that the failure curves are coincident for the first half of follow up and diverge thereafter in favor of Casodex. The logrank p-value is .12. Although a hazard ratio is not strictly proper here due to the non-uniform treatment effect, the confidence interval is (.62, .96).

Figure 4 displays the survival curves for the two groups. The sponsor's Cox regression produced a hazard ratio of .97 with 95% confidence interval (.70, 1.35).

'Subjective response' was defined in the protocol as no increase in performance score, bone pain score or analgesic score AND either decrease of total subjective score from baseline of 3 or more OR decrease from baseline of 2 or more for performance, bone pain or analgesic score. Approximately 50% of the patients on each treatment had a subjective response. The 95% confidence interval for the difference in proportions is (-13%, 8%). Logistic regression including the same covariates as the Cox model produced a confidence interval of (.72 to 1.72) for the odd ratio of Casodex to flutamide on subjective response for patients who were symptomatic (apparently ECOG score of at least 1) at entry. Caution is required due to the attrition from the study.

There were no statistical differences for any of the quality of life items except 'physical capacity' at 6 months which was in favor of Casodex. However, only 50% of the randomized patients have evaluations at 6 months.

Conclusions

1. This trial provides evidence that the rate of treatment failure on Casodex is not greater than that on flutamide whether or not 'adverse event' is included as an endpoint
2. Subjective response is no worse on Casodex than on flutamide


David Hoberman, Ph.D.
Mathematical Statistician

TABLE 1

Demographic characteristics at entry

Characteristic	Number of patients (%)	
	CASODEX-LHRH (N = 404)	Flutamide-LHRH (N = 409)
Age (yr)		
Mean	70	70
Range	43 to 91	42 to 93
Race		
White	287 (71)	294 (72)
Black	95 (24)	91 (22)
Hispanic	13 (3)	19 (5)
Other	9 (2)	5 (1)
AUA classification		
D ₂	396 (98)	407 (99.5)
Non-D ₂	8 (2)	2 (0.5)
Extent of disease on bone scan*		
None	37 (9)	29 (7)
≤ 5 metastases	175 (43)	173 (42)
≥ 6 metastases	157 (39)	160 (39)
Superscan	24 (6)	27 (7)
Histological differentiation#		
Poor	132 (33)	148 (36)
Moderate	201 (50)	201 (49)
Well	58 (14)	43 (11)
Other	12 (3)	15 (4)
ECOG score		
0 - Full activity	221 (55)	208 (51)
1 - Symptoms but ambulatory	143 (35)	150 (37)
2 - In bed 50% of the time	40 (10)	51 (13)

*Stage D₂ disease is not always demonstrated by bone scan results.

#Three patients did not have either a sufficient sample to determine grading or a cytologic or histologic confirmation of disease.

AUA = American Urological Association

ECOG = Eastern Cooperative Oncology Group

TABLE 2

Details of therapy		
Result	Treatment group	
	CASODEX-LHRH (N = 404)	Flutamide-LHRH (N = 409)
Weeks of therapy received		
Number of patients	401	407
Median	48	44
Range	1 to 110	1 to 108
Reason for withdrawal of therapy		
Objective progression	72	96
Adverse event	28	49
Protocol violator	18	11
Patient choice	17	18
Investigator decision	15	25
Death	15	14
Refused randomized therapy	3	2
Other	0	2

FIGURE 1

Kaplan Meier probability of treatment failure

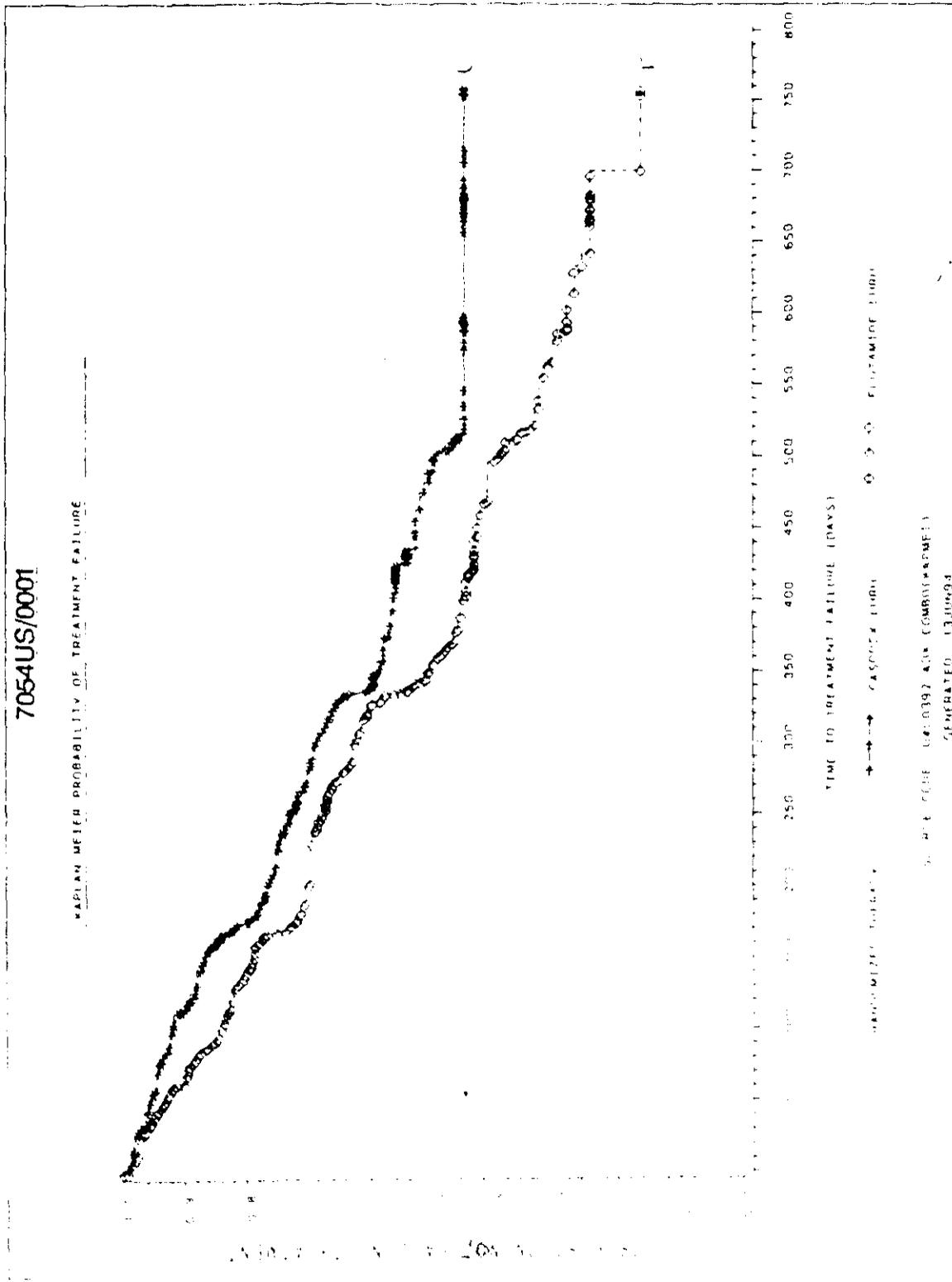


FIGURE 2

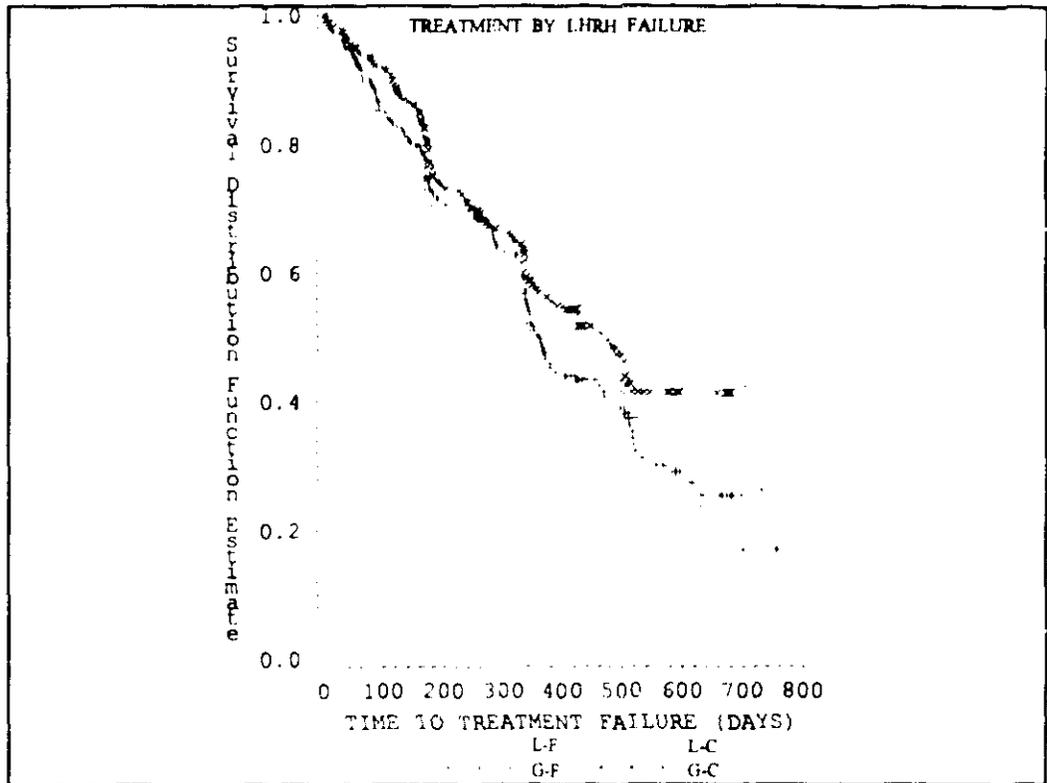


FIGURE 3

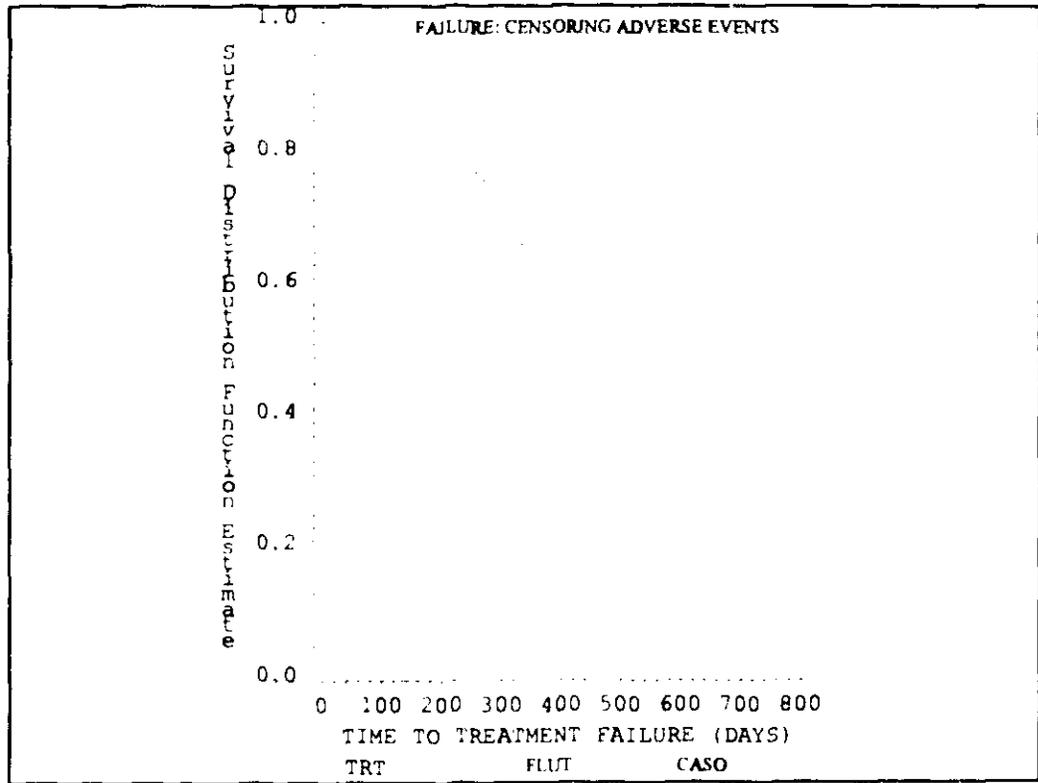
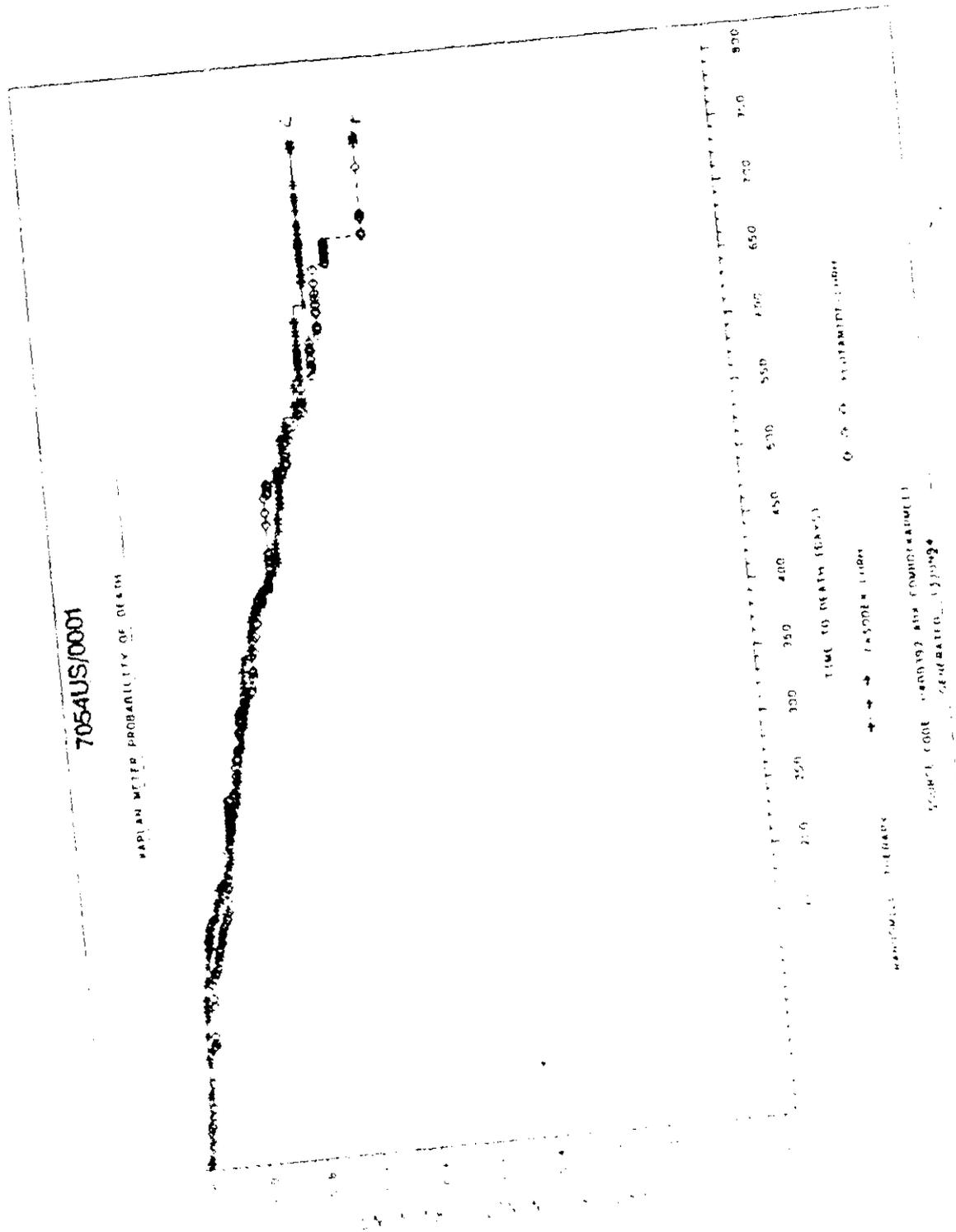


FIGURE 4

Kaplan Meier probability of death



Statistical Review and Evaluation

(Addendum)

Date: JUN 22 1995

NDA: 20-498

Applicant: Zeneca Pharmaceuticals Group

Name of Drug: Casodex (Bicalutamide)

Documents Reviewed: NDA Submission volumes 14 of 14,
Data on floppy diskette supplied by the sponsor.

I. Background

A report of statistical review and evaluation on the mouse and rat carcinogenicity studies of this NDA was issued by the Division of Biometrics on May 26, 1995. In that review due to an inadvertent mistake two of the tables (Table 2a and Table 5a) were not included. This addendum contains those tables.

Mohammad Aliar Rahman
Mohammad A. Rahman, Ph.D.,
Mathematical Statistician

Karl K. Lin 6/22/95
Concur: Karl K. Lin, Ph.D.,
Group Leader

cc: Original NDA 20-498

HFD-510/Dr. Schel

HFD-510/Dr. El Mage

HFD-710/Chron

HFD-715/Dr. K. Lin

HFD-715/Dr. Rahman

HFD-715/SARB Chron

HFD-715/DRU 2.1.1.1 NDA 20-498 Casodex Mouse and Rat
Carcinogenicity Studies

HFD-715/Diskette Rahman-CASODEX.AFN

Table 2a

P-values of tests for positive linear trend in mortality
in the mouse study

Test of homogeneity

<u>Sex</u>	<u>Test</u>	<u>P-value</u> (Chi-Sqr.)
Male	Cox	.8796
	Wilcoxon	.7645
Female	Cox	.7271
	Wilcoxon	.7643

Test of linear trend

<u>Sex</u>	<u>Test</u>	<u>P-value</u> (One tail Normal)
Male	Cox	.2143
	Wilcoxon	.1556
Female	Cox	.3363
	Wilcoxon	.3322

Table 5a

P-values of tests for positive linear trend in mortality
in the rat study

Test of homogeneity

<u>Sex</u>	<u>Test</u>	<u>P-value</u> (Chi-Sqr.)
Male	Cox	.0924
	Wilcoxon	.1349
Female	Cox	.2993
	Wilcoxon	.2401

Test of positive linear trend

<u>Sex</u>	<u>Test</u>	<u>P-value</u> (One tail Normal)
Male	Cox	.9793
	Wilcoxon	.9820
Female	Cox	.0987
	Wilcoxon	.0840

Statistical Review and Evaluation

NDA: 20-498

Date: MAY 26 1995

Applicant: Zeneca Pharmaceuticals Group

Name of Drug: Casodex (Bicalutamide)

Documents Reviewed: NDA Submission volumes 14 of 14,
Data on floppy diskette supplied by the sponsor.

I. Background

In this NDA submission two animal carcinogenicity studies, one in mice and one in rats, were included. These two studies were intended to assess the carcinogenicity potential of Casodex in mice and rats when administered orally through diets at some selected dose levels. The durations of both the mouse and rat studies were 104 weeks (728 days). The reviewing pharmacologist Dr. Jeri El Hage, HFD-510, requested the Division of Biometrics to perform the statistical review and evaluation of these studies. The results of the review have been discussed with Dr. Jeri El Hage.

II. The mouse study

IIa. Design: Two separate experiments, one in male and one in female mice, were conducted. In these two experiments there were three treated groups known as low, medium, and high, and one control group. Two hundred fifty male and equal number of female C57BL/10JfCD-1/Alpk strain mice were randomly divided into pre-selected sizes of 100, 50, 50, and 50 to form the control, low, medium, and high dose groups, respectively. The dose levels for the treated animals were 5, 15, and 75 mg/kg/day for low, medium, and high dose groups, respectively. The animals in the control group remained untreated.

The animals were checked daily for mortality and morbidity and were examined weekly for the presence of any palpable masses. A complete histopathological examination was performed on all animals found dead, killed moribund during the experiment or sacrificed at the end of the experiment.

IIb. Sponsor's analysis

Survival data analysis: Summaries of cumulative mortality for male and female mice were presented in tabular forms. The weekly percentages of survival rates of four groups were presented graphically. The survival distributions of pairs of treatment groups were compared using the log rank test. An overall chi-square

test was performed to test the homogeneity of survival in different treatment groups. The SAS LIFETEST procedure was used for this analysis with two-sided level of significance.

The test did not show any statistically significant difference in mortality among the treatment groups in either sex.

Tumor data analysis: The tumor data were analyzed using the methods described in the paper of Peto et al. (Peto R., Pike M.C., Day N.E., Gray R.G., Lee P.N., Pareish S., Peto J., Richards S., and Wahrendorf J., Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980). The intervals used for the mortality adjustment among treatment groups were 0-420, 421-532, 533-616, 617-672, and more than 672 days. Tumors with 5 or fewer number of tumor bearing animals were analyzed using the permutation test (Exact test) as was suggested by Mantel (Mantel N., Assessing laboratory evidence for neoplastic activity, Biometrics, 36, 381-399, 1980). It was not mentioned what type scores were used for this test.

Adjustment for the effect of multiple testings was done using a method due to Tukey (Mantel, 1980) and Mantel et al. (Mantel, N., Tukey J.W., Ciminera J.L., and Heyse J.F., Tumorigenicity assays, including use of the jackknife, Biom. J., 24, 579-596, 1982). This method adjusts the smallest observed pvalue $p_{(1)}$ as $p_{(1)} = 1 - (1 - p_{(1)})^{k_1}$, namely the probability of observing at least one p-value as $P_{(1)}$ among k_1 tumor sites, where k_1 = the one under consideration together with those with total incidence of tumors greater than 5, plus those others that could have given a p-value as extreme as the unadjusted one under consideration. The process is repeated with the next smallest unadjusted p-value $p_{(2)}$ excluding the tumor type that generated $p_{(1)}$.

The tests showed a statistically significant positive linear trend in the incidence of hepatocellular carcinoma in male mice. For this tumor type pairwise comparisons also showed a statistically significant increased tumor incidence in the high dose group when compared with the control.

Iic. Reviewer's analysis

The reviewer independently performed analyses on the survival and the tumor data. For survival data analysis the methods described in the papers of Cox (Cox D.R., Regression models and life tables, Journal of the Royal Statistical Society, B, 34 187-220, 1972), and of Gehan (Gehan E.A., A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika, 52 203-223, 1965)

were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test, developed by the Division of Biometrics. All data used in the reviewer's analysis were provided by the sponsor on a floppy diskette.

Survival analysis: The intercurrent mortality data are given in table 1. The plots of Kaplan-Meier estimates of the survival distributions of male and female mice are given in Figures 1a and 1b, respectively. The homogeneity of survival distributions of four groups (Control, Low, Medium, High) were tested separately for male and female mice using the Cox test and the Generalized Wilcoxon test. The tests did not show any statistically significant (at .05 level) positive linear trend or difference in mortality among the treatment groups in either sex.

The p-values of the positive linear trend and the pairwise tests are given in Tables 2a and 2b, respectively.

Tumor data analysis: The reviewer performed the trend test on data of all tumor types and the pairwise comparisons of the treated groups with the control for some selected tumor types. Since the sponsor classified the tumor types as 'cause of death' or 'not a cause of death', following Peto et al. (1980), the reviewer applied the 'death rate method' and the 'prevalence method' for testing positive linear trend in these two categories of tumor types, respectively. For tumor types occurring in both categories (i.e. same tumor found as cause of death for some animals and not cause of death for some other animals) a combined test was performed. The exact permutation method was used to calculate the p-values of all trend tests, except when the tumors were found in both categories, in which cases the continuity corrected normal test was used. The scores used were 0, 5, 15, and 75 for control, low, medium, and high dose groups, respectively. The time intervals used were 0-365, 366-548, 549-654, 655-728 days, and terminal sacrifice for both sexes.

The incidence rates of tumor types with p-values less than .05 are listed below.

<u>Male</u> <u>Organ/Tumor</u>	<u>Tumor rate</u>				<u>P-values</u>	
	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>	<u>Trend</u>	<u>Pairwise</u>
	100	50	50	50		
Liver/ Hepatocellular adenoma	3	0	0	4	.0260	.1307 (C,H)
Liver/ Hepatocellular carcinoma	2	1	1	8	.0002	.0023 (C,H)
Liver/ Histiocytic sarcoma	2	0	3	4	.0257	.0926 (C,H)
Thyroid gland/ Follicular adenoma	8	0	0	7	.0133	.1475 (C,H)
<u>Female</u>						
Pituitary gland/Adenoma	6	7	4	8	.0452	.0392 (C,H)
Thyroid gland/ Follicular adenoma	0	1	1	2	.0450	.0937 (C,H)

Multiple testing adjustment: The rule proposed by Haseman (Haseman J.K., A re-examination of false-positive rates for carcinogenesis studies, Fundamental and Applied Toxicology, 3: 334-339, 1983) and a similar rule proposed by The Division of Biometrics (Lin K. and Rahman M., False Positive Rates in Tests for Linear Trends in Tumor Incidence in Animal Carcinogenicity Studies of New Drug, unpublished report, Division of Biometrics, CDER, FDA, 1995) were used to adjust the effect of multiple testings. The two rules state that in order to keep the false-positive rate at the nominal level of approximately ten percent, tumor types with spontaneous tumor rate of no greater than one percent should be tested at 0.05 level for pairwise comparisons, and at 0.025 level for positive linear trend tests and for tumor types with spontaneous tumor rate greater than or equal to one percent the level should be set at 0.01 for pairwise comparisons and 0.005 for the positive linear trend tests.

On the basis of the rule proposed by The Division of Biometrics the positive linear trend in hepatocellular carcinoma in male mice is considered to be statistically significant. Also on the basis of Haseman's rule the pairwise comparison of high dose group with the control for hepatocellular carcinoma in male mice is considered to be statistically significant.

III. The rat study

IIIa. Design: Two separate experiments, one in male and one in female rats were conducted. In each of these experiments there were three treated groups, known as low, medium, and high and one control group. Two hundred and fifty five male and two hundred and sixty female Alpk: AdfSD (Wistar derived) rats were randomly divided into selected sizes of 102, 51, 51, and 51 for control, low, medium, and high dose group, respectively for male and 104, 52, 52, and 52 for control, low, medium, and high dose group, respectively for female rats. The dose levels for the treated groups were 5, 15, and 75 mg/kg/day for low, medium, and high dose groups, respectively. The animals in the control group remained untreated.

The animals were checked daily for mortality and morbidity and were examined weekly for the presence of any palpable masses. A complete histopathological examination was performed on all animals found dead, killed moribund during the experiment or sacrificed at the end of the experiment.

IIIb. Sponsor's analysis

Survival data analysis: Summaries of cumulative mortality for male and female rats were presented in tabular forms. The weekly

percentages of survival rates of four groups were presented graphically. The survival distributions of pairs of treatment groups were compared using the log rank test. An overall chi-square test was performed to test the homogeneity of survival in different treatment groups. The SAS LIFETEST procedure was used for this analysis with two-sided level of significance.

The test did not show any statistically significant difference in mortality among the treatment groups in either sex.

Tumor data analysis: The tumor data were analyzed using the methods described in the paper of Peto et al. (1980). The intervals used for the mortality adjustment among treatment groups were 0-420, 421-532, 533-616, 617-672, and more than 672 days. Tumors with 5 or fewer number of tumor bearing animals were analyzed using permutation test (Exact test) as was suggested by Mantel (1980). It was not mentioned what type scores were used for this test.

Adjustment for the effect of multiple testings was done using a method due to Tukey (Mantel 1980) and Mantel et al. (1982). A brief description of the method is given in section IIb.

The tests showed statistically significant positive linear trends in the incidences of benign leydig cell tumor in testes and in follicular adenoma in thyroids in male mice, and follicular adenoma in thyroids and adenocarcinoma in uterus in female mice.

IIIc. Reviewer's analysis

The reviewer independently performed analyses on the survival and the tumor data. For survival data analysis the methods described in the papers of Cox (1972) and of Gehan (1965) were used. The tumor data analyses were performed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test, developed by the Division of Biometrics. All data used in the reviewer's analysis were provided by the sponsor on a floppy diskette.

Survival analysis: The intercurrent mortality data of the rat study are given in table 4. The plots of Kaplan-Meier estimates of the survival distributions for male and female rats are given in Figures 2a and 2b, respectively. The homogeneity of survival distributions of four groups (Control, Low, Medium, and High) were tested separately for male and female rats using the Cox test and the Generalized Wilcoxon test. The test did not show any statistically significant (at .05 level) positive linear trend in either sex. However, in female rats pairwise comparisons showed a statistically significant increased mortality in the high dose group when compared with the control.

The p-values of the trend and the pairwise tests are given in Tables 5a and 5b.

Tumor data analysis: The reviewer performed the trend test on data of all tumor types and the pairwise comparisons of the treated groups with the control for some selected tumor types. Since the sponsor classified the tumor types as 'cause of death' or 'not a cause of death', following Peto et al. (1980), the reviewer applied the 'death rate method' and the 'prevalence method' for testing the positive linear trend in these two categories of tumor types, respectively. For tumor types occurring in both categories a combined test was performed. The exact permutation trend method was used to calculate the p-values of all trend tests, except when the tumors were found in both categories, in which cases the continuity corrected normal test was used. The scores used were 0, 5, 15, and 75 for control, low, medium, and high dose groups, respectively. The time intervals used were 0-365, 366-548, 549-654, 655-728 days, and terminal sacrifice for both sexes.

The incidence rates of tumor types with p-values less than .05 are listed below.

<u>Male</u> <u>Organ/Tumor</u>	<u>Tumor rate</u>				<u>P-values</u>	
	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>	<u>Trend</u>	<u>Pairwise</u>
	100	50	50	50		
Testes/Benign leydig cell tumor	3	19	32	48	.0000	.0000(C,H)
Thyroid gland/Follicular adenoma	4	9	16	27	.0000	.0000(C,H)
<u>Female</u>						
Brain/Astrocytoma	0	0	0	2	.0358	.1065(C,H)
Thyroid gland/Follicular adenoma	0	2	8	22	.0000	.0000(C,H)
Uterus/Adenocarcinoma	0	0	1	5	.0002	.0023(C,H)

Multiple testing adjustment: The rules proposed by Haseman (1983) and The Division of Biometrics (1995) were used to adjust the effect of multiple testings.

On the basis of the rule proposed by The Division of Biometrics, the positive linear trends in all the above mentioned tumor types except astrocytoma in brain in females are considered to be statistically significant. Also on the basis of Haseman's rule the pairwise comparisons of high dose group with the control for all the above mentioned tumor types except astrocytoma in brain in females are considered to be statistically significant.

The incidence rates and p-values of all tumor types tested for positive linear trend are given in Table 6.

Table 1

Intercurrent mortality rates in the mouse study

Sex	Time(wks)	Control	Low	Medium	High
MALE					
	0 - 52	3/100 (3.00)	0/ 50 (0.00)	1/ 50 (2.00)	3/ 50 (6.00)
	53- 78	10/ 97 (13.00)	8/ 50 (16.00)	4/ 49 (10.00)	5/ 47 (16.00)
	79- 93	13/ 87 (26.00)	8/ 42 (32.00)	13/ 45 (36.00)	9/ 42 (34.00)
	94-104	22/ 74 (48.00)	12/ 34 (56.00)	10/ 32 (56.00)	10/ 33 (54.00)
	TERM. SACR	52/100 (52.00)	22/ 50 (44.00)	22/ 50 (44.00)	23/ 50 (46.00)
FEMALE					
	0 - 52	3/100 (3.00)	2/ 50 (4.00)	1/ 50 (2.00)	4/ 50 (8.00)
	53- 78	7/ 97 (10.00)	5/ 48 (14.00)	4/ 49 (10.00)	7/ 46 (22.00)
	79- 93	19/ 90 (29.00)	8/ 43 (30.00)	7/ 45 (24.00)	7/ 39 (36.00)
	94-104	20/ 71 (49.00)	10/ 35 (50.00)	13/ 38 (50.00)	9/ 32 (54.00)
	TERM. SACR	51/100 (51.00)	25/ 50 (50.00)	25/ 50 (50.00)	23/ 50 (46.00)

Note: Except the TERM. SACR. row, an entry of this table = number of animals dying or sacrificed in the time interval/number of animals entering the time interval. An entry in parenthesis = cumulative mortality rate; i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SACR. row = number of animals surviving to terminal sacrifice / initial number of animals. An entry in parenthesis in this row = percent of animals (of the initial number) surviving to terminal sacrifice.

Table 2b

P-values of pairwise tests for the differences in mortality between treatment groups in the mouse study

Male mouse

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DESMAP: a:\male\lta.mms

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST			GENERALIZED R/W ANALYSIS		
				EXACT	INVERSE	CONSERVATIVE	EXACT	INVERSE	CONSERVATIVE
0 VS. 1	CHISQ	.8634	POS	.6711	.6705	.8071	.8064		
	PROB	.2266		.4127	.4129	.3690	.3692		
0 VS. 2	CHISQ	.8634	POS	.6135	.6126	.6401	.6393		
	PROB	.2266		.4335	.4338	.4237	.4240		
0 VS. 3	CHISQ	.3700	POS	.3266	.3264	.4016	.4015		
	PROB	.3810		.5677	.5678	.4877	.4878		
1 VS. 2	CHISQ	.0000	POS	.0078	.0078	.0357	.0357		
	PROB	.9799		.9309	.9309	.9501	.9502		
1 VS. 3	CHISQ	.0000	NEG	.0067	.0067	.0346	.0346		
	PROB	.9999		.9347	.9347	.9524	.9525		
2 VS. 3	CHISQ	.0000	NEG	.0010	.0010	.0058	.0058		
	PROB	.9999		.9751	.9751	.9410	.9410		

Female mouse

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DESMAP: a:\male\lta.fem

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST			GENERALIZED R/W ANALYSIS		
				EXACT	INVERSE	CONSERVATIVE	EXACT	INVERSE	CONSERVATIVE
0 VS. 1	CHISQ	.0133	POS	.0168	.0168	.1375	.1375		
	PROB	.8229		.8969	.8970	.7108	.7108		
0 VS. 2	CHISQ	.0133	POS	.0151	.0151	.0078	.0078		
	PROB	.8229		.9022	.9022	.9311	.9311		
0 VS. 3	CHISQ	.1834	POS	.4749	.4749	1.0783	1.0786		
	PROB	.3455		.4907	.4908	.2995	.2997		
1 VS. 2	CHISQ	.0000	POS	.0110	.0110	.0546	.0546		
	PROB	.9792		.9163	.9164	.8152	.8152		
1 VS. 3	CHISQ	.0401	POS	.1171	.1170	.1392	.1391		
	PROB	.4287		.7322	.7323	.5603	.5603		
2 VS. 3	CHISQ	.0401	POS	.1682	.1680	.5586	.5581		
	PROB	.4207		.6817	.6819	.4588	.4590		

Table 3

Tumor rates and p-values of the tested tumor types for positive linear trend in mouse study

Male mice

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
BONE AND MARROW - FEMUR	Histiocytic sarcoma (M)	S	1.0000	0.82195	2	0	0	0
BONE AND MARROW - FEMUR	Mast cell tumour (M)	S	0.2093	0.02865	0	0	0	1
BONE AND MARROW - STERNUM	Angiosarcoma (M)	M	0.1042	0.08680	0	0	1	1
BRAIN	Meningeal composite lymphom	S	0.5990	0.68815	0	1	0	0
EAR	Squamous papilloma (B)	S	0.3782	0.54490	0	0	1	0
EPIDIDYMIDES	Histiocytic sarcoma (M)	M	0.9446	0.91920	4	2	1	0
HARDERIAN GLANDS	Adenoma (B)	S	0.3782	0.54490	0	0	1	0
HARDERIAN GLANDS	Cystadenoma (B)	M	0.2953	0.27375	5	1	1	3
INTESTINE - DUODENUM	Polyp (B)	S	1.0000	0.74450	1	0	0	0
INTESTINE - ILEUM	Composite lymphoma (M)	M	1.0000	0.86820	3	0	0	0
INTESTINE - JEJUNUM	Composite lymphoma (M)	M	0.3813	0.56205	0	0	2	0
LIVER	Angiosarcoma (M)	M	0.6870	0.77975	0	3	1	0
LIVER	Hepatocellular adenoma (B)	S	0.0260	0.00910	3	0	0	4
LIVER	Hepatocellular carcinoma (M)	M	0.0002	0.00000	2	1	1	8
LIVER	Histiocytic sarcoma (M)	M	0.0257	0.01975	2	0	3	4
LYMPH NODE - MANDIBULAR	Composite lymphoma (M)	M	0.5534	0.69735	1	0	2	0
LYMPH NODE - MESENTERIC	Angioma (B)	S	0.4255	0.34445	1	1	0	1
LYMPH NODE - MESENTERIC	Composite lymphoma (M)	M	0.6106	0.61470	40	24	18	19
LYMPH NODE - MESENTERIC	Histiocytic sarcoma (M)	S	0.1965	0.02365	0	0	0	1
LYMPH NODES - NON-PROTOCO	Composite lymphoma (M)	M	0.3753	0.31180	1	1	0	1
ORAL CAVITY	Osteosarcoma (M)	S	0.3906	0.54930	0	0	1	0
PITUITARY GLAND	Adenoma (B)	S	0.3769	0.55980	0	0	2	0
PREPUTIAL GLAND	Histiocytic sarcoma (M)	S	1.0000	0.73875	1	0	0	0
SALIVARY GLANDS - SUBMAXILL	Histiocytic sarcoma (M)	S	0.5631	0.67930	0	1	0	0
SEMINAL VESICLES	Histiocytic sarcoma (M)	S	1.0000	0.73965	1	0	0	0
SKIN - NON-PROTOCOLLED	Angioma (B)	S	0.4638	0.42435	1	2	0	1
SKIN - NON-PROTOCOLLED	Benign mastocytoma (B)	S	0.3704	0.53980	0	0	1	0
SKIN - NON-PROTOCOLLED	Histiocytic sarcoma (M)	S	0.5631	0.67930	0	1	0	0
SKIN - NON-PROTOCOLLED	Squamous papilloma (B)	S	0.1933	0.02245	0	0	0	1
SPINAL CORD	Histiocytic sarcoma (B)	S	1.0000	0.74490	1	0	0	0
SPLEEN	Angioma (B)	S	1.0000	0.83705	2	0	0	0
SPLEEN	Angiosarcoma (M)	M	0.5542	0.60330	3	1	2	1
SPLEEN	Composite lymphoma (M)	M	0.3096	0.35115	2	2	3	2
SPLEEN	Mast cell sarcoma (M)	S	1.0000	0.73965	1	0	0	0
TESTES	Angioma (B)	S	0.1933	0.02245	0	0	0	1
TESTES	Benign Leydig cell tumour (S	0.1870	0.25285	0	1	2	1
TESTES	Histiocytic sarcoma (M)	S	0.6623	0.75225	0	2	0	0
TESTES	Malignant Leydig cell tumou	S	0.5631	0.67930	0	1	0	0
THYROID GLAND	Adenoma - follicular (B)	S	0.0133	0.00870	8	0	0	7

Table 3 continued to the next page

Table 3 continued from the previous page

Female mice									
Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H	
ABDOMINAL CAVITY	Angioma (B)	S	1.0000	0.74085	1	0	0	0	
ADRENAL GLANDS	Benign pheochromocytoma (B)	S	0.6154	0.68170	0	1	0	0	
BONE AND MARROW - FEMUR	Angiosarcoma (M)	S	0.6154	0.68170	0	1	0	0	
BONE AND MARROW - FEMUR	Histiocytic sarcoma (M)	S	0.3977	0.54155	0	0	1	0	
BONE AND MARROW - STERNUM	Histiocytic sarcoma (M)	S	0.3245	0.14725	1	0	0	1	
BRAIN	Benign meningioma (B)	S	1.0000	0.74085	1	0	0	0	
CERVIX	Histiocytic sarcoma (M)	M	0.3854	0.39765	0	2	4	1	
GALL BLADDER	Papilloma (B)	S	1.0000	0.74085	1	0	0	0	
HARDERIAN GLANDS	Adenoma (B)	S	0.3414	0.51970	0	0	1	0	
HARDERIAN GLANDS	Cystadenoma (B)	M	0.5760	0.72755	0	2	1	0	
INTESTINE - DUODENUM	Polyp (B)	S	0.1550	0.05990	1	0	0	2	
INTESTINE - ILEUM	Composite lymphoma (M)	M	0.8294	0.78275	1	1	0	0	
INTESTINE - JEJUNUM	Composite lymphoma (M)	S	0.8328	0.78505	1	1	0	0	
INTESTINE - JEJUNUM	Polyp (B)	S	1.0000	0.79310	1	0	0	0	
LIMBS AND TAIL	Angiosarcoma (M)	M	1.0000	0.82035	2	0	0	0	
LIVER	Angioma (B)	S	0.8328	0.78505	1	1	0	0	
LIVER	Angiosarcoma (M)	S	1.0000	0.73715	1	0	0	0	
LIVER	Hepatocellular carcinoma (M)	S	0.5920	0.67855	0	1	0	0	
LIVER	Histiocytic sarcoma (M)	M	0.5334	0.59590	3	1	3	1	
LUNGS	Adenocarcinoma (M)	M	0.1630	0.08335	2	0	0	2	
LYMPH NODE - MANDIBULAR	Composite lymphoma (M)	M	0.3286	0.15650	1	0	0	1	
LYMPH NODE - MESENTERIC	Angioma (B)	S	1.0000	0.72645	1	0	0	0	
LYMPH NODE - MESENTERIC	Composite lymphoma (M)	S	0.8422	0.83985	47	27	25	20	
LYMPH NODES - NON-PROTOCO	Composite lymphoma (M)	M	0.3843	0.38785	4	1	2	2	
LYMPH NODES - NON-PROTOCO	Histiocytic sarcoma (M)	S	1.0000	0.79310	1	0	0	0	
OVARIES	Arrhenoblastoma (B)	S	0.6263	0.70325	1	0	1	0	
OVARIES	Granulosa cell adenoma (B)	S	1.0000	0.74085	1	0	0	0	
PITUITARY GLAND	Adenoma (B)	M	0.0452	0.03790	6	7	4	8	
SALIVARY GLANDS - SUBMAXILL	Histiocytic sarcoma (M)	S	0.1855	0.02000	0	0	0	1	
SKIN - NON-PROTOCOLLED	Angioma (B)	S	0.6783	0.76035	1	1	1	0	
SKIN - NON-PROTOCOLLED	Composite lymphoma (M)	S	0.4782	0.63870	0	0	1	0	
SKIN - NON-PROTOCOLLED	Fibroma (B)	S	0.1855	0.02000	0	0	0	1	
SKIN - NON-PROTOCOLLED	Histiocytic sarcoma (M)	S	1.0000	0.73630	1	0	0	0	
SPLEEN	Angiosarcoma (M)	S	0.1589	0.11440	2	0	1	2	
SPLEEN	Composite lymphoma (M)	M	0.2873	0.28145	3	3	6	3	
SPLEEN	Myeloid leukaemia (myelobla	S	0.3857	0.53410	0	0	1	0	
STOMACH	Squamous carcinoma (M)	S	0.1855	0.02000	0	0	0	1	
STOMACH	Squamous papilloma (B)	S	0.3190	0.14615	1	0	0	1	
THYROID GLAND	Adenoma - follicular (B)	S	0.0450	0.03675	0	1	1	2	
UTERUS	Angioma (B)	S	0.6375	0.74800	1	1	2	0	
UTERUS	Histiocytic sarcoma (M)	M	0.5056	0.52010	9	4	7	4	
VERTEBRAL COLUMN	Histiocytic sarcoma (M)	S	1.0000	0.74490	1	0	0	0	
VERTEBRAL COLUMN	Osteosarcoma (M)	S	1.0000	0.74410	1	0	0	0	

Table 4

Intercurrent mortality rates in the rat study

Sex	Time(wks)	Control	Low	Medium	High
		-----	---	-----	-----
MALE					
	0 - 52	7/102 (6.86)	7/ 51 (13.73)	1/ 51 (1.96)	0/ 51 (0.00)
	53- 78	20/ 95 (26.47)	6/ 44 (25.49)	12/ 50 (25.49)	7/ 51 (13.73)
	79- 93	19/ 75 (45.10)	10/ 38 (45.10)	10/ 38 (45.10)	12/ 44 (37.25)
	94-104	19/ 56 (63.73)	16/ 28 (76.47)	7/ 28 (58.82)	7/ 32 (50.98)
	TERM. SACR	37/102 (36.27)	12/ 51 (23.53)	21/ 51 (41.18)	25/ 51 (49.02)
FEMALE					
	0 - 52	6/104 (5.77)	0/ 52 (0.00)	1/ 52 (1.92)	3/ 52 (5.77)
	53- 78	9/ 98 (14.42)	4/ 52 (7.69)	3/ 51 (7.69)	9/ 49 (23.08)
	79- 93	18/ 89 (31.73)	7/ 48 (21.15)	12/ 48 (30.77)	10/ 40 (42.31)
	94-104	22/ 71 (52.92)	11/ 41 (42.31)	10/ 36 (53.85)	9/ 30 (59.62)
	TERM. .	7/104 (7.12)	30/ 52 (57.69)	24/ 52 (46.15)	31/ 52 (46.38)

Note: Except the TERM. SACR. row, an entry of this table = number of animals dying or sacrificed in the time interval/number of animals entering the time interval. An entry in parenthesis = cumulative mortality rate; i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SACR. row = number of animals surviving to terminal sacrifice / initial number of animals. An entry in parenthesis in this row = percent of animals (of the initial number) surviving to terminal sacrifice.

Table 5b

P-values of pairwise tests for the differences in mortality between treatment groups in the rat study

Male rat

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: a:\male\lta.frc

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE (2X2 # IN DEN)	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED L/W ANALYSIS	
				EXACT	CONSERVATIVE	EXACT	CONSERVATIVE
0 VS. 1	CHI-SQ PROB	1.9851 .1598	POS	1.9403 .1632	1.0886 .3038	.8143 .4723	.8140 .4724
0 VS. 2	CHI-SQ PROB	.1701 .6800	NEG	.2282 .6329	.2279 .6331	.3621 .5530	.3516 .5531
0 VS. 3	CHI-SQ PROB	1.7932 .1805	NEG	2.4805 .1151	2.4768 .1155	1.3735 .0663	1.3700 .0664
1 VS. 2	CHI-SQ PROB	2.8669 .0904	NEG	2.0682 .1504	2.0535 .1519	1.4226 .2313	1.4205 .2320
1 VS. 3	CHI-SQ PROB	6.1075 .0235*	NEG	5.7993 .0160*	5.7850 .0164*	5.2725 .0217*	5.2534 .0219*
2 VS. 3	CHI-SQ PROB	.3544 .5505	NEG	.6742 .4116	.6738 .4117	1.1807 .2756	1.1878 .2768

Female rat

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: a:\male\lta.frc

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE (2X2 # IN DEN)	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED L/W ANALYSIS	
				EXACT	CONSERVATIVE	EXACT	CONSERVATIVE
0 VS. 1	CHI-SQ PROB	1.1572 .2820	NEG	1.5276 .2165	1.5268 .2166	2.1170 .1457	2.1156 .1458
0 VS. 2	CHI-SQ PROB	.0129 .9097	POS	.0000 .9988	.0000 .9988	.0188 .8909	.0188 .8909
0 VS. 3	CHI-SQ PROB	.1919 .6613	POS	.4785 .4891	.4782 .4892	.6919 .4055	.6916 .4056
1 VS. 2	CHI-SQ PROB	.9630 .3264	POS	1.1944 .2765	1.1821 .2769	1.5190 .2178	1.5164 .2182
1 VS. 3	CHI-SQ PROB	2.4624 .1164	POS	1.1324 .0748	1.1272 .0770	4.1562 .0415*	4.1488 .0417*
2 VS. 3	CHI-SQ PROB	.1567 .6922	POS	.3557 .5509	.3554 .5511	.8351 .3608	.8343 .3610

Table 6

Tumor rates and p-values of the tested tumor types for positive linear trend in rat study

<u>Male rats</u>				Exact	Asymptotic	C	L	M	H
Organ Name	Tumor Name	MSFLG	P-Value	P-value					
ADRENAL GLANDS	Benign pheochromocytoma (B)	S	0.3539	0.34135	3	4	1	3	
ADRENAL GLANDS	Cortical adenoma (B)	M	0.7721	0.73955	5	0	0	1	
ADRENAL GLANDS	Malignant pheochromocytoma	S	0.2857	0.49190	0	0	1	0	
BRAIN	Astrocytoma (B)	M	0.8453	0.85470	2	2	1	0	
BRAIN	Malignant meningioma (M)	M	0.0833	0.05010	1	2	0	3	
BRAIN	Malignant oligodendroglioma	S	1.0000	0.75740	1	0	0	0	
EARS	Squamous papilloma (B)	S	1.0000	0.71750	1	0	0	0	
EPIDIDYMIDES	Adjacent tissue angioma (B)	S	1.0000	0.77625	1	0	0	0	
EPIDIDYMIDES	Benign mesothelioma (B)	S	0.1429	0.00810	0	0	0	1	
INTESTINE - DUODENUM	Adenocarcinoma (M)	M	0.2727	0.26520	1	0	1	1	
KIDNEYS	Tubular adenoma (B)	S	0.2520	0.22845	0	1	0	1	
LIMBS AND TAIL	Angioma (B)	S	0.6105	0.72550	0	1	0	0	
LIMBS AND TAIL	Keratoacanthoma (B)	S	0.6122	0.64690	0	1	0	0	
LIMBS AND TAIL	Osteosarcoma (M)	S	1.0000	0.75565	1	0	0	0	
LIMBS AND TAIL	Squamous papilloma (B)	S	1.0000	0.83820	2	0	0	0	
LIVER	Hepatocellular adenoma (B)	S	0.5873	0.66930	1	0	1	0	
LIVER	Hepatocellular carcinoma (M)	S	0.6275	0.70885	0	1	0	0	
LUNGS	Cystic adenoma (B)	S	0.2632	0.04990	0	0	0	1	
LYMPH NODE - MANDIBULAR	Malignant lymphoma - lympho	S	0.6947	0.76470	0	2	0	0	
LYMPH NODE - MESENTERIC	Angioma (B)	S	0.7812	0.75250	4	1	1	1	
LYMPH NODE - MESENTERIC	Malignant lymphoma - lympho	S	0.8547	0.84050	1	2	0	0	
LYMPH NODES - NON-PROTOCOLL	Pancreatic node malignant 1	S	1.0000	0.77625	1	0	0	0	
MAMMARY GLANDS	Adenocarcinoma (M)	S	1.0000	0.77625	1	0	0	0	
MAMMARY GLANDS	Fibroadenoma (B)	S	1.0000	0.82960	2	0	0	0	
MAMMARY GLANDS	Histiocytic sarcoma (M)	S	0.4107	0.57195	0	0	1	0	
MUSCLE - SKELETAL	Neurofibroma (B)	S	1.0000	0.77625	1	0	0	0	
ORAL CAVITY	Basal cell carcinoma (M)	S	1.0000	0.75805	1	0	0	0	
ORAL CAVITY	Squamous carcinoma (M)	S	0.1676	0.14945	0	0	1	1	
PANCREAS	Exocrine adenocarcinoma (M)	S	0.2632	0.04990	0	0	0	1	
PANCREAS	Exocrine adenoma (B)	S	0.2307	0.22260	8	4	2	6	
PANCREAS	Islet cell adenoma (B)	S	0.4228	0.34310	1	1	0	1	
PARATHYROID GLANDS	Adenoma (B)	S	0.4223	0.52050	0	0	1	0	
PITUITARY GLAND	Adenoma - angiomatous (B)	M	0.3153	0.31560	15	12	9	13	
PITUITARY GLAND	Adenoma - solid (B)	M	0.9466	0.94170	25	10	9	8	
PROSTATE GLAND	Adenoma (B)	S	1.0000	0.77625	1	0	0	0	
SALIVARY GLANDS - PAROTID	Acinar adenoma (B)	S	0.5433	0.41225	2	0	0	1	
SEMINAL VESICLES	Adenocarcinoma (M)	M	1.0000	0.84940	2	0	0	0	
SKIN - NON-PROTOCOLLED	Angioma (B)	S	0.3684	0.17910	1	0	0	1	
SKIN - NON-PROTOCOLLED	Basal cell adenoma (B)	S	1.0000	0.77625	1	0	0	0	
SKIN - NON-PROTOCOLLED	Basal cell carcinoma (M)	S	1.0000	0.77625	1	0	0	0	
SKIN - NON-PROTOCOLLED	Fibroma (B)	S	0.1502	0.14600	2	1	2	3	
SKIN - NON-PROTOCOLLED	Lipoma (B)	S	1.0000	0.77625	1	0	0	0	
SKIN - NON-PROTOCOLLED	Malignant fibrohistiocytic	S	0.8496	0.80445	1	1	0	0	
SKIN - NON-PROTOCOLLED	Sebaceous adenoma (B)	S	1.0000	0.77625	1	0	0	0	
SKIN - NON-PROTOCOLLED	Squamous carcinoma (M)	S	0.4843	0.60970	0	0	1	0	
SKIN - NON-PROTOCOLLED	Squamous papilloma (B)	S	0.8941	0.87745	7	1	0	1	
SPLEEN	Histiocytic sarcoma (M)	S	0.2632	0.04990	0	0	0	1	
SPLEEN	Malignant lymphoma - lympho	S	0.4436	0.58665	0	0	1	0	
TESTES	Benign Leydig cell tumour (S	0.0000	0.00000	3	19	32	48	
TESTES	Benign mesothelioma (B)	S	0.8716	0.86725	7	1	3	1	
TESTES	Histiocytic sarcoma (M)	S	1.0000	0.77720	1	0	0	0	
THYMUS	Adenocarcinoma (M)	S	0.6122	0.6469	0	1	0	0	
THYMUS	Adenoma (B)	S	0.8759	0.8818	2	1	1	0	
THYMUS	Benign mixed thymoma (B)	M	0.4199	0.4176	1	5	5	3	
THYMUS	Malignant thymic lymphoma -	S	1.0000	0.8599	2	0	0	0	
THYROID GLAND	Adenoma - follicular (B)	S	0.0000	0.0000	4	9	16	27	
THYROID GLAND	Parafollicular adenoma (B)	S	0.3513	0.3216	4	1	1	3	
THYROID GLAND	Parafollicular cell carcino	S	0.8167	0.8229	2	0	1	0	
TONGUE	Squamous papilloma (B)	S	0.1556	0.0118	0	0	0	1	

NDA20498

CASODEX

2 OF 3

Table 6 continued from the previous page

Female rats

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
ABDOMINAL CAVITY	Malignant fibrohistiocytic	M	0.3243	0.15050	1	0	0	1
ADRENAL GLANDS	Benign pheochromocytoma (B)	S	0.3501	0.26065	1	1	0	1
ADRENAL GLANDS	Cortical adenoma (B)	S	0.9595	0.93400	4	4	1	0
BONE AND MARROW - STERNUM	Adjacent muscle fibrosarcom	S	0.1997	0.02455	0	0	0	1
BRAIN	Astrocytoma (B)	S	0.0358	0.00205	0	0	0	2
BRAIN	Benign meningioma (B)	S	0.3889	0.52775	0	0	1	0
CERVIX	Benign fibrous histiocytoma	S	1.0000	0.76115	1	0	0	0
CERVIX	Granular cell myoblastoma (S	1.0000	0.73665	1	0	0	0
CERVIX	Histiocytic sarcoma (M)	S	0.1694	0.01505	0	0	0	1
CERVIX	Malignant fibrohistiocytic	M	0.9390	0.85280	2	1	0	0
CERVIX	Polyp (stromal) (B)	S	0.3629	0.52695	0	0	1	0
INTESTINE - CAECUM	Leiomyoma (B)	S	1.0000	0.80560	1	0	0	0
INTESTINE - ILEUM	Malignant fibrohistiocytic	S	1.0000	0.74235	1	0	0	0
INTESTINE - JEJUNUM	Adenocarcinoma (M)	S	0.1958	0.02330	0	0	0	1
KIDNEYS	Nephroblastoma (M)	S	1.0000	0.74640	1	0	0	0
KIDNEYS	Tubular cystadenoma (B)	S	0.6170	0.70440	0	1	0	0
LIMBS AND TAIL	Squamous papilloma (B)	S	0.3440	0.16930	1	0	0	1
LIVER	Hepatocellular adenoma (B)	S	0.3674	0.39765	1	1	1	1
LIVER	Hepatocellular carcinoma (M)	S	1.0000	0.73465	1	0	0	0
LYMPH NODE - MANDIBULAR	Malignant fibrohistiocytic	S	1.0000	0.73665	1	0	0	0
LYMPH NODE - MESENTERIC	Angioma (B)	S	0.1762	0.10985	0	1	0	1
MAMMARY GLANDS	Adenocarcinoma (M)	S	0.9995	0.97785	8	2	0	0
MAMMARY GLANDS	Adenoma (B)	M	0.9686	0.94575	6	2	2	0
MAMMARY GLANDS	Fibroadenoma (B)	M	0.9977	0.99520	29	6	6	3
MAMMARY GLANDS	Fibroma (B)	S	1.0000	0.81330	2	0	0	0
MASSES AT NECROPSY	Histiocytic sarcoma (M)	S	1.0000	0.74435	1	0	0	0
ORAL CAVITY	Squamous papilloma (B)	S	0.4684	0.25595	1	0	0	1
OVARIES	Arrhenoblastoma (B)	S	0.7647	0.77865	2	0	1	0
OVARIES	Granulosa cell adenoma (B)	M	0.0998	0.10145	1	1	2	2
OVARIES	Granulosa cell carcinoma (M)	S	0.8458	0.77570	1	1	0	0
PANCREAS	Exocrine adenoma (B)	S	0.3112	0.34450	1	0	4	1
PANCREAS	Islet cell adenoma (B)	S	0.5066	0.67135	1	0	2	0
PITUITARY GLAND	Adenoma - angiomatous (B)	M	0.3774	0.37795	66	33	34	33
PITUITARY GLAND	Adenoma - solid (B)	M	0.9884	0.98440	26	10	10	5
SALIVARY GLANDS - PAROTID	Acinar adenoma (B)	S	0.3629	0.52695	0	0	1	0
SALIVARY GLANDS - SUBMAXILL	Adenocarcinoma (M)	S	1.0000	0.73800	1	0	0	0
SKIN - NON-PROTOCOLLED	Benign fibrous histiocytoma	M	0.8389	0.78020	1	1	0	0
SKIN - NON-PROTOCOLLED	Fibroma (B)	M	0.6634	0.75150	1	1	1	0
SKIN - NON-PROTOCOLLED	Lipoma (B)	S	1.0000	0.73465	1	0	0	0
SKIN - NON-PROTOCOLLED	Malignant fibrohistiocytic	S	0.3959	0.54915	0	0	1	0
SKIN - NON-PROTOCOLLED	Squamous carcinoma (M)	S	1.0000	0.73665	1	0	0	0
SKIN - NON-PROTOCOLLED	Squamous papilloma (B)	S	0.0936	0.06785	0	0	1	1
SPLEEN	Angiosarcoma (M)	S	0.6032	0.68375	0	1	0	0
SPLEEN	Malignant lymphoma - lympho	S	1.0000	0.74880	1	0	0	0
SPLEEN	Monocytic leukaemia (M)	S	0.1901	0.02150	0	0	0	1
STOMACH	Squamous papilloma (B)	S	1.0000	0.80560	1	0	0	0
THYMUS	Adenocarcinoma (M)	S	0.1811	0.01850	0	0	0	1
THYMUS	Adenoma (B)	S	0.6048	0.67020	0	1	0	0
THYMUS	Adjacent tissue fibrosarcom	S	1.0000	0.73550	1	0	0	0
THYMUS	Benign mixed thymoma (B)	M	0.7751	0.77580	17	7	5	5
THYMUS	Malignant thymic lymphoma -	S	1.0000	0.73465	1	0	0	0
THYROID GLAND	Adenoma - follicular (B)	S	0.0000	0.00000	0	2	8	22
THYROID GLAND	Parafollicular adenoma (B)	S	0.8443	0.82080	7	1	1	1
THYROID GLAND	Parafollicular cell carcino	S	0.7038	0.78665	1	2	1	0
UTERUS	Adenocarcinoma (M)	M	0.0002	0.00000	0	0	1	5
UTERUS	Polyp (adenomatous) (B)	S	0.1972	0.13975	0	1	0	1
UTERUS	Polyp (stromal) (B)	S	0.5372	0.54100	18	6	7	7
UTERUS	Squamous carcinoma (M)	S	0.1694	0.01505	0	0	0	1
VAGINA	Malignant fibrohistiocytic	S	0.5296	0.68300	1	0	2	0

Figure 1a

Kaplan-Meier Estimates of the survival distributions
(Male mice)

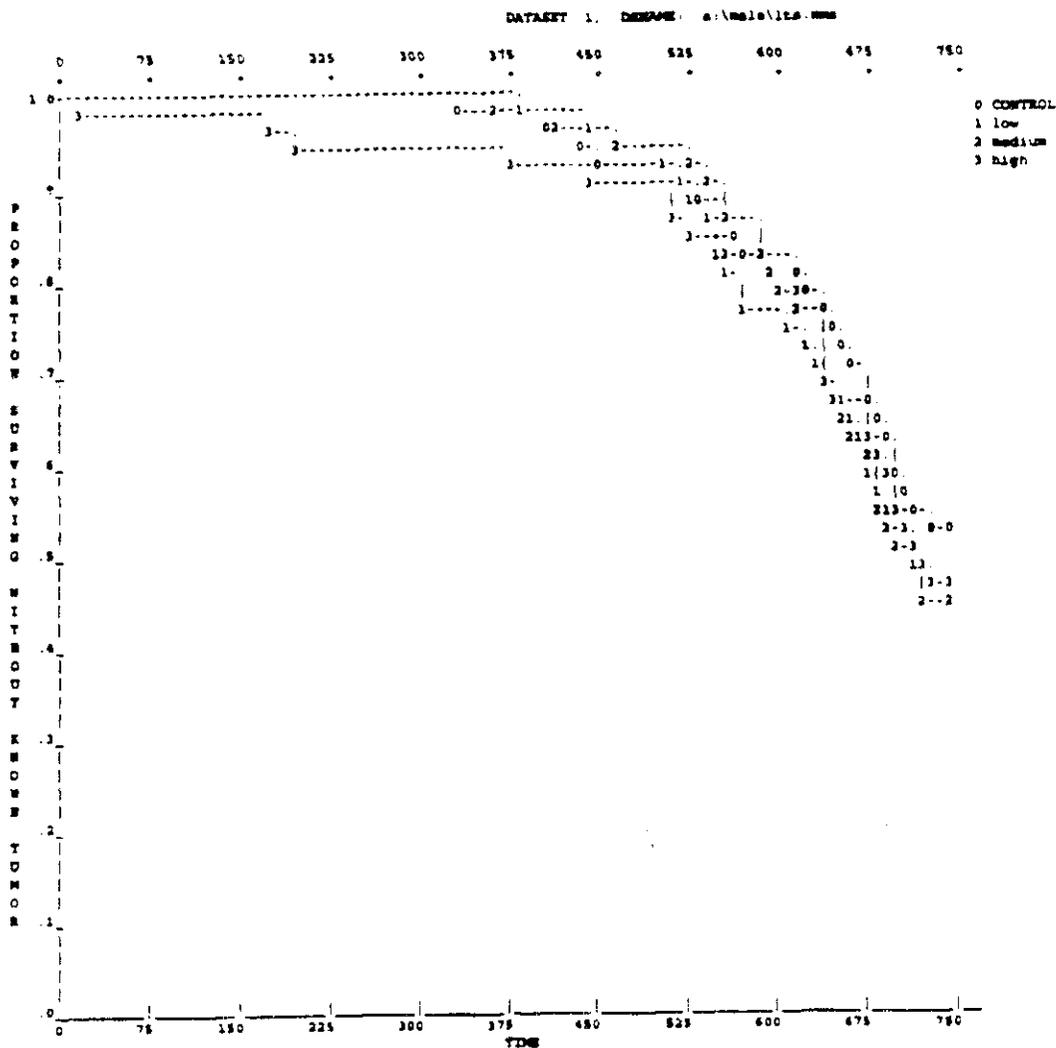


Figure 1b

Kaplan-Meier Estimates of the survival distributions
(Female mice)

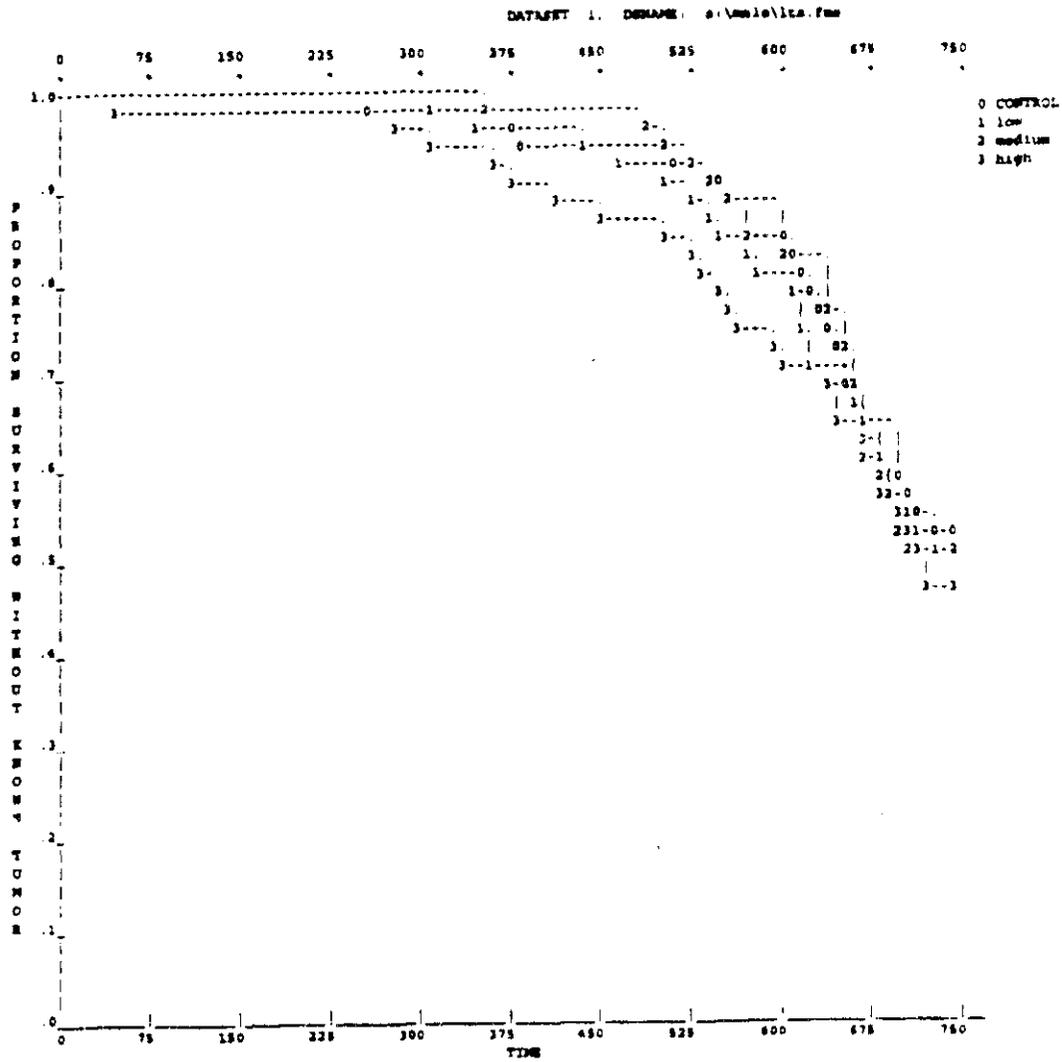


Figure 2a

Kaplan-Meier Estimates of the survival distributions
(Male rats)

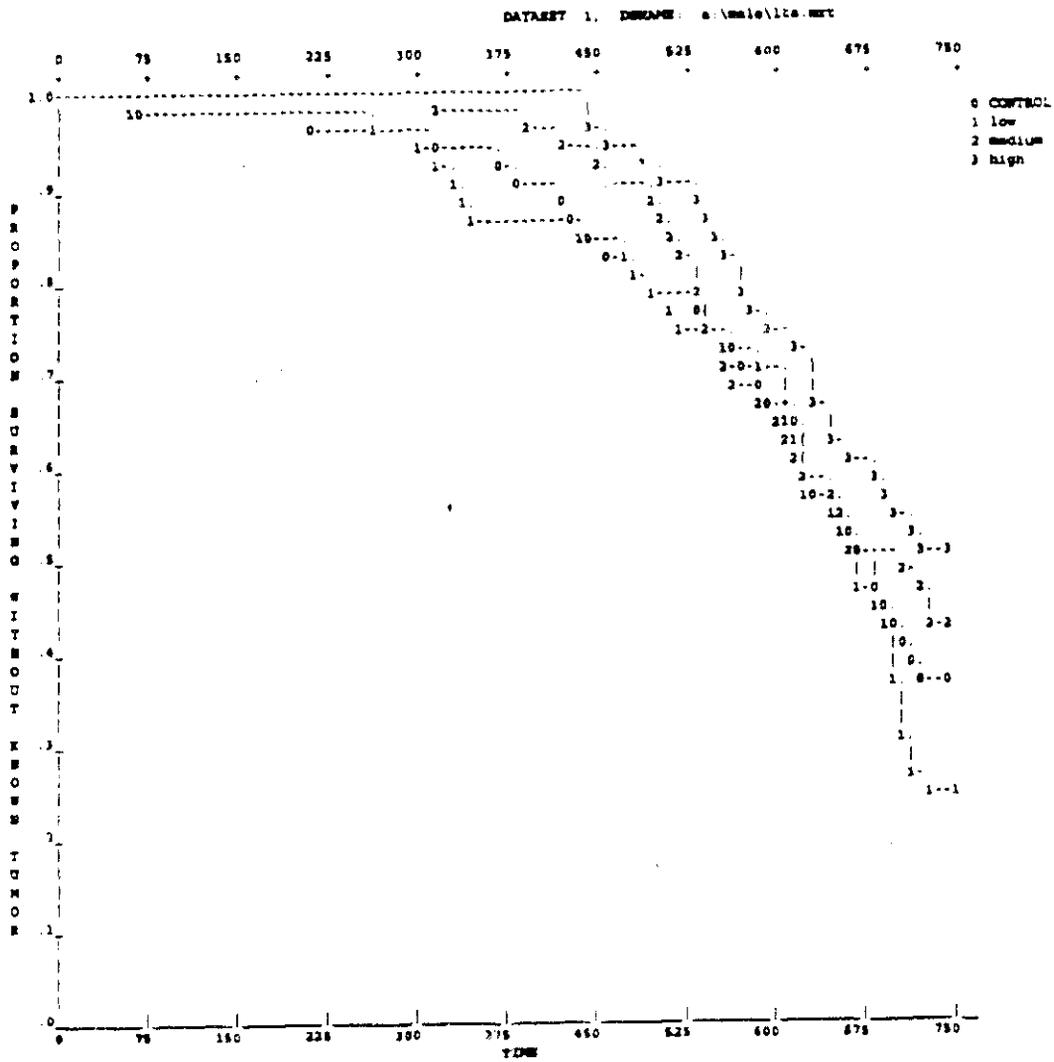
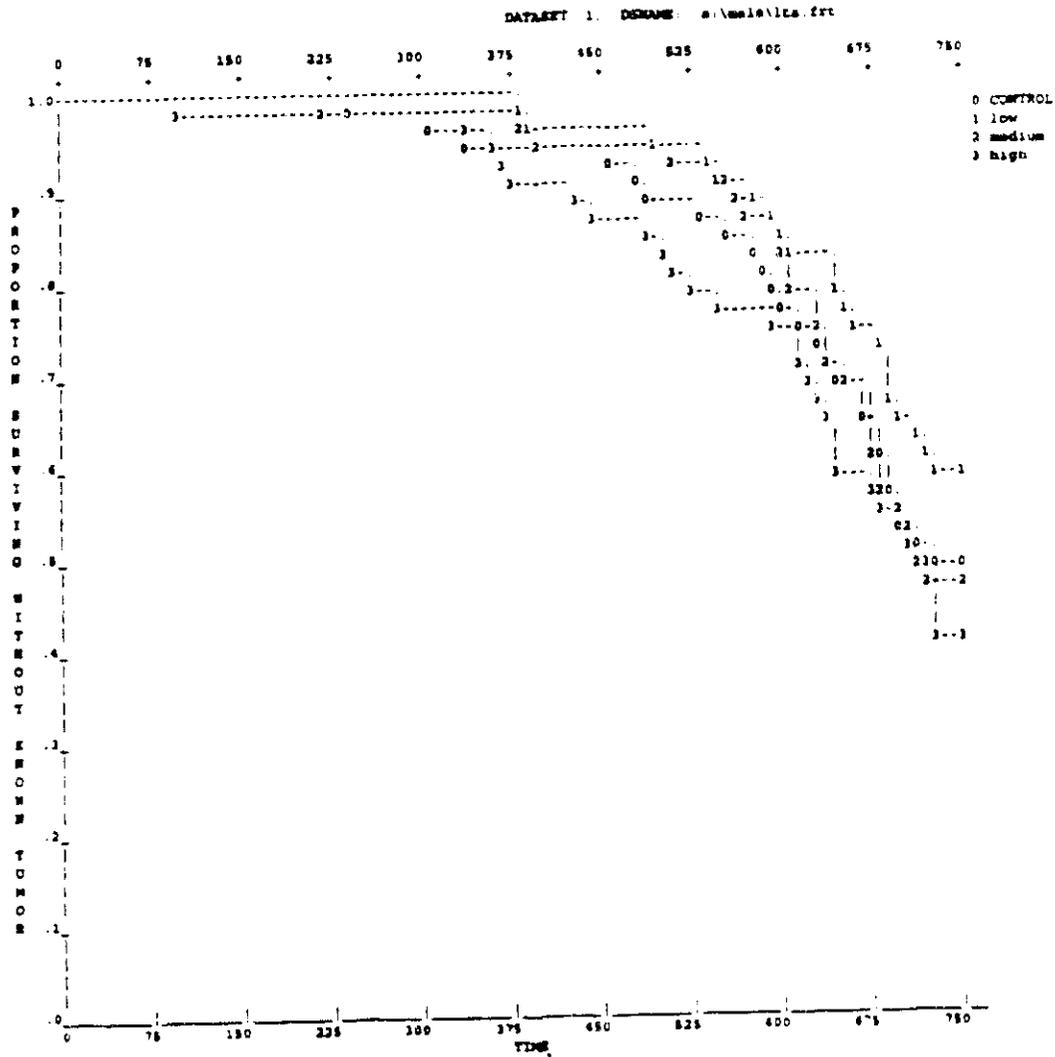


Figure 2b

Kaplan-Meier Estimates of the survival distributions
(Female rats)



NDA:	20-498	
Bicalutamide 50 mg tablets (Casodex[®])		JUL 19 1995
Submission Date:	9/14/94	
Sponsor:	Zeneca Pharmaceuticals Group Wilmington, Delaware	
Type of Submission:	New Drug Application (1S-NME)	
Reviewer:	Michael J. Fossler, Pharm. D., Ph. D.	

Synopsis

Bicalutamide is a non-steroidal anti-androgen which has been found to be useful in the treatment of advanced prostate cancer in combination with either surgical or medical castration. The Sponsor seeks approval for a 50 mg tablet, with the proposed dose being 50 mg daily. Bicalutamide is to be marketed as the racemate. The R isomer is the active isomer and has a half-life of about 6 days. The S isomer is essentially inactive and has a half-life of around 30 hours. Enantiomeric conversion has not been shown to occur in rats.

The absolute bioavailability of bicalutamide is unknown, as no intravenous formulation exists, but it appears that at least 50% of the dose is absorbed. The tablet formulation used in the pivotal clinical trials is equally bioavailable relative to an aqueous suspension and is unaffected by food. The to-be marketed formulation is bioequivalent to the clinical trials formulation.

A single-dose study in 22 prostate cancer patients showed that the racemate has a $t_{1/2}$ of 6.3 days. Other studies using a chiral assay have shown that the R (active) isomer has a much larger AUC, $t_{1/2}$, t_{max} and C_{max} than the S isomer. The steady-state kinetics of the compound are linear from 10-50 mg. Because of the great difference in elimination rates for the two enantiomers, at steady-state it is estimated that more than 99% of the steady-state plasma level is the R isomer.

Radiolabeled metabolism studies in male volunteers indicate that the compound is well-absorbed following oral administration. The drug is 96% protein-bound, primarily to albumin. The compound is metabolized primarily by glucuronidation, followed by elimination in the urine and feces. An oxidative metabolite is also formed, which is also glucuronidated. Virtually all of the compound eliminated in the first two days is the S form. Chronic administration of bicalutamide to patients has no significant inductive effect on P-450 enzymes.

Mild to moderate hepatic disease has no significant effect on the elimination of either enantiomer; however, subjects with severe liver disease showed

prolonged half-lives of the R isomer. No significant change occurred in the elimination of the S isomer. No relationship was found between steady-state concentrations of either enantiomer and age or renal function. Data from two clinical efficacy trials were used to show that no clinically relevant interactions exist between bicalutamide and LHRH analogues.

Data from two monotherapy trials which were included in the submission suggest that a concentration-effect relationship exists between plasma levels of bicalutamide and prostate-specific antigen levels in patients with prostate cancer. The data suggest that, for maximum suppression of PSA in monotherapy, steady-state levels of bicalutamide should be $\geq 10 \mu\text{g/mL}$. For the present indication, no PK/PD data are available, as both castration and bicalutamide affect PSA levels.

The HPLC assay used in all of the pivotal pharmacokinetic trials is a chiral assay with a limit of quantitation of 10 ng/mL. The validation data included in the submission show that the assay is precise and accurate.

The proposed dissolution method is _____ as the dissolution medium. The proposed dissolution specification is $Q =$ _____ @ 45 minutes. Data were included to show that the method is discriminating with regard to several tablet process variables.

Recommendation

The Biopharmaceutics portion of NDA 20-498 is approved. The recommended dissolution specification for the 50 mg tablet is _____ in not less than 30 minutes using _____. The text under XI.

Labeling Comments should be sent to the Sponsor, as should Comment 2 under X. **General Comments.**

Table of Contents

Page

Background..... 4
 Summary of Bioavailability/Pharmacokinetics/Pharmacodynamics..... 5
 General Comments 19
 Labeling Comments (to be sent to Sponsor)..... 20

Appendix I: Study Summaries (available upon request)

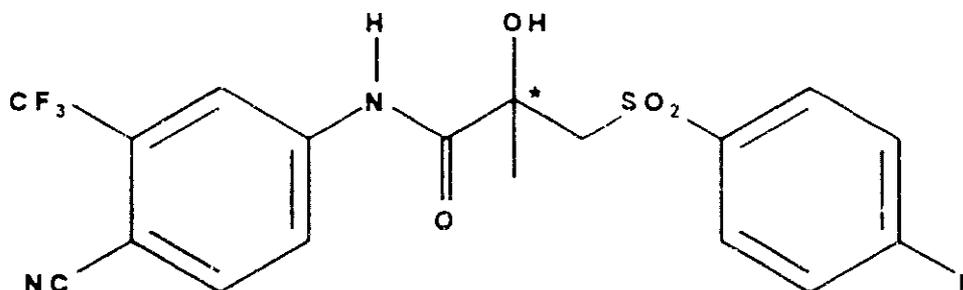
Study Number	Title	Page
176334/0001	An Open Study to Determine the Pharmacokinetics and Tolerability of Single Oral Doses of CASODEX (176.334) in Patients with Advanced Prostatic Carcinoma	25
7054IL/0005	An Open Randomized Crossover Trial to Assess the Bioequivalence in 50-mg Tablets of the Sales Formulation of CASODEX™ Relative to the Clinical Trials Formulation of CASODEX	27
176334/0006	The Metabolism and Pharmacokinetics of CASODEX™ (176.334) in Healthy Male Volunteers Following the Administration of a Single Oral Dose (50 mg) of [¹⁴ C]- (176.334)	31
176334/0007	An Open Patient Volunteer Study of the Effects of Impaired Hepatic Function on the Pharmacokinetics of a Single Oral Dose of 50 mg CASODEX™ (176.334)	33
176334/0008	An Open Randomized, Cross-Over Study to Compare the Bioavailability of the CASODEX™ (176.334) Clinical Trials Tablet with an Aqueous Suspension and to Assess the Effect of Food on the Bioavailability of the Clinical Trials Tablet, in Healthy Male Volunteers	35
176334/0010	An open patient volunteer study of the effects of impaired hepatic function on the pharmacokinetics of a single oral dose of 150 mg CASODEX	37
176334/0012	An open, randomized, cross-over study to assess the bioequivalence of a CASODEX (176.334) Intended Sales tablet and the CASODEX (176.334) Clinical Trials tablet (50 mg) in healthy male volunteers	41
176334/0304	An open study to assess liver enzyme induction in patients receiving CASODEX (176.334) 50 mg daily for the treatment of metastatic prostate cancer	44
176334/0308	An open study to assess liver enzyme induction in patients receiving CASODEX (176.334) 150 mg daily for the treatment of advanced prostate cancer	46

176334/0002, 0003, 0005	A summary of tolerability, efficacy, endocrine and pharmacokinetic data from three studies in which patients with advanced prostatic carcinoma were treated with CASODEX	49
176334/0204, 0205	Two Open Phase II Studies to Determine the Safety, Efficacy, and Long-term Endocrine Effects of CASODEX (176.334) in Patients With Advanced Prostatic Carcinoma	53
7054US/0001	A Randomized, Comparative Trial of CASODEX (50 mg) Versus Flutamide Each Used in Combination With Medical Castration in Patients With Untreated Metastatic Prostate Cancer	57
7054US/0002	Comparative Bioavailability Study of U.S. Marketed and Unmarked Flutamide Capsules	60
7054IL/0003	Comparative Bioavailability Study of Marketed Canadian Flutamide Tablets and Unmarked Clinical Trial Flutamide Capsules	63

Abbreviations: LHRH - luteinizing hormone releasing hormone

Background

Zeneca Pharmaceuticals Group has filed NDA 20-498 seeking approval for bicalutamide (Casodex[®]) 50 mg tablets. Bicalutamide is a non-steroidal anti-androgen which competitively inhibits the binding of androgens to cytosolic receptors. The proposed indication is for the treatment of advanced prostate cancer in combination with either an LHRH analog or surgical castration. The recommended dose is one 50 mg tablet daily. The chemical structure is shown below:



Bicalutamide (C₁₈H₁₄N₂O₄F₄S) has a molecular weight of 430.37 and a pK_a of 12. The compound is practically insoluble in water (~ 5 mg/L), but is soluble in organic solvents.

The compound will be marketed as the racemate. In the figure above, the chiral carbon is marked with an asterisk. The R isomer is the active anti-androgen;

the S-isomer has essentially no anti-androgenic activity. The pharmacokinetics of the two compounds are quite different, (as will be discussed), with the R-isomer having a $t_{1/2}$ of 6 days and the S-isomer having a $t_{1/2}$ of only 9 hours.

Summary of Bioavailability/Pharmacokinetics/Pharmacodynamics

I. Bioavailability/Bioequivalence

A. Bioavailability

Because of the lack of an intravenous formulation (due to solubility concerns), the absolute bioavailability of bicalutamide has not been determined. The bioavailability of the clinical trials tablet formulation relative to a suspension of the compound under both fasting and fed conditions was investigated in 15 healthy male volunteers. The results (Table 1) show that the tablet is absorbed as well as the suspension, and that food had little effect on the rate and extent of absorption of the compound from the tablet formulation. Studies investigating the effect of food on the absorption of bicalutamide from the to-be-marketed formulation have not been performed.

Table 1: Back-transformed means and 90% confidence limits for Study 176334/0008, comparing the clinical trials tablet under fasting and fed conditions, and comparing the tablet relative to an aqueous suspension (fasted conditions). [lower 90% CI, mean ratio, upper 90% CI]. n = 15. Data depicted refer to the R isomer (active).

Parameter	Clinical Trials Tablet vs Suspension	Fed vs. Fasted (CT tablet)
AUC(0-∞)	[105, 114, 123]	[94.9, 103, 111]
AUC(0-last)	[104, 113, 123]	[95.2, 103, 112]
Cmax	[104, 116, 129]	[103, 114, 126]

B. Bioequivalence

The pivotal bioequivalence trial (Study 7054IL/0005) compares the clinical

trials tablet formulation (used in the pivotal efficacy studies) with the to-be-marketed tablet. Thirty young healthy males received one of the formulations in a randomized crossover fashion under fasting conditions. The washout period between treatments was 9 weeks. Examining the data for the R isomer, it is noted that although the two formulations are bioequivalent by the two one-sided tests procedure (Table 2), significant period effects are noted in all parameters examined. Although only two subjects show pre-dose levels during Period 2, inadequate washout is most likely the cause of the period effect, as the data for the S isomer (which has a much shorter $t_{1/2}$ than the R isomer) does not show this period effect. Based on the R isomer data, the two formulations are bioequivalent.

Because one of the clinical efficacy studies was a double-blind comparison study between bicalutamide and flutamide (Eulexin[®] - Schering), the Sponsor elected to manufacture its own unmarked flutamide capsules in order to preserve the blinding. Two bioequivalence studies were performed to assess the bioequivalence of the unmarked flutamide capsules relative to the commercially available products in North America. Study 7054US/0002 compared the Zeneca formulation of flutamide to the product available in the US (Eulexin[®] - Schering) in 24 healthy non-smoking elderly males. The two formulations of flutamide were found to be bioequivalent. Study 7054IL/0003 was a standard two period crossover study comparing the bioequivalence of the unmarked Zeneca capsules to the Canadian tablet (Euflex[®] - Schering Canada). Table 3 shows that the Zeneca formulation is about 1.6 times as bioavailable as the Canadian tablet¹.

Table 2: Results of a bioequivalence study (Study 7054IL/0005) comparing the formulation used in the clinical efficacy trials (CT tablet) to the to-be-marketed formulation (TBM tablet). Although the R isomer data showed significant period effects in all parameters, the S isomer does not.

Parameter (n = 27)	90% confidence limits (R isomer)	90% confidence limits (S isomer)
AUC(0-last)	[98, 101, 104]	[93, 101, 110]
AUC(0-∞)	[99, 102, 106]	[85, 101, 119]
Cmax	[98, 101, 104]	[82, 89, 96]

¹ A study comparing the marketed US capsule to a tablet formulation identical to that currently marketed in Canada was reviewed by the Agency on 5/16/88. This study showed that the tablet was less bioavailable than the capsule formulation. (See the Biopharm review dated 5/16/88 by Dr. Anita Shah)

Table 3: Results of the Canadian flutamide bioequivalence study (7054IL/0003). The unmarked flutamide capsules manufactured by Zeneca are bioinequivalent to the commercial tablet available in Canada, with the Zeneca capsules about 60% more bioavailable than the Canadian tablet.

Parameter (n = 24)	90% confidence limits (2-OH flutamide)
AUC(0-last)	[150, 164, 179]
AUC(0-∞)	[148, 161, 176]
Cmax	[184, 206, 231]

II. Pharmacokinetics

Single Dose Studies

A study in 22 prostate cancer patients was performed to assess the single-dose pharmacokinetics of bicalutamide after doses of 10 mg (n = 7), 30 mg (n = 8) and 50 mg (n = 7). All subjects had normal renal and hepatic function as assessed by laboratory studies. Blood was collected over 29 days. The assay used in this study measured total drug and not the individual enantiomers. The results (Table 4) show that the Cmax and AUC(0-∞) increase linearly with dose. The racemate has a $t_{1/2}$ of about 6 days. Figure 1 shows the mean concentration vs. time plots for the racemate.

In the pivotal bioequivalence study (Study 7054IL/0005) a chiral assay was used to measure both isomers. From Table 5, it is noted that the pharmacokinetics of the two enantiomers are quite different, with the S isomer having a much earlier peak, lower plasma levels, and much shorter half-life than the R isomer. Figure 2 shows a representative plot of the two enantiomers. Studies in rats have shown no enantiomer interconversion, but no studies have been performed in humans.

Table 4 : Mean (sd) single-dose pharmacokinetics of 10, 30, and 50 mg single doses in men with prostate cancer. Data analyzed using an achiral assay. (Study 176334/0001).

Parameter	10 mg (n = 7)	30 mg (n = 8)	50 mg (n = 7)
AUC(0-∞) (μg*hr/mL)	41.2 (12.2)	112.4 (24.9)	216.2 (54.9)
t _{1/2} (hours)	143.5 (40.8)	130.8 (31.2)	151.2 (36.0)
C _{max} (ng/mL)	224.5 (40.2)	599.8 (107)	844.8 (143)
t _{max} (hours)	5 (median)	5 (median)	12* (median)

* two values at 24 and 48 hours have skewed this value relative to the other doses.

Figure 1: Mean plasma concentration vs. time profiles for bicalutamide racemate in males with prostate cancer. (Study 176334/0001)

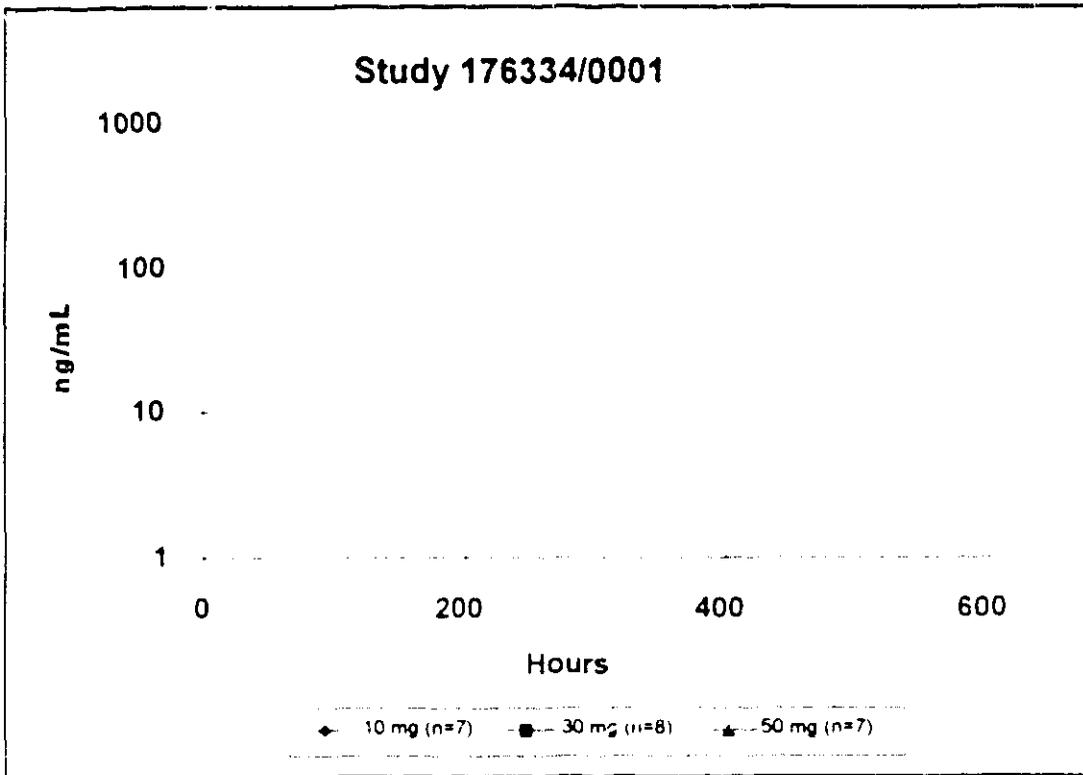
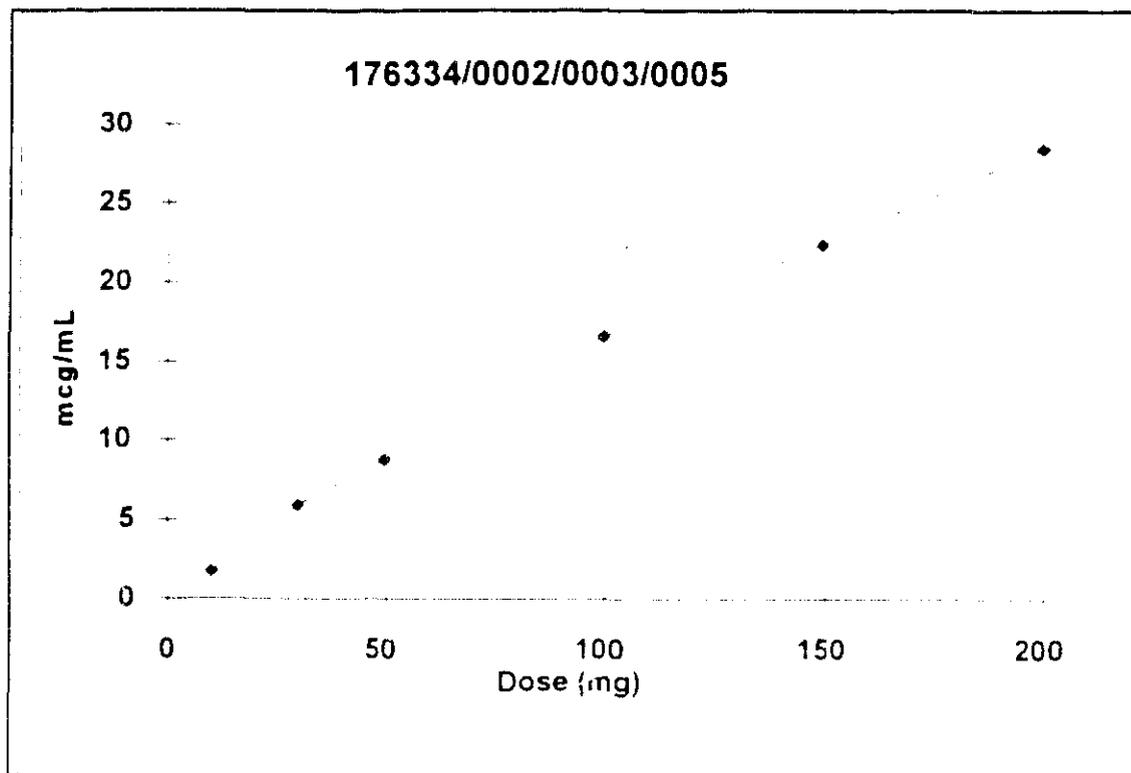


Table 5: Mean (sd) pharmacokinetic parameters of R and S isomers of bicalutamide in healthy men. Data depicted are based on the to-be-marketed formulation. The 50 mg data are from Study 7054IL/0005; the 150 mg data are from Study 176334/0012.

Dose	AUC(0-∞) (µg*hr/mL)		Cmax (ng/mL)		tmax (hrs)		t½ (hrs)	
	R isomer	S isomer	R isomer	S isomer	R isomer	S isomer	R isomer	S isomer
50 mg (n = 27)	172.3 (55.5)	2.09 (0.52)	768.4 (178.03)	59.3 (17.02)	31.3 (14.5)	3.1 (1.9)	138.9 (54.9)	32.9 (11.9)
150 mg (n = 28)	324.8 (71.8)	3.95 (1.1)	1430.5 (287.4)	124.1 (54.5)	39.8 (16.9)	3.2 (1.6)	133.7 (27.9)	34.8 (11.6)

Figure 3: Mean steady-state bicalutamide racemate levels as a function of dose. Deviations from dose proportionality at the higher doses is likely due to decreased absorption. Although the racemate levels were measured and not the individual enantiomers, the data most likely represent the R (active) isomer, due to the short $t_{1/2}$ of the S isomer.



randomized safety and efficacy trials conducted in men with advanced prostate cancer. Patients were administered 50 mg daily for up to 48 weeks. Steady-state plasma levels were taken in a group of 32 patients starting at week 12. The mean steady-state level achieved was 8.53 $\mu\text{g/mL}$, with a range of 4.7-14.2 $\mu\text{g/mL}$.

III. Metabolism

A single dose of ^{14}C -bicalutamide, (labelled in the monofluoro-phenyl group) was administered to 5 healthy male volunteers. Blood samples were collected up to 28 days post-dose. All urine and feces were collected from the volunteers during the nine days post-dose. Plasma, urine and feces were analyzed for bicalutamide using a chiral HPLC assay. Urine and feces extracts were subjected

to TLC. Over 9 days about 36% of the radioactivity was recovered in the urine, and 42% was recovered in the feces. As nearly 17% of the dose is recovered in the feces during days 3-9, biliary excretion, rather than non-absorption of drug is the most likely explanation for the large amount of drug present in the feces. This also indicates that bicalutamide is relatively well-absorbed following oral administration.

The metabolism of the two enantiomers is quite different. Virtually all of the compound excreted during the first 48 hours is the glucuronidated S isomer. The Sponsor suggests that the reason for this observation is that the S isomer may have a higher affinity for glucuronyl transferase than the R isomer (the site of attachment of the glucuronide is the hydroxy group on the chiral carbon). Figure A1 (Appendix) displays the structures of the major metabolites in man. In contrast, the R isomer is first hydroxylated on the monofluoro-phenyl ring and then conjugated at that site, which accounts for its longer $t_{1/2}$.

Analysis of fecal extracts reveal that both parent compound and the hydroxy metabolite are present, but not the glucuronide forms. The lack of glucuronide forms in the feces is likely a result of hydrolysis by gut micro-organisms. Similar results have been found in the rat.

Twelve weeks of bicalutamide 50 mg daily was shown to have no effect on antipyrine metabolism. At 150 mg daily, the percent of 4-OH-antipyrine excreted in the urine increased by 38%, indicating some mild induction may be taking place.

IV. Dose and Dosage Form Proportionality

Bicalutamide will be available in 50 mg tablets. The recommended dose will be one 50 mg tablet daily, in combination with medical or surgical castration. The

V. Special Populations

Two studies examined the effect of hepatic dysfunction on the pharmacokinetics of bicalutamide. Study 176334/0007 was an open-label parallel study in 20 men, half of which had mild-to moderate liver disease as assessed by biopsy. Each subject was given a single 50 mg dose of bicalutamide under fasting conditions. The results showed no significant differences between the two groups in C_{max} , t_{max} , $t_{1/2}$, or $AUC(0-\infty)$ for either enantiomer, except that t_{max} for the S isomer was significantly shorter than that in the normal group.

Study 176334/0010 was an open label parallel study in 28 men. Fourteen of the subjects were normal healthy men, the other group comprised 10 men with mild-moderate liver disease and 4 of whom were shown to have severe liver disease. Both $AUC(0-\infty)$ and $t_{1/2}$ of the R isomer were increased in the subjects

with severe liver disease by 40 and 66%, respectively. The S isomer showed no change except for an increased C_{max} in the liver disease group.

The effects of age and renal function on the pharmacokinetics of bicalutamide were investigated using steady-state data from Study 176334/0002/0003/0005. No relationship between steady-state concentration of either enantiomer and age or renal function was noted.

Because of the pharmacologic class of the compound and its proposed indication, studies in women and pediatric subjects were not performed.

VI. Drug Interactions

Data from two clinical efficacy trials were used to show that there are no clinically relevant interactions between bicalutamide and LHRH analogues. A total of 40 steady-state blood samples were taken from 40 patients being treated with bicalutamide plus a LHRH analog for 90 days (either goserelin, n = 29 or leuprolide n = 13) in Study 7054US/0001. These measurements were compared with similar 90 day bicalutamide monotherapy data from Study 176334/0002/0003/0005. The mean steady-state levels in patients being treated with bicalutamide plus a LHRH analog was $8.93 \pm 3.48 \mu\text{g/mL}$, while the mean steady-state bicalutamide levels in patients being treated with bicalutamide only was $9.35 \pm 3.21 \mu\text{g/mL}$ (p = 0.5). It appears that concomitant treatment with LHRH analogues does not affect steady-state bicalutamide levels.

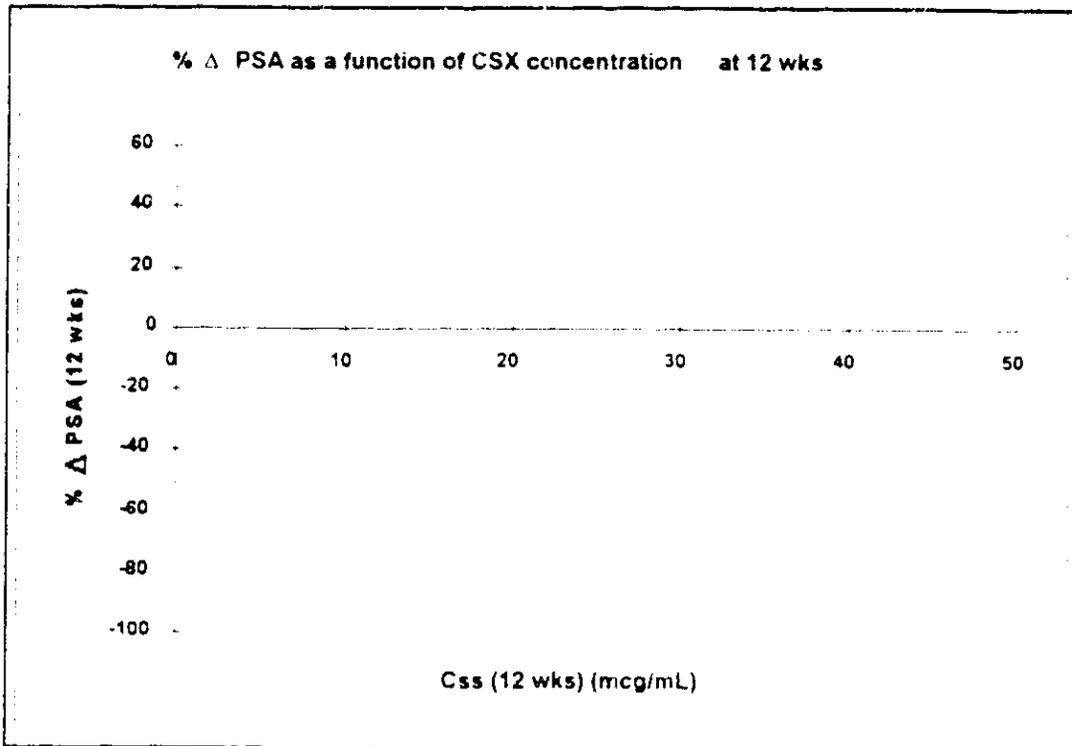
Serum testosterone levels were within the castrate range for those patients treated with bicalutamide plus a LHRH analog, indicating that bicalutamide does not influence LHRH therapy.

VII. Pharmacokinetic/Pharmacodynamic Relationships

For the present indication (treatment of advanced prostate cancer in combination with either an LHRH analog or surgical castration), no PK/PD data are available, since the combination of therapies affects the usual markers of efficacy (prostate-specific antigen (PSA), or prostatic acid phosphatase (PAP) levels).

Two monotherapy trials in which bicalutamide levels and PSA levels were determined suggest that a concentration-effect relationship exists with the compound. Looking at Figure 4, it is noted that subjects' PSA levels at 12 weeks tend to be maximally suppressed at plasma concentrations $\geq 10 \mu\text{g/mL}$. Data from Study 176334/0002/0003/0005 indicate that the mean concentration achieved on 50 mg daily is $9.4 \mu\text{g/mL}$.

Figure 4: Percent change in PSA from baseline as a function of steady-state concentrations of bicalutamide (R isomer) in prostate cancer patients. Data from Studies 176334/0002/0003/0005 and 176334/0204/0205. Doses ranged from 50-200 mg daily.



VIII. Formulation

The to-be-marketed formulation is detailed in Table 7.

Table 7: Composition of clinical trials tablet and to-be-marketed formulation. Numbers in table are in mg/tablet.

<i>Excipient</i>	<i>50 mg clinical trials tablet</i>	<i>50 mg to-be-marketed tablet</i>
Tablet Core		
Lactose		
Corn Starch		
Na starch glycolate		
PVP		
Mag. stearate		
Tablet Coating		
Methylhydroxypropyl cellulose		
PEG 300		
Titanium dioxide		
Iron oxide (black)		
Iron oxide (yellow)		
Formulation number		

The proposed dissolution method is _____ The proposed dissolution specification is Q: _____ after 45 minutes. Data from a full size production batch used in the pivotal bioequivalence trial shows that at 45 minutes,

99.9% of the dosage form is dissolved (n = 12, range 95-104%, CV% = 3.5). Data were presented to show that 1% SLS is the lowest concentration of surfactant that will give sufficient solubility to attain sink conditions.

Dissolution studies were performed to determine how discriminating the method is with respect to tablet process variables such as bulk drug specific surface area, volume of water used in wet granulation, and tablet hardness. The results are presented in Table 8. The method is fairly discriminating with regard to all of the variables examined, but the current dissolution specification would allow all of the tested lots to pass except that made with unmilled material. No *in vivo-in vitro* correlation has been established.

IX. Assays

Table 8: Dissolution of tablets using the proposed method ($Q =$ @ 45 min) on tablets made under the normal process^e and under varying specific surface areas (SSA), compression forces and amounts of water added to granulation. The results indicate that the method is fairly discriminating, although most batches would pass the proposed specification.

Time (min)	Normal process	SSA 665 (cm ² /g) *	SSA 15,600 (cm ² /g)#	SSA 29,000 (cm ² /g)#	40% reduction in granulation H ₂ O	20% increase in granulation H ₂ O	Low Comp. (4.5 Kp)	High Comp. (11 Kp)
15								
30								
45								

^ehardness 7.8 Kp, bulk drug SSA 17000-29000 cm²/g, 1 kg H₂O/5 kg granulation mix

Extraction Efficiency - The extraction efficiency for the assay at 10 ng/mL is 78% and 70% for the R and S isomer, and 69% and 66% for the R and S isomer at 1000 ng/mL.

Precision

	Intra-assay Precision (CV%)		Inter-assay Precision (CV%)	
	25 ng/mL (n = 16)	4000 ng/mL (n = 16)	25 ng/mL (n = 16)	4000 ng/mL (n = 16)
R Isomer	14	5	22	8
S Isomer	11	5	12	9

Accuracy

	Accuracy (%)	
	10 ng/mL (n = 15)	8000 ng/mL (n = 81)
R Isomer	99.7	99
S Isomer	102.5	98.6

Limit of quantitation

The limit of quantitation for both enantiomers is 10 ng/mL.

X. General Comments

Comment to the reviewing chemist (do not send to Sponsor)

1. Table 8 in this review summarizes the results of the dissolution method for bicalutamide. It appears that, although the method does a reasonable job of discriminating batches with varying bulk drug particle sizes, degrees of hardness and different granulations, using the current dissolution specification (Q = @ 45 min) would result in the acceptance of all of the tablet lots except that made with the unmilled bulk drug. Therefore, the Division of Biopharmaceutics (HFD-

420) recommends a revised specification of Q at 30 minutes using the same dissolution apparatus and medium.

at 30 minutes using the

Comment to the Sponsor

2. The metabolism data presented in this NDA showed stereospecific metabolism, with the S isomer undergoing glucuronidation at the secondary alcohol. In contrast, the R (active) species undergoes oxidation of the monofluoro-phenyl ring followed by glucuronidation at that site. However, no data were presented to identify the P-450 enzyme(s) responsible for this oxidation, which is the rate-limiting step of the elimination of the active compound. Thus, there exists the potential for metabolic drug-drug interactions which could lead to the accumulation of the active species. Therefore, the Division requests Phase IV *in vitro* metabolism studies to determine the isozyme(s) responsible for the oxidation of the R isomer, so that potentially interacting drugs may be identified.

XI. Labeling Comments (to be sent to Sponsor)

1) The text in the current labeling under **Pharmacokinetics and Metabolism** should be replaced with the following:

Pharmacokinetics

Absorption

Bicalutamide is well-absorbed following oral administration, although the absolute bioavailability is unknown. Co-administration of bicalutamide with food has no clinically significant effect on rate or extent of absorption.

Distribution

Bicalutamide is highly protein-bound (96%). See *Drug-Drug Interactions* below.

Metabolism/Elimination

Bicalutamide undergoes stereospecific metabolism. The S (inactive) isomer is metabolized primarily by glucuronidation. The R (active) isomer undergoes oxidation to an inactive metabolite followed by glucuronidation. Both the parent and metabolite glucuronides are eliminated in the urine and feces. The S enantiomer is rapidly cleared relative to the R enantiomer, with the R enantiomer accounting for about 99% of total steady-state plasma levels.

Special Populations

Geriatric

in patients given 50 or 150 mg daily, no significant relationship between age and levels of total bicalutamide or the active R enantiomer has been shown.

Hepatic Insufficiency

A statistically significant difference in the pharmacokinetics of either enantiomer of bicalutamide was noted in patients with mild-to-moderate hepatic disease as compared to healthy controls. Patients with severe liver disease have significantly longer half-life values for the R enantiomer.

Renal Insufficiency

Renal impairment (as measured by creatinine clearance) had no significant effect on the elimination of either enantiomer of bicalutamide.

Women, Pediatrics

Because of the mechanism of action and the indication, bicalutamide has not been studied in women and pediatric subjects.

Drug-Drug Interactions

Clinical studies have not shown any drug interactions between bicalutamide and LHRH analogues (goserelin or leuprolide). There is no evidence that bicalutamide induces hepatic enzymes. *In vitro* protein binding studies have shown that bicalutamide can displace coumarin anticoagulants from binding sites. Prothrombin times should be closely monitored in patients already receiving coumarin anticoagulants who are started on CASODEX.

Pharmacokinetics of the active enantiomer of CASODEX in normal males and patients with prostate cancer.

Parameter (n = 27 except where noted)	Mean	CV%	95% Confidence Interval
Apparent Oral Clearance (L/hr)	0.332	31.6	0.282, 0.363
Single Dose Peak Concentration (µg/mL)	0.768	23.1	0.702, 0.835
Single Dose Time to Peak Concentration (hours)	31.3	46.3	25.9, 36.7
Half Life (days)	5.8	39.4	4.9, 6.7

Mean Steady State Concentration in Patients (n = 23) given 50 mg daily (µg/mL)	8.53	34.3	7.3, 9.8
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[Handwritten signature] 7/19/95

Michael J. Fossler, Pharm. D., Ph. D.
Pharmacokinetics Evaluation Branch II

RD initialed by John Hunt, Section Head 7/5/95

FT initialed by John Hunt, Section Head *[Signature]* 7/19/95

Biopharm Day held 7/18/95 at 11:00 AM. Attendees: Ludden, Chen, Collins, Fleischer, Hepp, Hussain, Hunt, Fossler

cc: NDA 20-498 (pink), HFD-510(Fourcroy, Pauls, MJRhee), HFD-426(Fleischer),
HFD-427(M. Chen, Fossler), Drug file, Chron. file, Review. FOI (HFD-19)
rev 3/8/95

OCT 19 1994

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF RESEARCH RESOURCES
DIVISION OF BIOPHARMACEUTICS

Date: October 19, 1994

To: Thomas Ludden, Ph.D.
Henry Malinowski, Ph.D.
Mei-Ling Chen, Ph.D.

Through: Section Head: John Hunt

From: Hae-Young Ahn, Ph.D.

RE: Pre-45 Day Filing Meeting for NDA 20-498 (CASODEX[®])

Meeting date: October 20 at 12:30 p.m.

Place: Mei-Ling's Office

The sponsor, Zeneca Inc., submitted a new NDA seeking approval for marketing CASODEX[®] 50 mg tablet for use in combination therapy with either a LHRH analogue or surgical castration in the treatment of advanced prostate cancer. CASODEX is a non-steroidal antiandrogen and has two enantiomers. (R)-CASODEX is primarily responsible for the antiandrogenic activity of CASODEX, with the activity of (S)-CASODEX being at least 2000-fold lower than that of (R)-CASODEX. The recommended dose for CASODEX is one 50 mg tablet once daily (morning or evening) with or without food.

Information regarding demographic data, formulation, analytical method (chiral and achiral HPLC assay) and assay validation data for CASODEX, (R)-CASODEX and (S)-CASODEX, bioavailability (clinical trials tablet vs aqueous suspension), single dose pharmacokinetics, multiple dose pharmacokinetics, dose linearity, stereospecific pharmacokinetics, food effect, special populations (hepatic impairment, renal impairment and elderly), bioequivalence (clinical trials tablet vs the to-be-marketed tablet), dissolution method and data at three time points, individual plasma profiles and pharmacokinetic parameters of CASODEX, (R)-CASODEX and (S)-CASODEX were included in this submission. The to-be-marketed tablet used in the bioequivalence study was from a full scale production size batch.

The pharmacokinetics of CASODEX and its enantiomers were investigated after administration of single oral doses of 10 to 50 mg to healthy volunteers and 50 to 150 mg to prostate cancer patients. Multiple-dose pharmacokinetic data during daily administration of 10 to 200 mg were obtained from prostate cancer patients. Dose proportionality was investigated in a single oral dose study (10, 30 and 50 mg) and multiple dose oral dose studies (10 mg to 200 mg).

Formulations which were used in clinical trials and the to-be-marketed formulation were different. The sponsor conducted a bioequivalence study and the CASODEX 50 mg to-be-marketed tablet seems to be bioequivalent to CASODEX 50 mg clinical trials tablet.

Enzyme induction on daily dosing with CASODEX was assessed in two studies. The pharmacokinetic profiles of antipyrine following a single oral dose of 1000 mg were assessed before the start of therapy with CASODEX and at the end of 12 weeks' daily dosing with CASODEX 50 mg (Study 0304) and 150 mg (Study 0308). The sponsor stated that no induction or inhibition of P450 enzymes by CASODEX was found at these dose levels.

Metabolism data was obtained by administration of a single oral dose (50 mg; $42\mu\text{Ci}$ [^{14}C]-CASODEX) to human volunteers. No parent compound was found in urine; metabolites were identified as the glucuronide conjugate of CASODEX and a glucuronide conjugate of a CASODEX metabolite (hydroxy CASODEX).

The relationship between CASODEX dose and decline in prostate specific antigen (PSA) concentration was assessed over the dose range 10 to 200 mg in three studies. The sponsor claimed that the data showed a clear trend to decreasing PSA with increasing CASODEX dose. The relationship between percentage change in PSA and CASODEX or (R)-CASODEX C_{ss} was also investigated and no clear correlation between the percentage change in PSA and C_{ss} was found.

The drug-drug interaction between CASODEX and the LHRH analogues (leuprolide acetate or goserelin acetate depot) was studied. The effect of CASODEX on the pharmacological activity of the LHRH analogues was investigated by measuring serum concentrations of testosterone and comparing them with those of medically castrated patients. It was stated that the data demonstrated that CASODEX did not interfere with the efficacy of either leuprolide acetate or goserelin acetate. The effect of the LHRH analogues on the pharmacokinetics of CASODEX was assessed by measuring trough plasma CASODEX concentrations and comparing them with data after 3 months of dosing with CASODEX 50 mg in the monotherapy. It was concluded that LHRH analogues did not alter CASODEX plasma concentrations.

The binding of CASODEX to human plasma proteins in vitro was studied over the concentration range of 100 to 10000 ng/mL. The displacement of CASODEX from its binding sites on human plasma proteins by drugs likely to be co-administered (prazosin, indomethacin, warfarin, diclofenac and warfarin) was assessed.

It was stated that age, renal impairment and mild to moderate hepatic impairment did not have any clinically relevant effect on the pharmacokinetics of (R)-CASODEX.

RECOMMENDATION:

Overall, the information included in the "Human Pharmacokinetics" section of this submission appears to be adequate to support the filing of NDA 20-498 for CASODEX. However, random review was done and it was found that in a few studies (i.e., Studies 0002, 0003, 0005 and 0006) individual plasma profiles of CASODEX were not submitted. Therefore, it is requested that individual plasma profile of CASODEX be provided in all studies.

cc: drug file

ATTACHMENT I

includes

Biopharmaceutic Study Summary

TABLE A1 Summary of CASODEX clinical studies

Study number	Principal investigator	Study design	Objectives	CASODEX		Subjects		Pharmacokinetic and metabolic results
				Dosage form(s)	Dose (mg)	Number*	Type	
Bioavailability and bioequivalence studies								
0008		Single-dose, three-way crossover	Bioavailability, food interaction, tolerance	Film-coated tablets Aqueous suspension	50 50	15	Healthy volunteers	Release characteristics of the tablet were similar to those of the 'freely available' suspension. Food consumption had no clinically relevant effect. Plasma concentrations of (R)-CASODEX were much higher and declined much more slowly than those of (S)-CASODEX.
IL0005		Single-dose, two-way bioequivalence		Film-coated Clinical Trial Tablet Film-coated Intended Sales Tablet	50 50	30	Healthy volunteers	The 50-mg Intended Sales Tablet was bioequivalent to the 50-mg Clinical Trials Tablet.
0012		Single-dose, two-way bioequivalence		Film coated Clinical Trial Tablets Film-coated 150-mg tablet	150 150	28	Healthy volunteers	The 150-mg tablet was bioequivalent to three 50-mg Clinical Trials Tablets.
Pharmacokinetic studies								
0001		Single dose	Tolerance, pharmacokinetics	Uncoated tablets	10 30 50	7 8 7	Prostate cancer patients	CASODEX was slowly absorbed, particularly after the 50-mg dose, and was eliminated from plasma with a half-life of about 6 days. AUC values increased in proportion to the dose.

CASODEX was taken orally in all studies

*Number of subjects providing assessable pharmacokinetic data

(continued)

(continued)

TABLE A1 Summary of CASODEX clinical studies

Study number	Principal investigator	Study design Objectives	CASODEX		Subjects		Pharmacokinetic and metabolic results
			Dosage form(s)	Dose (mg)	Number*	Type	
Pharmacokinetic studies (continued)							
US0001		Daily dosing Efficacy, pharmacokinetics at 3 months and interaction with LHRH analogues	film-coated tablets	50	40	Prostate cancer patients	(R)-CASODEX constituted 99.3% of circulating drug at 3 months. No interaction between CASODEX and LHRH analogues.
USA							
0002,0003,0005		Daily dosing for 3 months Efficacy, tolerance, pharmacokinetic dose-linearity, effect of age and renal impairment	Film coated tablets	10 30 50 100 150 200	43 46 116 52 42 29	Prostate cancer patients	Trough plasma concentrations of CASODEX during dosing with 10, 30 and 50 mg, and of the active enantiomer (R)-CASODEX during dosing with 100, 150 and 200 mg, increased about 10-fold over the dosing period. Trough plasma concentrations increased in proportion to dose over the 10 to 50 mg range, but slightly less than proportionately over the 50 to 200 mg range. Age and renal impairment had no clinically relevant effect on the pharmacokinetics of CASODEX or (R)-CASODEX. There was no clear relationship between the proportional decline in prostate specific antigen during dosing and the (R)-CASODEX steady-state concentration. The pharmacokinetics of (R)-CASODEX were very similar to those measured as CASODEX.

(continued)

CASODEX was taken orally in all studies
*Number of subjects providing assessable pharmacokinetic data

(continued)

TABLE A1 Summary of CASODEX clinical studies

Study number	Principal Investigator	Study design Objectives	CASODEX		Subjects		Pharmacokinetic and metabolic results
			Dosage form(s)	Dose (mg)	Number*	Type	
Pharmacokinetic studies (continued)							
0006		Single dose Metabolism, pharmacokinetics	[¹⁴ C] CASODEX powder in gelatin capsules	50	5	Healthy volunteers	Recovery data indicated that the dose was well absorbed. Little evidence for the presence of metabolites in the circulation, but predominantly metabolites in excreta. The major urinary metabolites were the glucuronido conjugates of both CASODEX and hydroxy-CASODEX. The pharmacokinetics of (R)-CASODEX were very similar to those measured as CASODEX.
0007		Single dose Pharmacokinetics in hepatic impairment	Film-coated tablets	50	10	Hepatic impairment Volunteers with normal hepatic function	No effect of hepatic impairment on the pharmacokinetics of either enantiomer. The pharmacokinetics of the enantiomers were as previously defined.
0010		Single dose Pharmacokinetics in hepatic impairment	Film-coated tablets	150	14 14	Hepatic impairment Volunteers with normal hepatic function	No effect of mild to moderate hepatic impairment on the pharmacokinetics of either enantiomer. Some evidence of slower elimination of (R)-CASODEX in subjects with severe hepatic impairment. The pharmacokinetics of the enantiomers were as previously defined.

(continued)

CASODEX was taken orally in all studies.
*Number of subjects providing assessable pharmacokinetic data

(continued)

TABLE A1 Summary of CASODEX clinical studies

Study number	Principal Investigator	Study design Objectives	CASODEX		Subjects		Pharmacokinetic and metabolic results
			Dosage form(s)	Dose (mg)	Number*	Type	
Other in vivo studies							
0304		Daily dosing for 3 months Assessment of enzyme induction	Film-coated tablets	50	7	Prostate cancer patients	CASODEX had no clinically relevant effect on hepatic enzyme systems involved in the metabolism of antipyrine.
0308		Daily dosing for 3 months Assessment of enzyme induction	Film-coated tablets	150	12	Prostate cancer patients	CASODEX had no clinically relevant effect on the hepatic enzyme systems involved in the metabolism of antipyrine.
0205		Daily dosing Efficacy, tolerance, steady-state plasma concentration	Uncoated tablets Film coated tablets	50	23	Prostate cancer patients	Apparent steady-state trough plasma CASODEX concentrations were within the range observed with the 50-mg dose in Study 0002.

CASODEX was taken orally in all studies

*Number of subjects providing assessable pharmacokinetic data

TABLE A2 Summary of flutamide clinical studies

Study number Principal investigator (Volume number)	Study design Objectives	Flutamide		Subjects		Pharmacokinetic and metabolic results
		Dosage form(s)	Dose (mg)	Number *	Type	
US0002	Single dose two way bioequivalence	125-mg marketed EULEXIN capsule 125 mg unmarked clinical trial capsule	250 250	24	Healthy elderly volunteers	The 125-mg unmarked capsule was bioequivalent to the EULEXIN capsule
IL0003	Single dose two way bioequivalence	250 mg marketed EUFLEX tablet 125 mg unmarked clinical trial capsule	250 250	24	Healthy elderly volunteers	The bioavailability of 2-hydroxy-flutamide from the capsule was about 1.6-fold greater than that from the EUFLEX tablet.

Flutamide was taken orally in both studies

*Number of subjects providing assessable pharmacokinetic data

JUL 28 1995

NDA 20-498

Drug: Casodex (Bicalutamide)

Sponsor: Zeneca Limited, Macclesfield, England

APPEARS THIS WAY
ON ORIGINAL

Recommendations:

1. **NDA 20-498 is Approvable.** The Pharmacology/Toxicology data are adequate to support the safety of the proposed 50 mg/day dose for use in men with prostate cancer.
2. Zeneca is evaluating the effects of higher doses of Casodex (150 mg) in subjects with cancer and benign prostatic hyperplasia. The rat and mouse carcinogenicity studies were not performed utilizing the maximum tolerated dose. In addition, the high dose level used produces exposures (C_{ss} and AUC) in rodents which are very low multiples of human exposures with the 50 mg/day dose. If the sponsor plans to seek approval for a BPH indication, the 2 year rodent carcinogenicity studies should be repeated utilizing the MTD. Data will be presented to the Pharmacology/Toxicology Carcinogenicity Assessment Committee on August 8, 1995 to obtain their recommendations on this issue.
3. Labelling changes are on page 43.

Jeri El-Hage, Ph.D.

Jeri El-Hage 7/24/95
A Jordan 7/28

CC: NDA 20-498, HFD-510 NDA, HFD-345
HFD-510/ A Jordan/ J El-Hage
20498.nda

STUDIES INCLUDED IN THIS REVIEW

1. Pharmacology	p. 4
2. Absorption, Distribution, Metabolism Data	pp.5-11
3. Acute Toxicity- Mouse, Rat, Rabbit, Dog	p. 12
4. Oral Toxicity in the Rat	
Four Week Study	pp. 12-13
3 Month Dose-Finding Study	pp. 14-16
6 Month Study	pp. 16-18
12 Month Study	pp. 19-22
2 Year Carcinogenicity Study	pp. 22-24
5. Carcinogenicity in Mice	
3 Month Dose-Finding Study	pp. 25-28
3 Month Liver Toxicity Study	p. 28
2 Year Carcinogenicity Study	pp. 29-30
6. Oral Toxicity in the Dog	
6 Week Dose-Finding Study	pp. 30-31
6 Month Study	pp. 31-35
12 Month Study	pp. 35-37
7. Reproductive Toxicity	
Male Fertility Study	p. 37
Reproductive Study in Female Rats	pp. 37-38
Teratology Study in Rats	pp. 38-39
Teratology Study in Rabbits	pp. 39-40
8. Genotoxicity	
Ames Tests	p. 40
Mammalian Cell Mutation/HPRT Assay	p. 41
In vitro Cytogenetics in Human Lymphocytes	p. 41
Mouse Micronucleus Test	p. 41
Cytogenetic Study in Rats	p. 41
9. Special Toxicity	
Contact Sensitization Study	p. 42
Cutaneous Anaphylaxis -Guinea pig, Mouse	p. 42
Dermal Tolerance in Rabbits	p. 42
Ocular Tolerance in Rabbits	p. 42
10. Labelling Revisions	p. 43

A 20-498

July 17, 1995

Sponsor: Zeneca Pharmaceuticals, Wilmington, DE 19897
Zeneca Ltd., Macclesfield, Cheshire, England

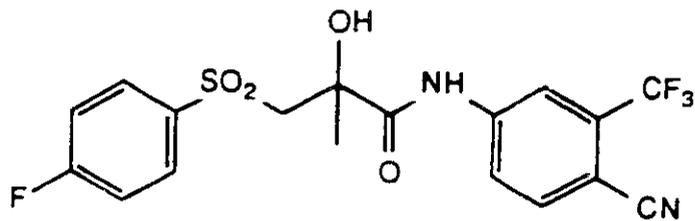
Submission Date: September 14, 1994

NDA Review of Pharmacology and Toxicology Data

Drug: 176,334; N[4-cyano-3-trifluoromethyl)-phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl (+,-) propanamide

Proprietary name: Casodex
USAN name: Bicalutamide

Structure:



M.W. = 430.37

M.F. = $C_{18}H_{14}N_2O_4F_4S$

Category: Nonsteroidal anti-androgen

Indication: Prostate cancer in combination with surgical or medical castration

Related INDS:

Formulation - 50 mg tablet containing the following

Ingredient	mg/tablet
176,334	50
Lactose	
Sodium starch glycolate	
Povidone BP	
Magnesium stearate	
Methylhydroxypropylcellulose	
Titanium dioxide	

PHARMACOLOGY

Casodex is a nonsteroidal anti-androgen that competitively binds with cytosolic androgen receptors in target tissues. It is a racemate with antiandrogenic activity exhibited almost entirely in the R-enantiomer. Casodex binds 50 times **less effectively** than dihydrotestosterone (DHT) to rat androgen receptors. However, the affinity of Casodex for androgen receptors is 4-fold higher in the prostate and 10-times higher in the pituitary than hydroxyflutamide.

Casodex is unique among the antiandrogens in that it binds to mutated androgen receptors in human LNCaP prostate tumor cells and inhibits their growth.

Casodex also inhibits the growth of the androgen-sensitive Shionogi SII5 mouse mammary tumor cell line. Oral administration of Casodex (5 and 25 mg/kg/day) to male rats inhibits the growth of transplanted Dunning prostate tumors to values seen in surgically castrated rats.

Administration of Casodex (1, 5 and 25 mg/kg) to mature male rats for 154 days inhibits accessory sex organ growth without increasing serum LH or testosterone. ED₅₀ values were 2.5 mg/kg for seminal vesicles and 7.4 mg/kg for ventral prostate. Similarly, orally administered Casodex inhibits prostate growth in dogs (ED₅₀ = 0.1 mg/kg) without elevating serum testosterone concentrations.

General Pharmacology -

Casodex has no progestational, estrogenic, glucocorticoid, or mineralocorticoid agonist or antagonist activity.

-Administration of 50 mg/kg,po for 14 days to conscious normotensive dogs produced mild increases in heart rate without effects on mean arterial pressure or total peripheral resistance. A dose of 2.5 mg/kg,po had no effects.

Casodex (50 mg/kg,po) had no effects on platelet aggregation or blood clotting ex vivo in rats.

-Casodex (50 mg/kg,po) had no CNS effects in mice or rats (rotarod, electroshock threshold, barbital sleeping time, Irwin test).

Casodex (40 mg/kg,iv) had no effects on airway resistance, compliance or histamine-induced bronchospasm in guinea pigs. Casodex (10 mg/kg,iv) had no pulmonary effects in anesthetized dogs.

-Casodex (50 mg/kg,po) had no diuretic or antidiuretic activity in rats.

-Casodex had no effects on human angiotensin converting enzyme or renin.

-Casodex (50 mg/kg,po) has no anti-inflammatory or analgesic activity.

-Casodex (50 mg/kg,po for 10 days) displayed no immunosuppressant effects

-Casodex (50 mg/kg,po) produced a slight increase in GI motility but had no influence on GI secretion.

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

Absorption, Metabolism, Excretion of ¹⁴C 176,334 in the Black Mouse (KMM 019)

Male black mice (n = 4) were administered single oral or iv doses of 8 mg/kg ¹⁴C-bicalutamide and urine and feces were collected for 7 days. 90% of administered dose was recovered in 4 days. Radioactivity in feces was primarily parent compound; 72% after iv, 91% after oral dosing. Radioactivity in urine was attributable to metabolites.

<u>Route</u>	<u>Absorption</u>	<u>% of Radioactivity</u>	
		<u>Urinary</u>	<u>Fecal</u>
Oral	87%	25%	64%
Intravenous		32%	62%

Disposition of ¹⁴C 176,334 in Rats (KMR 006, lot # ADM 60022/84)

Rats were administered 25 mg/kg,po or 2 mg/kg,iv ¹⁴C-bicalutamide and urine and feces were collected for 7 days. Oral bioavailability was 61-62%, Tmax after oral dosing occurred at 12 hours, Cmax = 10.9-11.6 ug/ml. 80-90% of radioactivity was recovered within 2 days. V_d = 1.2 L/kg, Plasma clearance (C_p) = 0.79 ml/min/kg in males and 0.64 ml/min/kg in females.

<u>Route</u>	<u>Absorption</u>	<u>Half-life (hrs)</u>	<u>% of Total Radioactivity</u>
			<u>Excretion</u>
oral	M	17	62% fecal
	F	21	69%
intravenous			58% M
			29% F

Radioactivity measured in the plasma and feces was primarily parent drug. No parent compound detected in the urine with the sulphate conjugate as primary metabolite.

Metabolism of Bicalutamide after Single Oral Doses in Male Rats
(KMR 028, lot #ADM 56041/85)

Male rats (n = 4) were administered 25 mg/kg, po ¹⁴C-bicalutamide. The oral bioavailability was 47%. AUC = 250 ug.hr/ml. C_{max} = 8.75 ug/ml, T_{max} = 12 hours. T_{1/2} = 17 hours. 72% of radioactivity was excreted in the feces (80% parent compound) and 26% of radioactivity was excreted in the urine as a carboxylic acid metabolite. The majority of radioactivity in the plasma (90%) was parent compound.

Single Dose Pharmacokinetics of Bicalutamide in the Dog (KPD/084, lots 63054, 63055, 63056/84)

Male beagle dogs (n = 3/gp) received single oral doses of 0.1, 2.5, 10 or 100 mg/kg bicalutamide. T_{1/2} = 5-6 days at all dose levels, V_d = 14L, Cl_p = 1 ml/min/kg. Drug concentrations (C_{max} and AUC) increased with increasing dose. Oral bioavailability decreased with increasing dose suggesting saturation of absorption, as is seen in the rat.

<u>Dose (mg/kg)</u>	<u>C_{max} (ug/ml)</u>	<u>AUC (ug hr/ml)</u>	<u>Bioavailability</u>
0.1	0.13	29	100%
2.5	2.3	519	66%
10	5.8	1802	58%
100	27.8	9550	31%

Disposition of Single Oral and Intravenous Doses of Bicalutamide in Male Dogs (KMD 085, lot # 60022/84)

Male beagle dogs (n=4/gp) were administered ¹⁴C-bicalutamide, 2.5 mg/kg, po and 0.25 or 2.5 mg/kg, iv. Urine and feces were collected for 4 days. Only 25% of total radioactivity was recovered within 4 days and, therefore, the data are incomplete. Disposition appeared similar to the rat with the majority of radioactivity in plasma as unchanged drug. The majority of radioactivity in the feces was also unchanged (not absorbed?) drug. Radioactivity detectable in the urine was metabolites (not identified).

Disposition of ¹⁴C Bicalutamide in Male Dogs (KMD006, lot# ADM 56041/85)

Male beagle dogs (n = 4) were administered a single oral dose of 2.5 mg/kg ¹⁴C-bicalutamide and urine/feces were collected for 5 days. C_{max} = 0.56 ug/ml; T_{max} = 15 hours. T_{1/2} = 5.7 days. 75% of radioactivity in plasma was parent compound. 65-85% of total radioactivity was recovered within the 5 day sampling time. Urinary excretion represented 3% of radioactivity (44% parent compound, 49% major metabolite). 69% of radioactivity was recovered in the feces (90% parent compound).

Protein Binding of Bicalutamide (KPD/94) 11

<u>Species</u>	<u>% Bound</u>	<u>Concentration Range (ug/ml)</u>
Rat	95%	0.5 - 202
Mouse	95%	2 - 207
Rabbit (female)	91%	0.5 - 202
Dog	95%	0.5 - 202
Man	96%	0.1 - 10

No saturation of binding was observed over the concentration ranges tested. No significant sex differences in binding in mice, rats, humans.

Binding of Bicalutamide to Human Plasma Proteins

	<u>% Binding</u>
Human Serum Albumin	94.7%
α -acid glycoprotein	24.8%
ABG G (α, β, γ -globulins)	62.1%

Binding of drug to HSA accounts for the majority of plasma protein binding.

Tissue Distribution/Autoradiography Study of Bicalutamide in Albino and Hooded Rats (KMR 007, KMR 024 lot # ADM 50022/84) KMR 007

Wistar rats of both sexes and male hooded rats (n = 4) were administered a single oral dose of 30 mg/kg ¹⁴C-bicalutamide. One animal from each group was killed at 4, 24, 72 and 168 hours after dosing and autoradiographs were prepared.

At 4 and 24 hours: Stomach, GI tract > liver, harderian gland, salivary gland > cardiac muscle, kidney. Low concentrations were distributed to most other tissues except brain and eye.

At 72 hours radioactivity was present in GI tract, liver and harderian, salivary glands only. No radioactivity was detectable at the 168 hour sacrifice (2 days).

KMR 024

Male albino and hooded rats were administered 25 mg/kg ¹⁴C-bicalutamide, killed at 4, 24, 72 and 120 hours after dosing and autoradiographs were prepared.

At 4 and 24 hours: Stomach, GI tract, bladder > liver, adrenal, harderian gland > kidney, cardiac muscle, pituitary glands > lungs > all other tissues. Very little radioactivity observed in blood, brain or eyes.

At 72 hours: GI tract > liver > harderian gland, kidney
At 120 hours: No radioactivity detectable in tissues.

NDA 20-498
Casodex/ Bicalutamide

Quantitative Tissue Distribution of Radioactivity in the Male Rat
KMR 018, KMR 038 lot # ADM 650036/84

KMR 018- Single Dose Study

Male rats were administered a single oral dose of 10 mg/kg ¹⁴C-bicalutamide and killed 6, 24, 48, 72 and 120 hours after dosing (n = 3/timepoint) for quantification of radioactivity by sample oxidation/scintillation counting. Concentrations of radioactivity are presented in table 2 (vol 1.52, pg 113).

The distribution of radioactivity displayed the same pattern at all timepoints as follows:
Liver > GI tract, kidney > heart, lung > blood, testes > brain, eyes.
Liver > GI tract, kidney > heart, lung > blood, testes > brain, eyes.

Concentrations in liver were 6-fold higher than blood.
Concentrations in GI tract, kidney were 3-fold higher than blood.
Concentrations in heart, lungs were 2-fold higher than blood.
(NOTE: Adrenal concentrations were not measured).

KMR 038- Multiple Dose Study

Male rats were administered 10 mg/kg/day ¹⁴C-bicalutamide orally for 10 days and killed 6, 24, 48, 96 and 168 hours after the final dose for tissue quantification of radioactivity.

Concentrations of radioactivity after multiple dosing were equivalent to those seen after a single dose and suggest no accumulation of drug with multiple dosing. This result is consistent with other data which calculated tissue drug half-lives at 22-26 hours.

SINGLE DOSE

Sample	Mean μ g equiv/g (/ml)				
	6 h	24 h	48 h	96 h	168 h
Brain	1.27 \pm 0.04	0.52 \pm 0.01	0.21 \pm 0.01	0.05 \pm 0.00	0.01 \pm 0.00
Fat (white)	9.06 \pm 0.16	3.33 \pm 0.06	1.35 \pm 0.10	0.27 \pm 0.02	0.03 \pm 0.01
Kidney	13.00 \pm 0.46	4.88 \pm 0.14	2.13 \pm 0.05	0.52 \pm 0.03	0.07 \pm 0.01
Liver	25.62 \pm 0.29	9.28 \pm 0.25	4.27 \pm 0.12	1.00 \pm 0.01	0.21 \pm 0.02
Muscle	5.82 \pm 0.17	2.09 \pm 0.09	0.83 \pm 0.03	0.17 \pm 0.01	0.02 \pm 0.00
Plasma (/ml)	6.34 \pm 0.29	2.45 \pm 0.11	1.05 \pm 0.05	0.23 \pm 0.01	0.03 \pm 0.01

POST DOSE 10

Sample	Mean μ g equiv/g (/ml)				
	6 h*	24 h*	48 h*	96 h*	168 h*
Brain	1.35	0.62	0.20	0.05	0.01
Fat (white)	10.20	3.78	1.23	0.30	0.06
Kidney	16.40	6.70	2.78	0.92	0.26
Liver	33.74	14.44	5.96	2.09	0.72
Muscle	6.15	2.25	0.72	0.18	0.04
Plasma (/ml)	7.48	3.44	1.13	0.25	0.04

Animal number	Time after dose (h)	Blood	Brain	Eyes	Heart	Kidney	Liver	Lungs	Testes	Gastro-intestinal tract
1	6	2330	700	924	6090	7639	16777	5320	1782	10804
2		3430	1073	697	8822	11981	20221	6716	1817	16102
3		3766	1082	3168	9842	12724	24873	7302	3555	12923
Mean ± SE		3175±434	952±126	1596±789	8252±1120	10781±1586	20624±2346	6446±588	2385±585	13276±1540
4	24	1795	534	763	3794	5013	10650	3877	1434	5516
5		1463	423	642	3031	3698	8305	2767	1057	4086
6		1395	530	624	2848	3412	7246	2686	1190	4027
Mean ± SE		1511±124	496±36	676±44	3225±290	4041±493	8734±1006	3110±384	1227±110	4543±487
7	48	876	247	426	1822	2377	5213	1810	566	3181
8		729	179	291	1371	1855	3907	1404	461	2727
9		882	174	226	1060	1672	3356	1100	459	2419
Mean ± SE		829±50	200±24	314±59	1418±221	1968±211	4159±551	1638±206	495±35	2775±221
10	72	350	94	160	643	1028	2114	779	253	1148
11		351	94	130	647	694	2206	742	212	1362
12		299	136	143	912	1219	3084	909	217	1512
Mean ± SE		333±17	108±14	144±9	734±89	980±153	2468±309	810±51	228±13	1341±106
13	120	59	23	123	167	250	540	197	52	165
14		99	22	43	154	246	605	184	55	349
15		113	27	44	165	261	694	203	57	481
Mean ± SE		90±16	24±1	70±26	162±4	252±5	613±45	195±6	55±1	332±92

Values are expressed as ng equivalents/g of wet tissue or /ml of blood.

Table 2 : 176334 KHR 018 : Tissue concentrations of radioactivity in individual animals following a single oral dose (10 mg/kg) of [¹⁴C]-ICI 176,334.

Effect of Bicalutamide on Hepatic Microsomal Mixed Function Oxidase Enzymes of the Rat (KMR 011, lot #60036/84)

AlpK Wistar rats (n = 4/sex) were administered 0, 10 and 250 mg/kg/day bicalutamide orally by gavage for 10 days. Treatment with 250 mg/kg produced liver enlargement (21% M; 37% F). Liver enzyme induction was observed in both sexes. NADPH-cyt C reductase and ethoxycoumarin O-deethylase were increased in MD, HD males and HD females. Aldrin epoxidase decreased in HD males and increased in HD females. Cytochrome P450 and ethoxyresorufin O-deethylase activity were unchanged.

Reversibility of Enzyme Induction Produced by Bicalutamide in the Male Rat (KMR 037, lot ADM 44008/90)

Male rats were administered 250 mg/kg bicalutamide orally for 14 days and killed on study days 15, 17, 22 and 29 (1,3,7,14 days after treatment). Bicalutamide treatment produced induction of ethoxycoumarin O deethylase, ethoxyresorufin O-deethylase and erythromycin N-demethylase (measurable 1 and 3 days after dosing). Enzyme levels had returned to baseline 7 and 14 days after dosing.

Conclusion- Bicalutamide (250 mg/kg) induces several liver enzymes in male rats. The MFO levels return to baseline one week after drug withdrawal.

Metabolism of Bicalutamide in the Male Rat (KMR 022, lot #60036/84)

Male rats (n = 10) were administered 50 mg/kg bicalutamide orally for 3 days and 50 mg/kg ¹⁴C-bicalutamide on day 4. Urine samples were collected for 6 days for isolation and identification of urinary metabolites. The major metabolite (70% of radioactivity) is a tetra-substituted benzene resulting from cleavage of the amide bond, ring hydroxylation and sulphation of the hydroxyl group.

Metabolism and Excretion of Bicalutamide in Bile Duct Cannulated Rats (KMR 031, lot # 44008/90)

Male rats (n=3) were administered a single oral dose of 25 mg/kg ¹⁴C-bicalutamide and bile, feces and urine were collected for 2 days (80% recovery of radioactivity). Recovery of radioactivity was as follows: 29% in bile, 20% in feces, 25% in urine. Radioactivity in feces is probably unabsorbed drug. The majority of radioactivity in bile was polar metabolites, two of which co-chromatograph with glucuronide metabolites seen in human urine.

Table 48 The effects of CASODEX on the hepatic microsomal mixed function oxidase enzymes of the male and female rat. (Study Number 176,334 KMR 011)

Dose level (mg/kg/day)	P450 (nmol/mg)	Cyt c (nmol/mg/min)	AE (nmol/mg/min)	ECOD (nmol/mg/min)	EROD (pmol/mg/min)
Male					
0	0.86 ± 0.10	262 ± 10	3.39 ± 0.06	0.96 ± 0.08	8.0 ± 0.2
10	1.02 ± 0.13	296 ± 10*	3.39 ± 0.20	1.36 ± 0.03**	8.1 ± 0.8
250	1.01 ± 0.11	398 ± 13***	2.73 ± 0.15**	1.79 ± 0.08***	8.5 ± 0.9
Female					
0	0.89 ± 0.04	249 ± 23	0.63 ± 0.04	0.26 ± 0.03	8.3 ± 0.5
10	0.71 ± 0.07*	264 ± 7	0.86 ± 0.05**	0.31 ± 0.03	8.3 ± 0.6
250	0.69 ± 0.02*	385 ± 22**	1.20 ± 0.03***	0.36 ± 0.02*	7.6 ± 0.3

* p < 5%, ** p < 1%, *** p < 0.1%
 Values show the mean ± standard error obtained from four animals in each group.

Table 46 The effects of CASODEX on the hepatic microsomal mixed function oxidase enzymes of the male and female mouse. (Study Number TKH/766)

Dose level (mg/kg/day)	P450 (nmol/mg)	Cyt c (nmol/mg/min)	AE (nmol/mg/min)	ECOD (nmol/mg/min)	EROD (pmol/mg/min)	PROD (pmol/mg/min)
Male						
0	0.58 ± 0.03	130 ± 9	1.67 ± 0.29	0.81 ± 0.03	63 ± 7	19 ± 2
5	0.85 ± 0.02***	181 ± 27	1.43 ± 0.03	1.08 ± 0.04**	59 ± 17	78 ± 14**
75	1.27 ± 0.04***	258 ± 10***	2.22 ± 0.06	2.80 ± 0.10***	58 ± 6	230 ± 48**
Female						
0	0.70 ± 0.03	190 ± 20	1.22 ± 0.06	0.85 ± 0.02	51 ± 4	38 ± 7
5	0.80 ± 0.03*	191 ± 14	1.39 ± 0.05	0.88 ± 0.07	62 ± 1*	93 ± 13**
75	1.06 ± 0.01***	307 ± 16***	2.18 ± 0.07***	2.88 ± 0.10***	73 ± 2**	335 ± 23***

* p < 5%, ** p < 1%, *** p < 0.1%

Values show the mean ± standard error obtained from four pooled liver samples in each group.

117

Vol 1.0
9B

Metabolism of Bicalutamide in Intact and Bile Cannulated Male Rats (KMR 034, lot 44008/90)

Bile-duct cannulated or intact male rats (n =3) were administered a single oral dose or 13 daily doses of 10 mg/kg ¹⁴C-bicalutamide. Results are summarized below-

	% Radioactivity		
	Bile	Feces	Urine
Single Dose			
Intact		19%	36%
Cannulated	18.5%	6.6%	33%
Multiple Dose			
Intact		34%	24%
Cannulated	32%	5.8%	19%

88% of radioactivity in urine was the previously identified acid metabolite. The radioactivity in the bile was glucuronide conjugates of bicalutamide or hydroxylated bicalutamide (see Figure 1, taken from vol 1.53, pg 71).

Metabolic Disposition and Stereochemical Inversion of the Enantiomers of Bicalutamide in Male Rats (KKR 035, lot 44023/89)

Intact or bile-cannulated rats were administered 10 mg/kg of pseudo-racemic mixtures of bicalutamide containing ¹⁴C-labelled R (187,555) or S (187,556) enantiomer and unlabelled opposite enantiomer. No inversion of enantiomers was observed after administration of either the R or S-labelled compound. Elimination half-lives of the racemate and the R-enantiomer were similar (23-24 hours). Half-life of the S-enantiomer could not be calculated but was <6 hours. (S-enantiomer cleared more rapidly as is observed in men). The excretion of the enantiomers displayed the following pattern (24 hour collection) -

	% of Radioactivity			
	Urine	Bile	Feces	Absorption
187,555 (R)	43%	21%	11%	90%
187,556 (S)	37%	50%	20%	80%

Pharmacokinetics of racemate (176,334) and R-enantiomer (187,555) are summarized below (vol 1.53,pg 114).

Parameter	R-Labelled	176,334	S-Labelled	176,334
	176,334	187,555	176,334	187,555
C _{max} (µg/ml)	4.05 ± 0.07	3.50 ± 0.05	3.45 ± 0.19	2.88 ± 0.16
t _{max} (h)	6	12	6	12
AUC (µg.h/ml)	129.6	121.4	121.2	108.7
t _½ (h)	24.1	23.5	23.0	22.0

page

PURGED

Absorption, Metabolism and Excretion of Bicalutamide by Female Rabbits (KMB 013, lot 60036/84)

Female rabbits received single oral doses of 9 mg/kg (n =8) or a single intravenous dose of 1 mg/kg (n =4) ¹⁴C-bicalutamide and urine and feces were collected for 7 days for quantification of radioactivity.

<u>Route</u>	% of Radioactivity		
	<u>Urine</u>	<u>Feces</u>	<u>Absorption</u>
iv	28%	67%	
oral	22%	64%	100%

Metabolism and Excretion of Bicalutamide in the Dog (KMD 032, lot #ADM 44008/90)

Male dogs (n= 3) with bile duct cannulae were administered a single oral dose of 2.5 mg/kg ¹⁴C-bicalutamide and urine, feces and bile were collected for 2 days for quantitation of radioactivity. Only 27% of radioactivity was recovered. 14.9 % of radioactive dose was recovered in the feces, presumably unabsorbed drug. 4.4% was recovered in the urine, 6.9% was recovered in the bile.

TOXICOLOGY

Toxicology studies were performed according to GLP at

All studies used

176,334, the racemic mixture.

ACUTE TOXICITY - All studies performed with the racemate 176,334 except for one study performed in the rat with the R-enantiomer 187,555. Lot numbers for 176,334 (racemate) were 60022/84 in the mouse and rat studies, 60036/84 in the rabbit study, and 44008/90 in the dog study. The lot number for the R-enantiomer 187,555 used in the rat study was 44022/89.

<u>Species/strain</u>	<u>Route</u>	<u>LD 50(mg/kg)</u>	<u>Observations</u>
Mice, CD-1 (5/sex)	oral	> 2000	No deaths or signs
	ip	> 2000	Abdominal discomfort No deaths; hepatic necrosis in 1 mouse
Rat, Wistar (5/sex)	176,334,po	> 2000	No deaths or signs
	187,555,po	> 2000	No deaths or signs
	ip	>2000	Abdominal discomfort No deaths
Rabbit, Dutch (3/sex)	oral	> 200	No deaths or signs
Dog, beagle (2 M)	oral	> 2000	No deaths or signs

Four Week Oral Toxicity in Rats(Study TAR/1211, lot ADM 60022/84)

Wistar rats (n = 10/sex/dose) were administered 0, 25, 100 and 500 mg/kg/day 176,334 in 0.5% polysorbate 80 orally by gavage for 28 day.. An additional 15/sex/dose were treated for pharmacokinetics evaluation.

Mortality/signs - none.

Body weight/food consumption/water consumption - unremarkable

ECG/Ophthalmology - unremarkable

Hematology- unremarkable

Blood chemistry (days 24-25)

Total protein/albumin - mildly increased MD, HD rats

creatinine - increased MD, HD rats

ALT/AST- significantly decreased in treated males

Drug plasma concentrations- see Table 7 taken directly from the submission (Vol 1.2i, p 38)

<u>Dose(mg/kg)</u>	<u>Cmax(ug/ml)</u>	<u>Cmin</u>	<u>Multiple of HTD</u>
25	10-12	4	1 X
100	15-18	4-8	1-2 X
500	20-25	8-17	2-3 X

Css = 8.6 ug/ml in men receiving 50 mg Casodex/day.

Urinalysis - unremarkable

Organ weights -

Adrenals - dose-related increase in abs wts

24% MD, 50 % HD males; 16%, 27% HD females

Liver - dose-related increased wts 21% MD, 35% HD males;

36% LD, 55% MD, 90% HD females

Ventral prostate - decreased 60%, 59% and 68% in LD, MD, HD males

Seminal vesicle - decreased 84, 85 and 90% in LD, MD, HD males

Ovary - wts not measured

Histopathology -

Adrenals- cortical cell necrosis-

5/20 C, 13/20 LD, 8/20 MD, 14/20 HD

cortical vacuolization- 4/10 C, 3/10 LD, 5/10 MD, 8/10 HD

Liver - increased basophilia of hepatocyte cytoplasm

3/20 C, 17/20 LD, 19/20 MD, 17/20 HD

increased RNA in hepatocyte cytoplasm

3/20 C, 12/20 LD, 18/20 MD, 14/20 HD

Pituitary - increased castration cells

4/10 C, 10/10 all treated male groups

Prostate/seminal vesicles - atrophy - 0/10 C, 10/10 LD, MD, HD

Testes- diffuse bilateral leydig cell hyperplasia

0/10 C, 7/10 LD, 8/10 MD, 10/10 HD males

Thyroid - hypertrophic follicular epithelium -

0/10 C, 10/10 LD, MD, HD males

0/10 C, 4/10 LD, 3/10 MD, 9/10 HD

reduced colloid - 0/10 C, 4/10 LD, 3/10 MD, 9/10 HD M; 3/10 HD F

Summary -

Administration of 25, 100 and 200 mg/kg/day 176,334 (1, 1.5 and 3 times human therapeutic plasma drug exposures) produced little toxicity in rats treated for 28 days. There were no drug effects on mortality, signs, body weight, food consumption, hematology or clinical chemistry.

Dose-related increases in adrenal and liver weights were observed in MD, HD rats. Maximal reductions of ventral prostate and seminal vesicle weights were observed in male rats at all dose levels (desired pharmacologic effect). Adrenal cortical cell vacuolization and necrosis were observed in drug-treated rats of both sexes. 176,334 also increased basophilia and RNA in hepatocyte cytoplasm.

Conclusion - The doses utilized produce exposures equivalent to human therapeutic exposure. The histologic changes observed are expected consequences of high dose anti-androgen therapy. Toxicity studies should employ higher dose levels to elucidate target organs of toxicity.

Ninety Day Dose-Finding Study in Rats (dietary administration).
(Study THR/1294; lots ADM 56041/85 and 50082/85)

Wistar rats (n = 30/sex/dose) were administered 0, 10, 100, 500 and 1000 mg/kg/day or 5% 176,334 in NDD diet for 98 days. Achieved doses for the sexes combined were 10, 101, 507, 1016 and 4600-5000 mg/kg/day.

Mortality - none

Signs- increased incidence of redness and sores and/or necrosis of the tip of the tail and missing tip of tail in HE (5% in diet) rats.

Ophthalmology - unremarkable

Body weight - dose-related decrease in body weight gain .
3% , 15%, 17%, 18%, and 20% in gp II - VI males
1%, 7%, 7%, 11%, and 11% in gp II -VI females

Food consumption - decreased approximately 10% in males receiving \geq 100 mg/kg/day. Consistent decreases in food consumption were also observed in two highest dose groups of female rats.

Water consumption (week 10) - decrease of 15% in treated males and females

Hematology (weeks 4 and 15) -
Hgb - mild decreases at doses \geq 100 mkd
Packed cell/mean cell volumes - decreased at doses \geq 500 mkd

Blood chemistry (weeks 4 and 15)
total protein - increased \geq 500 mg/kg

Urinalysis- (wks 4 and 12) measured pH and volume only
urine volume decreased in Gp VI females

Pharmacokinetics Data - Blood samples were collected at 4 hour intervals on days 93-94 of dosing. Steady state kinetics data are summarized below.

<u>Dose (mg/kg)</u>	<u>Cmax(ug/ml)</u>		<u>AUC 0-24</u> (ug.hr/ml)		<u>Multiple of HTD</u>
	Males	Females	Males	Females	
10	5.6	7.0	105	143	1/2 X
100	21.7	23.5	450	512	3 X
500	32.2	43.3	650	880	4-5 X
1000	37	42.4	750	890	5 X
5000 (5%)	34	42	755	945	5 X

Css in men receiving 50 mg/day = 8.6 ug/ml
AUC in men receiving 50 mg/day = 165-205 ug.hr/ml.

Organ weights -

Prostate- abs/rel wts decreased at all dose levels

Uterus- abs/rel wts decreased \geq 1000 mkd

Adrenals - abs/rel wts dose-related increase \geq 100 mkd

Liver - abs/rel wts increased \geq 100 mkd

Histopathology -

Testes- mild leydig cell hyperplasia

0/5 C, 0/5, 2/5, 2/5, 3/5, 5/5 Gps II - VI, respectively
seminiferous tubule atrophy-

1/5 C, 0/5, 2/5, 4/5, 4/5, 5/5, gps II-VI

Epididymes -

exfoliated seminiferous epithelial cells

1/5 gp III, 1/5 GP IV, 3/5 gp V

no spermatozoa

1/5 C, 2/5, 4/5, 3/5, 4/5 gps III-VI

Prostate/seminal vesicles- atrophy in most treated males, dose-related in severity (mild in LD to severe in HD)

Adrenal- cortical vacuolization

2/5 gp III, 5/5 gps IV, V and VI males

1/5 gp IV, 1/5 gp V, 2/5 gp VI females

Pituitary - increased castration cells (enlarged gonadotropin secretory cells) 1/5 C, 4/5 gp II, 5/5 gps III- VI males

Liver - hepatocyte basophilia (due to increased RNA with many free ribosomes)

0/10 C, 6/10, 9/10, 10/10, 10/10, 10/10 gps II - VI

hepatocyte hypertrophy -

0/10 C, 0/10, 3/10, 8/10, 6/10, 8/10 gps II-VI

single cell necrosis-

0/10 C, 0/10 gp II, 1/10, 7/10, 3/10, 4/10 gps III-VI

hepatocyte polyploidy (large multinucleated hepatocytes)

0/5 gps I & II, 2/5 gps III & IV, 4/5 gps V & VI

Kidney -

minimal to mild pigmentation (hemosiderin) of proximal tubule epithelium with more marked changes in females.

males - 0/5, 0/5, 4/5, 4/5, 4/5, 5/5 gps I -VI

females - 0/5, 4/5, 4/5, 5/5, 5/5, 4/5 gps I-VI

Summary - Drug treatment produced no mortality or signs, and no toxicologically significant changes in hematology, blood chemistry or urinalysis. Body weight was decreased in treated rats secondary to decreased food consumption due to poor palatability. Rats dosed with up to 500 mg/kg/day by gavage for one month displayed no decreases in body weight or food consumption.

Expected pharmacologic effects on the male reproductive system were observed including prostate, seminal vesicle, and epididymal atrophy, increased castration cells in the pituitary and leydig cell hyperplasia secondary to altered testosterone feedback.

These effects on the male reproductive system and pituitary are observed with all anti-androgens. Hepatocyte hypertrophy and polyploidy were observed with dose-related frequency but were not severe enough to impact on survival in a 2 year carcinogenicity study.

Conclusions -

Pharmacokinetics data demonstrate that plasma drug concentrations of parent compound plateau at concentrations > 500 mkd. The ADME data suggests the plateau effect is secondary to saturation of absorption. Dose-related decreases in body weight (up to 11% in females; 20% in males) were observed in treated rats secondary to poor palatability of drug admixed with diet. No other dose limiting toxicity was observed.

Doses up to 500 mg/kg/day in diet were tolerated without decreases in body weight which would impact on nutritional status of rats in a 2 year study. Zeneca chose doses of 5, 15 and 75 mg/kg/day for their 2 year rat carcinogenicity study. The high dose produces AUC exposures in rats only 2 times the human therapeutic exposure obtained with the 50 mg/day dose. The dose selections for the rat carcinogenicity study are clearly inadequate (too low).

Six Month Oral Toxicity Study in Rats (study # TPR 1212, lot # ADM 60036/84)

Wistar rats (n = 10/sex/dose) were administered 0, 10, 50 and 250 mg/kg/day 176,334 in 0.5% polysorbate 80 by gavage for 6 months. An additional 12/sex/dose were treated for pharmacokinetics analysis. An additional 15/sex received the high dose and underwent a 12 week drug-free withdrawal period prior to sacrifice.

Mortality - 4 C, (2 M, 2 F), 1 LD M, 2 MD M and 1 HD M

Deaths were not drug-related. 5 deaths were associated with gavage accidents.

Signs - inflammation/irritation of upper respiratory tract during weeks 12-26 was observed in 40-75% of animals from all groups including controls.

Body weight - decreased gain in treated males; 5% in LD, MD, 7% in HD. No significant effects in females.

Food consumption - intermittent significant decreases in food consumption (4-10%) in males

Water consumption- unremarkable

Ophthalmology/ECG- no drug-related effects.

Hematology (measured weeks 5, 13, 25) -

Hgb- decreased in MD, HD females; HD males wks 13 and 25
Packed /mean cell volume - decreased MD, HD females wks 13,25
WBC/lymphocytes- increased HD females wks 13 and 25

Blood chemistry (measured weeks 5, 13 and 25)

total protein - dose-related increase in all treated females and
HD males all timepoints

albumin- increased in HD males; MD, HD females

alkaline phosphatase - dose-related decrease wk 25 in all groups
of treated males

Urinalysis-unremarkable

Organ weights-

Adrenal -increased abs/rel wts in LD, MD and HD males and MD
females

Kidney - decreased abs/rel wts in all treated males.

Liver- dose-related increase in abs/rel wts in MD, HD males, all
treated females.

Prostate/seminal vesicles - dose-related decrease in abs/rel wts
all groups of treated males

Pharmacokinetics - (see Tables 5 and 6 taken directly from the
submission). Plasma drug concentrations increased with increasing
dose but not dose-proportionally. Modest drug accumulation (2-
fold) was observed with multiple dosing and was more significant
in females.

Plasma drug concentrations were 2-fold higher in females than in
males at all dose levels at both sampling times (2 and 24 hours
post-dose).

Histopathology -

Prostate - atrophy of tubulo-alveolar glands and epithelium
0/20 C, 19/20 LD, 17/20 MD, 20/20 HD males

Seminal vesicles - atrophy characterized by reduced secretions
and atrophied epithelium which was dose-related in severity
mild in LD and moderate in HD
0/20 C, 20/20 LD, 20/20 MD, 20/20 HD males

Testes- small 0/20 C, 0/20 LD, 6/20 MD, 6/20 HD
enlarged 0/20 C, 0/20 LD, 0/20 MD, 9/20 HD
seminiferous tubule atrophy- 1/20C, 0/20 LD, 7/20 MD, 16/20 HD
leydig cell hyperplasia - 0/20 C, 2/20 LD, 11/20 MD, 12/20 HD

Ovaries - granulosa -thecal cell hyperplasia
0/20 C, 0/20 LD, 19/20 MD, 16/20 HD

Group/dose (mg/kg)	Sex	Time into study			
		Day 1	Day 28	Week 13	Week 27
II 10	♂	1.72 ± 0.12	4.50 ± 0.15	5.41 ± 0.51	5.02 ± 0.69
	♀	2.64 ± 0.96	5.76 ± 0.17	6.21 ± 0.68	9.91 ± 0.97
	♀/♂	1.53	1.28*	1.15	1.97*
III 50	♂	4.18 ± 0.53	7.25 ± 0.29	7.43 ± 0.38	8.39 ± 0.13
	♀	5.52 ± 0.36	7.90 ± 0.05	9.99 ± 1.41	15.5 ± 1.0
	♀/♂	1.32	1.09	1.34	1.84*
IV 250	♂	7.31 ± 0.64	10.8 ± 0.4	12.7 ± 2.0	13.6 ± 1.7
	♀	10.1 ± 0.7	13.8 ± 0.8	15.7 ± 5.0	25.2 ± 2.4
	♀/♂	1.38*	1.28*	1.24	1.85*

Multip.
of
HTD
1/2-1 X
1-2 X
19.3
1.5-3

* - Statistically significant male/female difference (p < 0.05).

CSS in men on 50mg/day = 86 µg/ml

Table 5 : ICI 176,334 : Six month oral toxicity study in rats. Study number TPR/1212.

Mean (+ S.E.) plasma concentrations (µg/ml) of ICI 176,334 in rats 2 hours post dose.

036

Group/dose (mg/kg)	Sex	Time into study			
		Day 2***	Day 29	Week 13	Week 27
II 10	♂	1.97 ± 0.41	3.08 ± 0.27	3.62 ± 0.11	3.08 ± 0.20
	♀	2.27 ± 0.33	3.52 ± 0.49	4.58 ± 0.54	6.82 ± 0.45
	♀/♂	1.15	1.14	1.27	2.21*
III 50	♂	5.49 ± 0.13	4.25 ± 0.29	5.73 ± 0.23	5.03 ± 0.61
	♀	5.40 ± 0.26	5.87 ± 1.15	7.93 ± 1.34	8.77 ± 0.65
	♀/♂	0.98	1.38	1.38	1.73*
IV 250	♂	13.2 ± 2.8	5.85 ± 0.57	4.62**	7.52 ± 1.21
	♀	14.0 ± 1.1	7.33 ± 0.98	9.74 ± 3.28	23.3 ± 5.2
	♀/♂	1.06	1.25	2.11	3.10*

* - Statistically significant male/female difference (p < 0.05).

** - n=2, no 't' test performed.

*** - 26 hours post dose

Table 6 : 176,334 : Six month oral toxicity study in rats. Study number TPR/1212.

Mean (+ S.E.) plasma concentrations (µg/ml) of 176,334 in rats 24 hours post dose.

037

20.

Adrenal - hypertrophy of zona fasciculata and reticularis
1/40 C, 18/40 LD, 27/40 MD, 35/39 HD both sexes
cortical vacuolization - dose-related in severity - mild in
control, LD, MD and moderate in HD
14/20 C, 11/20 LD, 18/20 MD, 17/20 HD males, 8/10 HD male
withdrawal dogs.

Pituitary - castration cells 11/20 C, 19/20 LD, 18/20 MD, 17/20
HD and 9/10 HD withdrawal male dogs. No pituitary effects
in females.

Thyroid- hypertrophic follicular epithelium
9/20 C, 20/20 LD, 20/20 MD, 19/20 HD males
4/20 C, 20/20 LD, 20/20 MD, 20/20 HD females

Drug-induced adrenal, pituitary and thyroid changes were not
reversible.

Summary - Administration of 10, 50 and 250 mg/kg/day
bicalutamide (176,334) produced plasma drug exposures in rats
0.5, 1 and 2 times human drug exposures (C_{ss}) in men receiving 50
mg/day. Drug treatment produced slight reductions in food
consumption and body weight gain (5%) in treated males. Mild
decreases in hemoglobin and packed cell volume and dose-related
increases in total protein and albumin were observed in MD, HD
females and HD males. Prostate and seminal vesicle atrophy, the
desired pharmacologic effects, were observed in all drug-treated
males. Drug-treatment also produced testicular seminiferous
tubule atrophy and leydig cell hyperplasia in MD, HD male rats.
Additional histologic changes observed in bicalutamide treated
rats included:

1. adrenal cortical and thyroid follicular cell hypertrophy in
both sexes.
2. testicular leydig cell hyperplasia in males; ovarian
granulosa cell hypertrophy in females
3. increased pituitary castration cells in treated males

Conclusions- Bicalutamide at doses up to 250 mg/kg/day (plasma
drug exposures in rats 2 times the exposure in men receiving the
proposed therapeutic dose of 50 mg/day) was well-tolerated in
rats. Toxicities observed were associated with

1. the desired pharmacologic effect -prostate, seminal vesicle,
testicular atrophy, pituitary castration cells.
2. drug-induced hormonal imbalance- either direct (adrenal
cortical hypertrophy) or indirect resulting from loss of
testosterone feedback at the hypothalamus and pituitary with
secondary elevations of LH (granulosa cell hypertrophy,
leydig cell hyperplasia).
3. induction of liver P450 enzymes (thyroid follicular
hypertrophy).

One Year Oral Toxicity Study in Rats (study # TFR/1297, lot#
ADM 56071/86)

Wistar rats (n=20/sex/dose) were administered 0, 5, 15 and 75 mg/kg/day 176,334 orally in NDD diet for 12 months. An additional 12/sex/dose were treated for pharmacokinetics evaluation. An additional 12 rats/sex were treated in the control and high dose groups and retained undosed for 24 weeks to assess the reversibility of drug-related effects. Drug analysis- achieved doses of drug were within \pm 10% of desired concentrations.

Mortality - 20 animals died or were killed in extremis during the course of the study. The deaths were not drug or dose-related. Signs - urine staining and small flaccid testes were observed with dose-related increase in frequency in drug-treated males. Increased incidence of missing whiskers in drug-treated females. Ophthalmology - unremarkable

Body weight - gain was decreased sporadically (wks 1-6 LD, wks 18-24 HD males, wks 1-13 MD females, wks 42-47 HD females) but overall there were no significant differences in LD, MD rats. Gain decreased 3% in HD males; 14% in HD females.

Food consumption -
males- decreased consumption (3 gm/day) in MD, HD males - wks 1-35 then increased consumption (2 gms/day over controls) for remainder of the study
females- MD, HD gpc increased (3 gms/day/rat) over control, LD

Water consumption- unremarkable

Hematology - (measured wks 13, 26, 51)
Hgb, Hct - decreased in HD females wks 13, 26, 51
mean cell volume/ Hgb - decreased in HD females wks 13, 26, 51

Blood chemistry -
total protein - dose-related increases in all treated females, HD males
Alkaline phosphatase, ALT, AST - decreased in all groups of drug-treated rats.

Changes in protein and liver enzymes were still present in HD rats after the 24 week withdrawal period.

Urinalyses - (only urine volume and pH measured)- unremarkable.

Pharmacokinetics (see Table 16 taken from vol 1.26, p 85)
Plasma drug concentrations in females were significantly greater than in males. Modest (1.5-3 fold) drug accumulation was obtained with chronic dosing.

Table 16 : 176,334 : Twelve month oral toxicity study in the rat: dietary administration.
 Study number TFR/1297. Mean (\pm SE) plasma concentrations (μ g/ml) of 176,334 for rats
 from Groups II, III and IV.

Group	Sex	Plasma concentration of ICI 176,334 (μ g/ml)								Week 52 Day 2 ratio
		Time into study								
		Day 2	Day 29	Week 13	Week 27	Week 40	Week 52			
II 5 mg/kg	Male	1.56 \pm 0.10	2.50 \pm 0.11	2.15 \pm 0.12	3.06 \pm 0.24	2.57 \pm 0.14	3.40 \pm 0.13	1.78*	2.2	
	Female	1.75 \pm 0.03	3.25 \pm 0.21	3.37 \pm 0.20	4.63 \pm 0.50	4.85 \pm 0.29	6.04 \pm 0.56			
	Female/ Male	1.12	1.29*	1.57*	1.51*	1.89*				
	Male									
III 15 mg/kg	Male	5.52 \pm 0.17	6.06 \pm 0.15	6.25 \pm 0.15	7.39 \pm 0.52	6.14 \pm 0.28	7.10 \pm 0.13	1.40*	1.3	
	Female	5.75 \pm 0.23	6.83 \pm 0.18	7.46 \pm 0.33	8.63 \pm 0.74	10.20 \pm 1.58	9.94 \pm 0.12			
	Female/ Male	1.04	1.13*	1.19*	1.17	1.66*				
	Male									
IV 75 mg/kg	Male	24.41 \pm 0.90	18.57 \pm 1.23	17.59 \pm 0.49	16.21 \pm 0.57	15.81 \pm 2.00	19.97 \pm 1.63	1.66*	0.8	
	Female	22.32 \pm 0.30	26.40 \pm 3.42	20.72 \pm 0.82	24.58 \pm 0.76	23.34 \pm 1.81	33.17 \pm 1.88			
	Female/ Male	0.91	1.42	1.18*	1.52*	1.48*				
	Male									

* = Statistically significant (p<0.05)

<u>Dose(mg/kg)</u>	<u>Cp(ug/ml)*</u>		<u>AUC(ug.hr/ml)*</u>	<u>Multiple of HTD</u>
	Males	Females		
5	3.4	6.0		1/2
15	7.1	10	100-150	1 X
75	20	33	330-400	2 X

Mean C_{ss} in men receiving 50 mg/day of Casodex = 8.6 ug/ml.

Mean AUC in men receiving 50 mg/day of Casodex = 165 ug.hr/ml.

* AUC values in rats receiving the 15 and 75 mkd doses were estimated using data from the 3 month rat dose-finding study (THR/1294).

Organ weights -

Testes- dose-related decrease in abs/rel wts, MD, HD males

Prostate- marked decrease in abs/rel wts all treated males

Adrenals- increased abs/rel wts MD, HD males.

Kidneys - decreased abs/rel wts LD, MD, HD males

increased abs/rel wts MD, HD females

Liver- dose-related increase in abs/rel wts MD, HD males

All changes in organ weights were reversible after drug withdrawal.

Histopathology - (n =20/sex/dose main test; 12/sex for 24 week drug withdrawal rats).

Neoplastic changes -

Testes- benign leydig cell adenomas

0/21 C, 1/21 LD, 1/21 MD, 8/21 HD male rats

0/12 C, 9/12 HD after 24 weeks of drug withdrawal

Thyroid - follicular cell adenoma

1/21 C, 1/21 LD, 1/21 MD, 7/21 HD males

0/20 C, 0/20 LD, 0/20 MD, 3/20 HD females

(thyroid changes were reversible -adenoma observed in only 1/24 HD withdrawal rats)

Uterus - adenocarcinoma 0/20 C, 0/20 LD, 0/20 MD, 0/20 HD

0/12 C, 2/12 HD withdrawal (these lesions were also observed in the rat carcinogenicity study)

Non-neoplastic changes-

Adrenal- cortical vacuolization -

6/20 C, 5/20 LD, 5/20 MD, 18/20 HD females

Heart - myocardial fibrosis

11/40 C (28%), 18/40 LD, 13/40 MD, 29/40 HD (73%)

Liver-

hepatocyte basophilia - 0/40 C, 2/40 LD, 2/40 MD, 16/40 HD
hepatocyte hypertrophy - 1/40 C, 0/40 LD, 1/40 MD, 31/40 HD
These data suggest liver enzyme induction was observed primarily
in HD rats.

Ovaries - atrophy - 2/20 C, 4/20 LD, 5/20 MD, 6/20 HD females

Pituitary - increased castration cells
1/20 C, 0/20 LD, 8/20 MD, 20/20 HD males

Seminal vesicles - atrophy 0/20 C, 16/20 LD, 20/20 MD, 20/20 HD
(4/12 HD withdrawal rats)

Testes-

tubular atrophy - 3/20 C, 2/20 LD, 14/20 MD, 20/20 HD
leydig cell hyperplasia- 0/20 C, 7/20 LD, 15/20 MD, 19/20 HD

Thyroid -

hypertrophic epithelium - 2/40 C, 20/40 LD, 36/40 MD, 40/40 HD
hyperplasia - 0/40 C, 1/40 LD, 14/40 MD, 30/40 HD
colloid basophilia - 13/40 C, 24/40 LD, 34/40 MD, 40/40 HD
Sponsor suggests thyroid changes may be secondary liver enzyme
induction resulting in increased thyroid hormone metabolism with
compensatory hyperplasia of the thyroid.

Summary

Administration of bicalutamide to rats at dose levels of 5, 15
and 75 mg/kg/day produced drug exposures in rats (plasma drug
concentrations and AUCs) 1/2, 1 and 2 times the exposures
obtained in men receiving the therapeutic dose of 50 mg/day.

Bicalutamide was fairly well tolerated with no drug-related
deaths or signs and sporadic mild reductions in body weight gain
secondary to decreased food consumption (poor palatability).

Minor changes in hematology included decreased hemoglobin,
hematocrit and packed cell volumes in high dose female rats.
Increases in total protein were observed in all drug-treated
female rats and HD males. Drug-related histologic changes were
similar to those observed in the 6 month study and included:

1. testicular leydig cell hyperplasia (also observed in male
rats treated with flutamide, nilutamide, finasteride).
2. prostate/ seminal vesicle/ ovarian atrophy
3. thyroid follicular cell hyperplasia (MD, HD) and adenoma (HD)
4. uterine adenocarcinoma (also observed in the rat
carcinogenicity study)
5. centrilobular hepatocyte hypertrophy in HD rats - (secondary
to liver enzyme induction)
6. adrenal cortical vacuolization

A new finding associated with bicalutamide treatment was an
increased incidence of myocardial fibrosis, especially in HD
rats.

Conclusion- Dose levels which produce low multiples (1-2 times) of the human therapeutic exposures were utilized in this study. Data from the 3 and 6 month studies demonstrate that plasma concentrations of parent drug continue to increase with doses up to 500 mg/kg/day. Dose levels up to 500 mg/kg/day are also well tolerated. This study is adequate to support safety for the current NDA (50 mg/day for stage D₂ prostate cancer).

Two Year Oral Carcinogenicity Study in Rats (#TCR/1296, lot # ADM 56071/86 and 56082/85)

Wistar rats were administered 0 (100/sex), 5, 15, and 75 mg/kg/day bicalutamide (N = 51 M, 52 F) in NDD diet for 104 weeks. Achieved doses were within \pm 10% and mean values equaled the targeted dose.

Mortality- no dose-related trends in survival were observed. Survival was increased in HD males secondary to decreased wt gain with a resultant decrease in age-related glomerulonephropathy. (deaths due to glomerulonephropathy in males 50% C, 49% LD, 58% MD, 27% HD).

% Survival-
Males 33% C, 24% LD, 39% MD, 49% HD
Females - 44% C, 58% LD, 46% MD, 37% HD

Signs - dose-related increase in testicular abnormalities including reduction in size, swollen, hard or flaccid testes were observed in treated males- 9% C, 25% LD, 75% MD, 96% HD

Body weight - decreased body weight gain
males- 8% in MD, 9% in HD; and females- 8% MD, 12% HD

Food consumption- small dose-related decreases in consumption (responsible for decreased body wt) were observed throughout the study.

Water consumption- significantly reduced in treated females.

Hematology - no drug-related changes

Pharmacokinetics- See data in 1 year rat study above.

Neoplastic lesions - the percentage of animals with multiple tumors and benign tumors increased in treated males, no increases were observed in treated female rats
multiple tumors - 34% C, 49% LD, 53% MD, 73% HD males
benign tumors - 66% C, 65% LD, 86% MD, 98% HD

Brain- malignant meningioma- 1% C, 4% LD, 0% MD, 6% HD rats

Testes- benign leydig cell adenoma
3% C, 38% LD, 64% MD, 96% HD males

Thyroid - follicular cell adenoma
2%, 11% LD, 24% MD, 51% HD rats

Uterus- adenocarcinoma 0/100 C, 0/52 LD, 1/52 MD, 5/52 HD females
squamous carcinoma 1/52 HD

Decreases in some tumor types were observed
pituitary adenomas- 25% C, 20% LD, 18% MD, 14% HD males
26% C, 20% LD, 20% MD, 10 % HD females

mammary gland tumors
fibroadenoma - 29% C, 12% LD, 12% MD, 6% HD females
adenocarcinoma - 8% C, 4% LD, 0% MD, 0% HD females

Non-neoplastic lesions-

Liver- decreased incidence of hepatocyte vacuolization/necrosis
in treated rats
vacuolization - 53% C, 30% LD, 23% MD, 24% HD
necrosis - 25% C, 29% LD, 13% MD, 19% HD

Epididymes -
reduced or no spermatozoa - 32% C, 62% LD, 90% MD, 100% HD males
ductal atrophy - 16% C, 50% LD, 82% MD, 100% HD

Testes-
atrophy - 81% C, 84% LD, 100% MD, 100% HD males
tubular mineralization - 22% C, 14% LD, 54% MD, 66% HD
leydig cell hyperplasia - 2% C, 40% LD, 50% MD, 62% HD

Prostate - atrophy 1% C, 88% LD, 90% MD, 90% HD

Seminal vesicle - atrophy 21% C, 98% LD, 100% MD, 98% HD

Thyroid-
follicular epithelial hypertrophy - 46% C, 56% LD, 73% MD, 91% HD
" " hyperplasia - 18% C, 17% LD, 15% MD, 37%HD

Kidney - no decrease in total incidence of glomerulonephropathy
but slight decrease in severity and deaths due to
nephropathy in treated animals

Bone- reduced osteitis fibrosa cystica in sternum, femur and
vertebra of HD rats

Mammary glands - reduced incidence of hyperplasia in HD females
91% C, 98% LD, 90% MD, 66% HD

Summary

Mild reductions in body weight gain were observed in mid and high dose rats, secondary to a parallel reduction in food consumption. Drug-related atrophy of the testes, epididymes, prostate, seminal vesicles, uterus, cervix and vagina are considered secondary to the antiandrogenic properties or hormonal imbalance produced by bicalutamide.

A dose-related increase in the incidence of thyroid follicular adenomas was observed. The sponsor suggests these adenomas develop secondary to increased thyroid hormone metabolism by the liver. Liver enzyme induction and increased thyroid hormone metabolism have been demonstrated in bicalutamide-treated rats.

A dose-related increase in the incidence of benign leydig cell adenomas was observed. This finding is common to all anti-androgens (flutamide, nilutamide) and 5 α -reductase inhibitors (finasteride, epristeride) which alter testosterone/DHT feedback at the hypothalamus and pituitary and produce consequent elevations of LH. Although elevations of LH have not been demonstrated in rodents treated with Casodex, a mechanism similar to other anti-androgens would be expected.

A significant increase in uterine adenomas (MD, HD) and carcinoma (HD only) were observed in bicalutamide-treated rats. Uterine neoplasia is a very uncommon spontaneous lesion in Wistar rats. The sponsor suggests the uterine neoplasms may also be a consequence of hormonal imbalance resulting from treatment with Casodex.

Conclusions - Administration of Casodex at concentrations of 5, 15 and 75 mg/kg/day (up to 2 times human therapeutic exposure) produced an increased incidence of benign testicular leydig cell adenomas, benign thyroid follicular cell adenomas and ovarian adenocarcinoma and squamous carcinoma. The neoplastic findings were secondary to drug-induced hormonal imbalance and not direct carcinogenic effects.

The data from the 3 month oral dose finding study in rats clearly demonstrate that 75 mg/kg/day is not the MTD in the rat. Rats tolerated doses up to 5% of diet with the only significant finding being decreased body weight gain. The decrease in body weight gain was due to decreased food consumption (poor palatability) not toxicity per se. The sponsor also argues that plasma drug concentrations plateau but increases in exposure were observed with doses up to 500 mg/kg.

If the sponsor intends to develop Casodex for benign prostatic hyperplasia (BPH) the carcinogenicity studies should be repeated utilizing the 500 mg/kg dose administered by gavage as the MTD.

Reductions in body weight secondary to decreased food consumption (poor palatability) are not acceptable for establishing an MTD. Plateauing of drug concentrations with increasing doses is a valid basis for dose selection. In addition, ADME studies demonstrate that the majority of radioactivity (90%) in the plasma of rats, dogs and humans is parent compound.

30 Day Pilot Study of Dietary Palatability and Pharmacokinetics of Bicalutamide in Mice (# TSM/633, lot 56071/86)

CD-1 Alpk mice (n = 10/sex/dose) were administered 0, 5, 15, and 75 mg/kg ICI 176,334 in CT1 rodent diet for 30 days.

Mortality - none

Signs - alopecia in some mice

Body weight - unremarkable

Food consumption/utilization - drug at dose levels up to 75 mg/kg/day had no effects

Pharmacokinetics - sampling time was not specified. No sex differences in plasma drug concentrations were observed. Plasma drug exposures increased with increasing dose but not dose proportionally.

<u>Dose (mg/kg)</u>	<u>Mean concentration (ug/ml)</u>
5	5.4 ± 0.1
15	13.3 ± 0.3
75	36 ± 0.7

90 Day Dose Finding Study in Mice (# THM/490, lot # 56041/85)

Alpk CD-1 mice (n=30/sex/dose) were administered 0, 10, 100, 500, 1000 mg/kg/day or 5% bicalutamide in diet for 92 days. Achieved concentrations were 10, 101, 504, 1007 and 7500 mg/kg/day. (Average body weight = 20 gm/ mouse; average food consumption = 3 gm/day. 3 gm/day x .05% of diet = 150 mg bicalutamide/day ingested. 150 mg/20 gms = 7500 mg/kg).

Mortality - 3 C, 0 gp I, 0 gp II, 3 gp IV, 2 gp V, 2 gp VI
cause of death not specified.

Signs - alopecia

Ophthalmology - unremarkable .

Body weights - decreased body weight gain in gps III- VI males (7-13%) and gp IV- gp VI females (3-5%)

Food consumption - no differences in gps II and III. Significant reductions in gp IV-VI males (10%) and females (15-20%). Therefore, decreases in body weight were due to poor drug palatability, not toxicity.

Water consumption- no change in gp II, III females or males at all dose levels. Decreased 21-34% in gps IV, V, and VI females

Hematology (wks 5,14)-

Hgb, RBC- mild decreases in gps IV, V, and VI

Blood chemistry (wks 5, 14)

glucose- increased plasma glucose in all bicalutamide treated groups wk 5, in gps IV, V, VI wk 14

urea- decreased gp IV, V, VI (500, 1000, 7500)

total protein- increased in gps IV, V, VI wk 5, all gps wk 14

ALT- dose-related increases (2-3 time baseline) in gps III-VI wks 5 and 14

Alkaline phosphatase- mildly increased gps IV, V, VI wk 14

potassium - decreased all dose groups wk 5, 14 (10.3 → 7.5 mm/L)

Urinalysis - (volume and pH only) - unremarkable

Pharmacokinetics -

Samples were taken at 9 am, 1, 4, 7, 11 pm and 1, 5 am

AUC exposures continued to increase with increasing doses up to 500 mg/kg/day. Drug exposures began to plateau at doses ≥ 1000 mg/kg/day.

Data on metabolite concentrations were not provided. No sex differences in metabolism were observed (see figure below).

Dose (mg/kg)	AUC 0-24 (ug.hr/ml)	Multiple of HTD*
10	200	1X
100	1194	7X
500	1850	11X
1000	2140	13X
7500	2230	13X

* Steady state AUC exposures in men receiving 50 mg/day = 165-205 ug.hr/ml.

Organ weights

liver - dose-related increases in abs/rel weights in gps III-VI both sexes

adrenals- increased abs/rel wts in gp III-VI males

kidneys- decreased abs/rel wts all drug-treated males; gp IV-VI females.

heart- decreased abs wts all drug-treated males.

prostate - decreased abs/rel wts all treated males

testes- dose-related decrease in abs/rel wts

Histopathology - (n = 10/sex/dose)

Adrenals-

minimal to mild hypertrophy of adrenal cortical cells
0/20 C, 5/20, 12/20, 20/20, 19/20, 20/20 gps II-VI

minimal to mild vacuolization of cortical cells
1/10 C, 0/20, 1/20, 10/20, 20/20, 21/21 gps II-VI

Pituitary - minimal basophil cell hyperplasia in most mice
receiving \geq 100 mg/kg/day.

Kidney- no histopathology to correlate with decreased kidney
weights

Liver-

generalized hepatocyte hypertrophy-

0/20 C, 0/20 gp II, 16/20 gp III, 20/20 in gps IV, V, VI

hepatocyte necrosis - occasional clusters of necrotic hepatocytes
in 10% of gp II, III, IV and majority of gp V, VI mice

0/20 C, 2/20, 3/20, 2/20, 17/20, 13/20 gps II-VI

Prostate-

atrophy- 0/10 C, 5/9 gp II, 10/10 gps III-VI

Seminal vesicles-

atrophy- 0/10 C, 8/10 gp II, 10/10 gps III-VI

Testes- mild to moderate leydig cell hyperplasia at doses
 \geq 100 mg/kg/day

Ovary- hyperplasia of interstitial cells, mild in gp III,
moderate in gps IV, V, VI

0/10 C, 0/10 gp I, 8/10 gp III, 10/10 gps IV-VI

absence of normal cycling - 0/10 C, 0/10 gp II, 5/10 gp III,
10/10 gps IV-VI

vagina- keratinization of vaginal epithelium

0/10 C, 0/9 gp II, 4/10 gp III, 8/10 gp IV, 9/10 gps V, VI

Summary- Administration of bicalutamide to mice at dose levels up to 7500 mg/kg/day (5% in diet) did not produce drug-related deaths or signs. Decreased body weight gain was observed in animals dosed with concentrations \geq 100 mkd in males and \geq 500 mkd in females, secondary to reductions in food consumption due to poor palatability. The low dose of 10 mg/kg/day (AUC comparable to human therapeutic exposure) was the no toxic effect dose.

Increases in liver weights and generalized hepatocyte hypertrophy were observed at all dose levels and are probably secondary to liver enzyme induction. Increases in ALT and alkaline phosphatase were observed at doses \geq 100 mkd and hepatocyte

necrosis was observed in mice at the two highest dose levels. (1000 and 7500 mg/kg/day) Prostate and seminal vesicle atrophy were observed at all dose levels and represent the desired pharmacologic effect. Other histological changes observed in the adrenal, pituitary, testes, ovaries and vagina are secondary to drug-induced hormonal imbalances.

Conclusion -The results of this study suggests 500 mg/kg/day should be chosen as the MTD for the mouse carcinogenicity study. Exposures to parent compound plateau at \geq 1000 mg/kg and liver hepatocyte necrosis was observed at the two highest dose levels of 1000 and 7500 mg/kg/day.

3 Month Investigative Study in Mice: Dietary Administration
(TKM/766; lot # ADM 45008/89, ADM 44015/91)

CD-1 mice (n=10/sex/dose) were administered 0, 5 and 75 mg/kg/day bicalutamide in NDD diet for 90 days to examine effects on the liver. Doses chosen were the low and high doses used in the 2 year carcinogenicity study. An additional 5/sex/gp were dosed to examine BrdU incorporation and 16/sex/gp were dosed for assessment of liver enzyme activity.

Mortality/signs- no drug-related effects

Body weight/food consumption- wt gain decreased in HD males consistent with a parallel decrease in consumption secondary to poor palatability.

Liver mixed function oxidase (MFO) Activity -Changes in liver enzymes were observed (see tables A4/1 and A4/2) which suggest a drug-induced increase in 2B1 activity. Immunochemical staining revealed a centrilobular distribution in males.

Histopathology-

Centrilobular hepatocyte hypertrophy- 0/20 C, 0/20 LD, 19/20 HD

Enlarged/multinucleate hepatocytes -

0/20C, 0/20 LD, 0/10 HD F, 10/10 HD males

hepatocyte necrosis - 0/20 C, 3/20 LD, 10/20 HD

BrdU study -

hepatocyte hypertrophy - 0/10 C, 0/10 LD, 9/10 HD wk 2

0/10 C, 0/9 LD, 7/10 HD wk 5

0/9 G, 0/10 LD, 9/10 HD wk 14

multinucleate hepatocytes- 0/10 C, 5/5 HD M, 1/5 HD F wk 14

Summary and Conclusions - Centrilobular hypertrophy, proliferation of smooth endoplasmic reticulum, and liver enzyme induction were observed in high dose mice of both sexes. Panlobular hepatocyte enlargement and polyploidy were observed in HD male mice and may be related to the liver carcinoma observed in high dose male mice only.

Two Year Oncogenicity Study in Mice: Dietary Administration
(study TCM/634, lot # 56071/86 and 45008/89)

CD-1 mice received 0 (n=100/sex), 5, 15 and 75 mg/kg/day bicalutamide (n = 50 sex/dose) in diet for 104 weeks.

Mortality- there were no drug-related effects on survival
% Survival

Males - 47% C, 40% LD, 42% MD, 42% HD
Females - 50% C, 50 %LD, 48% MD, 44% HD

Clinical signs - none

Body weight- small decrease in gain observed in males
5% LD, 4 % MD, 7% HD; no drug effects in females

Food consumption - mild decreases in consumption in treated males
(body wt decrease secondary to poor palatability)

Water consumption- unremarkable

Hematology- unremarkable

Neoplastic lesions-

Liver - an increased frequency of liver tumors and deaths due to liver tumors were observed in mice treated with the high dose of 75 mkd. However, the high dose is well below the MTD and therefore, the carcinogenic potency is most probably underestimated.

malignant carcinoma - 2/100 C, 1/50 LD, 1/50 MD, 8/50 HD males
(2% C, 2% LD, 2% MD, 16% HD)

histiocytic sarcoma - 2/100 C, 0/50 LD, 3/50 MD, 4/50 HD males
(2% C, 0% LD, 6% MD, 8% HD)

deaths due to liver tumors - 4% C, 4% LD, 6% MD, 12% HD males

Cervix- histiocytic sarcoma- 0% C, 4% LD, 8% MD, 2% HD

Pituitary -

Adenomas - 6% C, 14% LD, 8% MD, 16% HD

Non-neoplastic lesions

Liver-

polyploid hepatocytes- 12% C, 6% LD, 62% MD, 96% HD

hepatocyte cytomegaly- 0% C, 2% LD, 20% MD, 50% HD males

hepatocyte hypertrophy- 0% C, 2% LD, 46% MD, 76% HD males
0% C, 60% HD females

Ovaries - dose-related decrease in cysts

33% C, 22% LD, 20 % MD, 4% HD

Prostate - atrophy 1% C, 58% LD, 76% MD, 68% HD males

Seminal vesicles - atrophy 2% C, 84% LD, 92% MD, 88% HD

Thyroid -hyperplasia

6% C, 26% HD males; 0% C, 12% HD females

Summary and Conclusions- The 2 year carcinogenicity study in the mouse was conducted utilizing dose levels of 5, 15 and 75 mg/kg/day. The high dose was not the MTD which was established as ≥ 500 mg/kg/day in the mouse dose-finding study. Extrapolation from the pharmacokinetics data of the mouse dose-finding study suggest the dose levels of 5, 15 and 75 mkd produce AUC exposures in mice $< 1, 1.5,$ and 5 times the human therapeutic exposure with the 50 mg/day dose.

Administration of bicalutamide at dose levels of 5, 15 and 75 mkd for 2 years had no effects on survival, signs, or hematology. Mild decreases in body weight (4-7%) were observed in treated males which were secondary to decreased food consumption (poor palatability).

Hepatocyte hypertrophy, cytomegaly and increased polyploid hepatocytes were observed at doses ≥ 15 mkd (1.5 times therapeutic exposure in men receiving 50 mg/day). An increased frequency of malignant hepatocellular tumors and deaths due to liver tumors were observed in high dose mice (75 mkd = 5 times therapeutic exposure). However, the high dose tested is well below the MTD and the carcinogenic potency of bicalutamide is probably underestimated

Oral Dose-Finding Study in Dogs (TAD/384, lot #ADM 43040/84)

Beagle dogs (n=2/sex/dose) received 0, 25, 75, and 150 mg/kg/day bicalutamide for 6 weeks (50% ICI 176,334: 50% lactose in hard gelatin capsules).

Mortality/signs- none

Body weight - one HD male (#38466) lost 14% of body weight

Food consumption- decreased consumption in male with wt loss.
diet supplemented wks 5 and 6

Physiologic measurements - increased heart rate (30-40 bpm) in MD, HD wk 2, all drug-treated groups wk 5

decreased P-R interval in all bicalutamide-treated gps wks 2,5

No changes in blood pressure, respiratory rate, or rectal temperature.

Hematology- unremarkable

Blood chemistry -
alkaline phosphatase - elevated in all treated gps wks 4 and 6
cholesterol- dose-related elevations in all treated groups wks 2,
4, and 6.

Urinalysis- both MD females showed 3+ hematuria at week 6

Organ weights - decreased prostate, testes, epididymal weights
increased adrenal weights

Gross pathology -
Liver -pallor or yellow discoloration
0 C, 1/4 LD, 2/4 MD, 3/4 HD

Histopathology - (2/sex/dose)
Liver - increased canalicular alkaline phosphatase activity
0/4 C, 4/4 LD, 2/4 MD, 3/4 HD
Adrenal- bilateral coarse vacuolization - 0/4 C, 4/4LD, MD, HD
Epididymes -
no spermatozoa 0/2 C, 2/2 LD, MD, HD
microcystic degeneration - 0/2 C 2/2 LD, MD, HD
Prostate- diffuse atrophy- 0/2 C, 2/2 LD, MD, HD
Stomach - fundic mucosal mineralization -
0/4 C, 1/4 LD, 2/4 MD, 2/4 HD
Testes- atrophy 0/2 C, 2/2 LD, MD, HD
diffuse bilateral leydig cell hyperplasia 0/2 C, 2/2 LD, MD, HD
Thyroid - diffuse bilateral lymphocytic thyroiditis 2/2 MD males
Urinary bladder-
cystitis - 0/4 C, 4/4 LD, 1/4 MD, 0/4 HD
subepithelial hemorrhage - 0/4 C, 1/4 LD, 1/4 MD, 0/4 HD
epithelial hyperplasia - 0/4 C, 2/4 LD, 1/4 MD, 0/4 HD

Liver enzyme induction- administration of bicalutamide produced
mild induction of cytochrome P450 and aldrin epoxide.
Ethoxyresorufin-o-deethylase activity was unchanged.

Summary and Conclusions - No mortality or signs were observed in
this study. Weight loss was observed in one HD male. Mild
increases in alkaline phosphatase and cholesterol were observed
in treated dogs. Decreases in male reproductive organ wts and
increases in adrenal wts with correlated changes in histology
were observed. Dose-limiting toxicity was not observed with the
dose levels studied.

Six Month Oral Toxicity Study with Bicalutamide in Dogs
(#TFD/404, lot 60036/84)

Beagle dogs (n= 5/sex/dose) were administered 2.5, 10 and 100
mg/kg/day bicalutamide orally (1, 15 and 150 mg tablets in
gelatin capsules) for 6 months. Additional dogs(3/sex)were

treated in the control and HD groups and were retained undosed for 4 months as a drug withdrawal group.

Mortality - MD male # 38646 and HD male #38672 (day 64).

Signs - 1 HD female displayed wt loss and inappetance concurrent with an abscess on hindfoot days 135/140. Animal completely recovered after antibiotic treatment.

Dog 38646 (MD male) was killed on day 152 because of corneal ulceration and uveitis of the left eye (unresponsive to antibiotic therapy).

Dog 38672 (HD male) displayed pyrexia, inappetance, wt loss and an infected hindfoot. Infection resolved after antibiotic treatment but dog continued to deteriorate. Lost 3 kg during wks 7-9. Killed in extremis day 64.

Soft/loose feces- all drug-treated groups

Body weights-

Males - slight (≤ 1 kg = $< 5\%$) decrease in weight in all treated groups, not dose-related.

Females - controls, LD, HD gained wt (0.5 - 1 Kg). MD females had slight mean body wt decrease due to wt loss in dog 38653.

Food consumption - reduction in consumption in HD dogs for the first 6 wks of study.

Water consumption(measured wk 24)- unremarkable

Physiologic measurements -

heart rate - increased in HD dogs days 32 and 87

males - 4/5 LD, 2/5 MD, 3/5 HD

females- 2/5 LD, 3/5 MD, 3/5 HD.

P-R interval -dose-related decrease, significant at all dose levels at all measurement times (wks 5, 13, 19, 25)

No changes in blood pressure, rectal temperature.

Hematology -

WBC- dose-related decreases significant MD, HD dogs

Neutrophils - marked neutrophil depletion 1/10 MD, 5/13 HD dogs ((5/6 affected were males)

reticulocyte counts - increased in MD, HD males

Blood chemistry - (wks 5, 13, 25)

cholesterol - increased in MD, HD wks 5, 13 25

creatinine - mildly increased HD wks 13, 25; all treated groups
wk 25

urea- increased in MD, HD wks 5, 13, 25; LD, wk 25 only

albumin - decreased in HD animals wks 5, 13, 25
alkaline phosphatase - increased HD wks 5, 13, 25
MD wks 13, 25
ALT- mild increase in HD, weeks 13, 25, MD wk 25
sodium - decreased HD all timepoints
calcium- mild decrease HD wks 5, 13, 25; MD wk 26 only

Increases in creatinine, urea, alkaline phosphatase and ALT were progressive (observed at lower doses with increased duration of dosing).

Urinalysis- (pH, specific gravity)- unremarkable

Pharmacokinetics- Plasma half-life was 8 days. Blood samples were obtained immediately prior to dosing (i.e., 24 hours post-dose) during study weeks 1, 2, 3, 4, 8, 12, 16, 22 and 26. Steady state was reached after 12 weeks of dosing. Significant accumulation occurred with multiple dosing. There were no apparent sex differences in drug levels.

<u>Dose (mg/kg)</u>	<u>Cp (ug/ml)</u>		<u>AUC 0-∞</u> (ug.hr/ml)	<u>Multiple of HTD</u>
	Day 1	Wk 26		
2.5	2.07	24.6	519	3 X
10	6.1	53.4	1802	10 X
100	21.4	78.2	9549	50 X

Organ weights-

Adrenals - dose-related increase in abs/rel wts all dose levels
Liver- increased abs/rel wts HD dogs
Testes- decreased wt HD male dogs
Epididymes/prostate - dose-related decrease in abs/rel wts ,
significant at all dose levels
Heart- increased abs/rel wts all treated groups

Increased liver, heart, adrenal weights were not reversible after 4 month drug-free withdrawal period. The decrease in prostate and epididymal weights was reversible.

Histopathology-

Adrenal -

cortical vacuolization- increased incidence with dose-related severity, mild in LD to moderate/severe in HD
0/10 C, 4/10 LD, 8/10 MD, 9/10 HD
Not reversible, still present in 6/6 HD withdrawal dogs
zona fasciculata hypertrophy - 0/10 C, 4/10 LD, 6/10 MD, 6/10 HD

Bone and Marrow- moderate to severe mature neutrophil depletion
0/5 C, 0/5 LD, 1/5 MD, 1/5 HD males; 1/3 HD withdrawal

Cervix- diffuse keratinization 0/5 C, 1/5 LD, 2/5 MD, 1/5 HD
1/3 HD withdrawal females
Epididymes - no sperm 1/5 C, 1/5 LD, 4/5 MD, 5/5 HD males
ductal atrophy - 1/5 C, 5/5 LD, 5/5 MD, 5/5 HD,
1/3 HD withdrawal
epithelial vacuolization- 2/5 C, 5/5 LD, 4/5 MD, 5/5 HD
2/3 HD withdrawal
Heart- 1 HD withdrawal male with atrial myocardial necrosis,
fibrosis and myocarditis and diffuse pericarditis
Mammary glands - atrophy 0/5 C, 2/5 LD, 2/5 MD, 1/5 HD females
2/5 HD withdrawal
Prostate - moderate to severe glandular atrophy
0/5 C, 4/5 LD, 4/5 MD, 5/5 HD males, 1/3 withdrawal
interstitial hyperplasia- 1/5 C, 3/5 LD, 5/5 MD, 5/5 HD, 1/3 W
Spleen - extramedullary hematopoiesis
1/10 C, 4/10 LD, 8/10 MD, 8/10 HD
Testes - moderate spermatogenic arrest
0/5 C, 1/5 LD, 2/5 MD, 5/5 HD
leydig cell hyperplasia - 1/5 C, 4/5 LD, 5/5 MD, 5/5 HD
seminiferous tubule atrophy - 1/5 C, 2/5 LD, 2/5 MD, 5/5 HD
Uterus - glandular reduction - 0/5 C, 1/5 LD, 3/5 MD, 5/5 HD
Vagina - diffuse keratinization- 0/5 C, 1/5 LD, 2/5 MD, 1/5 HD

Summary

Dogs were administered 2.5, 10 and 100 mg/kg/day bicalutamide (3, 10, and 50 times human AUC exposures) for 6 months. Two male dogs (1 MD, 1 HD) were killed prematurely due to poor condition. The HD male displayed pyrexia, weight loss and infection and was killed on day 64. The MD dog was killed due to corneal ulceration and uveitis. All drug-treated dogs had loose feces and increased heart rates throughout the study.

Bicalutamide produced dose-related decreases in white blood cells and marked neutrophil depletion in high dose males. Bicalutamide also produced mild increases in cholesterol, creatinine, urea, alkaline phosphatase and alanine aminotransferase in mid and high dose dogs.

Prostate and epididymal atrophy and testicular leydig cell hyperplasia were observed in all drug-treated male dogs. Seminiferous tubule atrophy and spermatogenic arrest were observed in high dose males. Uterine and mammary gland atrophy were also observed in bicalutamide-treated female dogs. Dose-related adrenal hypertrophy and vacuolization were observed, as was seen in rats.

Conclusions- Bicalutamide at the low dose of 2.5 mg/kg/day (3 times human exposure) was well tolerated by dogs treated for 6 months. Administration of the higher doses of 10 and 100 mg/kg/day produced hematologic, blood chemistry and histologic changes consistent with its anti-androgenic activity or hormonal imbalance which occurred as a consequence of exaggerated pharmacologic effects of high dose levels.

12 Month Oral Toxicity Study in Dogs (# TFD/394, lot # ADM 56055/86)

Alderly Park beagle dogs were administered 1, 2.5 and 50 mg/kg/day bicalutamide for one year (tablets in gelatin capsules). An additional 3/sex were treated in the control and high dose groups and kept undosed for a 6 month drug-free withdrawal period.

Mortality/ Signs - none

Body weight - decreased weight gain in HD dogs. Control and LD dogs gained 1-1.2 kg; MD, HD dogs had no weight gain.
Food consumption- unremarkable.

ECG- PR-interval was decreased in dogs of both sexes during all examination weeks (5, 14, 26, 39, 51). 7-16% in MD, 16-22% in HD dogs. Heart rate was also increased in HD dogs. Changes in PR interval and heart rate were reversible upon drug withdrawal.

Hematology - unremarkable.

Blood chemistry - (weeks 26, 51)
glucose - increased in HD males, week 51
alkaline phosphatase- increased in HD males and females week 51
ALT - 2-fold increase in HD females weeks 26, 51
cholesterol - increased in HD males wks 26, 51

Pharmacokinetics- plasma drug concentrations were measured 24 hours after dosing. Data are presented in tables 9 and 10 taken directly from the submission (vol 1.42, p 60). Bicalutamide was detected in the plasma of 14/16 control animals during the main test and 5/6 controls during the withdrawal period. The sponsor provides no explanation but states levels were 1/30 those seen with the lowest dose.

Significant accumulation (10--fold in LD, MD; 4 fold in HD) was observed with multiple dosing. Steady state was achieved by the third month of dosing.

Organ weights -

Prostate- decreased absolute wts (70%) at all dose levels
Epididymes- decreased abs wts (30%) in HD males
Adrenal- increased abs wts in MD, HD both sexes

Table 9 : 176,34 : Twelve month oral toxicity study in dogs.
Study number TFD/394. Group mean (\pm SE) pre-dose plasma
concentrations (μ g/ml).

Time into study	Dose 176,334		
	1 mg/kg/day	2.5 mg/kg/day	50 mg/kg/day
1 day	0.94 \pm 0.05	2.60 \pm 0.14	15.38 \pm 1.31
1 month	8.88 \pm 0.42	19.47 \pm 0.90	61.69 \pm 2.38
3 months	11.46 \pm 0.48	21.91 \pm 1.24	69.74 \pm 2.23
6 months	12.12 \pm 0.55	24.70 \pm 1.38	68.48 \pm 1.64
9 months	12.17 \pm 0.47	26.25 \pm 1.13	71.30 \pm 1.93
12 months	11.25 \pm 0.57	22.81 \pm 1.30	63.15 \pm 2.24

Table 10 : 176,34 : Twelve month oral toxicity study in dogs.
Study number TFD/394. Mean (\pm SE) plasma concentrations
(μ g/ml) for Group IV (50 mg/kg/day) during withdrawal.

Time after final dose	Mean plasma concentrations
1 day	68.95 \pm 2.60
8 days	44.37 \pm 3.88
15 days	32.24 \pm 3.45
4 weeks	13.63 \pm 2.28
6 weeks	5.39 \pm 1.30
8 weeks	1.88 \pm 0.65
10 weeks	0.48 \pm 0.20
12 weeks	0.097 \pm 0.04
14 weeks	0.033 \pm 0.01

060

2.5 mg/kg = 3x human therapeutic exposure (AUC)
 50 mg/kg \approx 20x HTE

Heart- increased heart wts in MD F, HD males and females
Liver-increased abs/rel wts HD both sexes
ovary- increased ovarian wts MD, HD females

The changes in prostate, epididymal and liver weights were reversible.

The increase in adrenal, heart, and ovarian weights were observed in HD withdrawal dogs.

Histopathology-

Adrenal- hypertrophy of zona fasciculata/reticularis

0 C, 0 LD, 1/10 MD, 8/10 HD

vacuolization of zona fasciculata/reticularis with dose-related severity, minimal to mild in controls and LD, moderate in MD, HD
Not reversible in HD withdrawal dogs

6/10 C, 10/10 LD, MD, HD

Epididymes -

bilateral stromal hyperplasia 0 C, 1/5 LD, 2/5 MD, 3/5 HD
exfoliated seminiferous epithelial cells 0/5 C, LD, MD, 2/5 HD
ductal atrophy- 1/5C, 3/5 LD, 5/5 MD, 5/5 HD
sperm reduction - 1/5 C, 3/5 LD, 4/5 MD, 5/5 HD

Mammary glands -

reduced acinar differentiation - 0/5 C, 0/5 LD, 4/5 MD, 4/5 HD **F**
Not reversible still present in 3/3 HD withdrawal dogs

Prostate - severe atrophy 0/5 C, 5/5 LD, MD, HD

Testes- leydig cell hyperplasia 0/5 C, 4/5 LD, 5/5 MD, 5/5 HD
maturation arrest 0/5 C, 1/5 LD, 0/5 MD, 4/5 HD
seminiferous tubule vacuolization - 0/5C, 1/5LD, 2/5MD, 3/5 HD
exfoliated seminiferous tubule epithelium-
0/5 C, 1/5 LD, 2/5 MD, 5/5 HD
tubular giant cells - 0/5C, 0/5 LD, 1/5 MD, 4/5 HD

Prostate, testicular and epididymal changes were reversible upon drug withdrawal.

Summary

Administration of bicalutamide at doses up to 50 mg/kg/day to beagle dogs for one year produced no drug-related mortality or signs. Mild decreases in body weight, increases in heart rate, and increases in liver enzymes (alkaline phosphatase, ALT) and cholesterol were observed in HD dogs. Drug-related adrenal hypertrophy/vacuolization, epididymal and prostatic atrophy, and testicular leydig cell hyperplasia were observed in dogs at all dose levels (≥ 1 mkd). Doses of bicalutamide ≥ 2.5 mg/kg (3 times human exposure) reduced mammary gland differentiation in females, and produced seminiferous tubule exfoliation and

vacuolization and sperm reduction in male dogs. Prostate, testicular and epididymal changes were reversible upon drug withdrawal. Adrenal and mammary gland changes were not reversible.

Conclusion

Administration of bicalutamide to dogs at doses up to 50 mg/kg/day for one year were well-tolerated. The target organs of toxicity were the adrenal, male reproductive system and mammary glands. As in the rat, the toxicity observed can be attributed to expected antiandrogenic effects or hormonal imbalance secondary to high doses of anti-androgen.

REPRODUCTIVE TOXICITY

Fertility and Reproductive Performance in Male Rats (TGR/1291, lot # ADM 56041/85)

Male Wistar rats (n = 25/dose) were administered 0, 0.25, 5 or 250 mg/kg/day bicalutamide (0, 0.3, 3 times human exposure with 50 mg/day) by gavage for 11 weeks prior to mating. Males were paired with untreated female rats on the last day of dosing. Males were mated with additional untreated females 7 and 16 weeks after dosing to assess reversibility of effects.

A slight reduction in body weight gain was observed in HD male rats.

Time until mating (precoital interval) and time to successful mating were increased in MD and HD males mated immediately after dosing. These impairments were not observed during the matings 7 and 16 weeks after dosing. Although time until mating was increased, fertility (pregnancy rate) was not affected by drug treatment.

Treatment of males with bicalutamide had no effect on numbers of corpora lutea, implants or live fetuses in any of the 3 matings.

Conclusion - Administration of bicalutamide increased the time until mating (precoital interval) in treated males but had no other effects on mating or fertility.

Reproductive Study in Female Rats (TGR/1480, lot ADM 60036/84)

Female Wistar rats (n = 6/dose) were administered 0, 10 or 250 mg/kg/day bicalutamide for 2 weeks prior to mating, and throughout mating, pregnancy and lactation. Treated females were mated with untreated males.

Body weight- no drug effects on maternal wts prior to or during pregnancy or during lactation.

Treatment with bicalutamide had no effects on mating, fertility, gestation length, litter survival, sex ratios or external genitalia of F1 females. All male offspring of bicalutamide treated dams were externally feminized with decreased anogenital distance, hypospadias and prominent nipple development. Body weights of F1 males were significantly less than controls (\downarrow 3.6% LD, 7.5% HD). Findings are summarized in Table 16 taken directly from the submission (vol 1.47). Treatment of pregnant dams throughout pregnancy and lactation had no effects on developmental landmarks of pups (ear unfolding, crawling, hair growth, eye opening, startle response).

Conclusions- Male offspring of bicalutamide-treated dams were feminized and impotent due to hypospadias. A reproductive study involving interbreeding of the F1 generation is impractical because of the feminizing effects of doses \geq 10 mg/kg/day on male fetuses.

Teratology Study with Bicalutamide in Rats (TTR 1290, lot # ADM 60036/84)

Pregnant female Wistar rats (n = 20/dose) were administered doses of 0, 1, 10, 50 and 250 mg/kg/day bicalutamide by gavage on days 6-15 of pregnancy. Dams were killed on day 20 of pregnancy. Bicalutamide at doses of 10, 50 and 250 mg/kg/day produced plasma drug concentrations (Cp, AUC) in rats 1, 2 and 3 times those achieved in men receiving the 50 mg/day therapeutic dose.

Mortality/signs - none

No effects on number of corpora lutea, implants or preimplantation loss.

No effects on litter size, post-implantation loss, mean fetal weights or sex ratios.

Anogenital distance of male fetuses was significantly reduced at dose levels \geq 10 mkg. No effects on anogenital distance were observed in female pups. No increases in soft tissue or skeletal anomalies were observed in pups of bicalutamide-treated dams.

Pharmacokinetics-

Dose (mg/kg)	Maternal Cp (ug/ml)	Embryo concentration (ug/g)
250	16	7.5

Maternal exposures with highest dose = 2 times human therapeutic concentrations (C_{ss} = 8.6 ug/ml in men receiving 50 mg/day).

all the males in Groups II and III showed abnormal positioning of the scrotum, usually involving unilateral displacement anteriorly and into the midline. This finding was considered to be caused by unilateral cryptorchidism. Scrotal masses developed as the males became mature and occurred more frequently at the higher dose level (see section 3.2.11). Urine staining also occurred more frequently in Group III. In all males in Group III, opening of the pseudovagina was observed between 42 and 46 days of age. This last phenomenon was not observed in any male at the low dose of 176,334. A photographic record of the external appearance of selected males at various stages of development was made (see Appendix 28; Figures A28/3 to A28/6).

There were no other observations in males of significance with respect to dosing of the dams with 176,334.

Table 16 : 176,334 : Reproductive study in female rats - oral administration. Study number (TGR/1480). F₁ generation:
Male animal observations.

Observation	Number of animals in:		
	Group I	Group II	Group III
Hypospadias	0	20	20
Small urogenital papilla	0	0	4
Urine staining	0	5	18
Abnormal scrotum*	0	20	19
Vaginal opening	0	0	20

* Abnormal positioning and/or unilateral or bilateral swelling and/or hardness.

Summary and Conclusions -

Administration of bicalutamide to pregnant rats at doses up to 250 mg/kg/day (2 times therapeutic exposure) produced no unexpected internal or skeletal anomalies in fetuses.

Feminization of male fetuses was observed at doses \geq 10 mkd as decreased anogenital distance. In a separate study (TGR/1480) in which pups were allowed to develop through weaning, hypospadias, nipple development and development of female external genitalia were observed in male fetuses of dams treated with 10 and 250 mkd.

Teratology Study with Bicalutamide in Rabbits (TTB/1293, lot ADM 60036/84)

Pregnant Dutch belted rabbits were administered 0, 10, 50 and 200 mg/kg/day bicalutamide orally by gavage from days 6-18 of pregnancy. Dams were killed on day 28 of pregnancy for standard teratologic examination.

Mortality - 1C, 1 MD, 5 HD

Signs - decreased appetite/ body weight loss in 5 HD rabbits that died. Dose-related decreased defecation in treated rabbits.

Body weight - no significant differences, body weight gain was increased in MD, HD rabbits (wt gain 124-127 g in C,LD; 175-183 g in MD, HD)

No drug-related effects on pregnancy loss, number of implants, number of corpora lutea, pre- or post-implantation loss or live fetuses per litter. No effects on fetal weights, placental weights or sex ratios.

Pharmacokinetics- 6 animals/gp were dosed with 0 or 200 mg/kg/day bicalutamide for PK analysis. Animals were killed 2 hours after the last dose on day 18. Maternal and fetal plasma concentrations of bicalutamide are 1/3 concentrations in men receiving the 50 mg/day therapeutic dose.

Dose(mg/kg)	Maternal Cp(ug/ml)	Embryo concentration(ug/g)
200	2.7	2.8

Major anomalies - 1 LD fetus had microphthalmia

Soft tissue anomalies - dark red (bleeding) ovary in 1/46 HD female fetuses-this anomaly never previously observed

Skeletal anomalies - no increase in the fetuses of bicalutamide-treated fetuses.

Necropsy observations (dams) -
Liver- mottled 0 C, 3 LD, 2 MD, 3 HD
Heart- ventricles/atrium pale -1 LD
 pericardium inflamed 1 LD
Lung- numerous red spots (bleeding) 0 C, 2 LD, 1 MD, 3 HD

Summary and Conclusions- Increased mortality was observed in pregnant rabbits receiving 200 mg/kg/day bicalutamide suggesting the high dose was greater than the MTD. This dose level was also the maximum dose due to drug solubility/dosing volume considerations. However, the high dose of 200 mg/kg/day bicalutamide produced plasma drug concentrations in rabbits (dams and fetuses) only 1/3 drug concentrations in men receiving the 50 mg/day therapeutic dose. No evidence of teratogenic effects of bicalutamide were observed in this study. However, development of external genitalia in male rabbit fetuses occurs on gestational days 21-25, after the 6-18 day dosing period. Therefore, feminizing effects of bicalutamide in male rabbit fetuses can not be assessed in this study.

GENOTOXICITY

Gene Mutation/Conversion Test in Yeast (TKN 143, lot # ADM 60022/84)

Bicalutamide (50, 100, 150, 250 and 500 ug/ml) ± S9 was tested for its potential to produce gene mutation and/or conversion in *Saccharomyces cerevisiae* strain D7.

Conclusion- Bicalutamide did not cause gene mutation at the isoleucine locus or gene conversion at the tryptophan locus of *S. cerevisiae*.

Ames Tests (TMV/129, TMV/130, lot # 60022/84)

Salmonella typhimurium strains TA 1535, 1537, 1538, 98 and 100 were incubated with bicalutamide at concentrations of 50, 200, 500, 1000 and 2000 ug/plate ± S9. The 2000 ug/plate concentration precipitated and produced cytotoxicity in plates without S9 mix. No increases in revertant colonies was observed in any strain in the presence of bicalutamide ± S9.

Conclusion - Bicalutamide was not mutagenic in the Ames Test.

Bacterial Mutagenesis in E.coli (TMV/245, lot #60036/84)

E.coli strains WP2 and WP2uvrA pKM101 were incubated with bicalutamide at doses of 125, 250, 500, 1000 and 2000 ug/plate ± S9. This assay tests for base pair substitutions/point mutations. Bicalutamide at 2000 ug/plate was cytotoxic in both strains. No increase in revertant colonies were observed in either strain incubated with bicalutamide.

Conclusion - Bicalutamide was not mutagenic in *E.coli*.

Mammalian Cell Mutation Assay in Chinese Hamster Ovary Cells
/HPRT Locus Assay (TMV/246, lot #ADM 56041/85)

This study was conducted by

Chinese hamster ovary cells were incubated with bicalutamide (10-125 ug/ml ± S9) to test for forward mutations at the hypoxanthine-guanine phosphoribosyl transferase locus. No increases in mutant frequency were observed in bicalutamide treated cells.

Conclusion- 176,334 was not mutagenic in the CHO/HPRT assay.

In vitro Cytogenetic Study in Human Lymphocytes (TYX122, lot #56041/85)

Human lymphocytes were incubated with bicalutamide (7.5, 30, 75 ug/ml) ± S9 mix. Doses ≥ 150 ug/ml were cytotoxic. Metaphase chromosomes were analyzed after 24 hours of exposure at the first post-treatment cell division.

The mitotic index in cultures exposed to ≥ 30 ug/ml bicalutamide without S9 was reduced 37-75%. No increase in chromosome aberrations were observed in cultured human lymphocytes incubated with bicalutamide.

Conclusion - Bicalutamide was not mutagenic in this in vitro cytogenetic assay.

Mouse Micronucleus Test (TOM 458, lot # ADM 60022/84)

CCB F1 mice (n = 15/sex) were administered bicalutamide at a dose of 2000 mg/kg, ip. Bone marrow smears were prepared 24, 48 and 72 hours after dosing and polychromatic erythrocytes (PCE) were analyzed for the incidence of micronuclei. Bicalutamide did not increase the incidence of micronuclei in PCEs.

Conclusion: Bicalutamide was not mutagenic in the Mouse Micronucleus test.

Cytogenetic Study with Bicalutamide in the Rat (TYR/1284, lot ADM 60022/84)

Wistar rats (n = 10/sex) were administered vehicle or 2000 mg/kg, po bicalutamide and bone marrow samples were obtained 12 and 24 hours after dosing. Bicalutamide did not affect mitotic index or increase chromosomal aberrations in rat bone marrow cells.

Conclusion- Bicalutamide (200 mg/kg) did not produce cytotoxicity or chromosomal aberrations in rat bone marrow cells.

SPECIAL TOXICITY

Contact Sensitization Study in the Guinea Pig (TDG/86, lot # 6006/84)

Guinea pigs (n = 10M/gp) were administered 0.1% 1-chloro-2,4-dinitrobenzene (DNCB, positive control), bicalutamide at concentrations of 5 or 10 mg/0.1 ml (5 and 10 %), or vehicle (0.5 % polysorbate 80) intradermally on day 1 (induction procedure). On day 8 DNCB, 25% bicalutamide or vehicle were administered topically to shaved skin in the area of the injections. Contact sensitization was observed in all DNCB positive controls but not in vehicle or bicalutamide treated guinea pigs.

Conclusion -Bicalutamide did not cause contact sensitization in guinea pigs, the best model for human cutaneous sensitization.

Passive Cutaneous Anaphylaxis in Guinea Pigs (TDG 179)

Bicalutamide (0.625, 1.25 and 2.5 mg/kg) did not produce passive cutaneous responses in guinea pigs (n = 16/dose).

Passive Cutaneous Anaphylaxis in the Mouse (TDM/798)

Bicalutamide (2.5 mg/kg) did not produce passive cutaneous anaphylactic responses in mice.

Dermal Tolerance in Rabbits (TIB/267)

Rabbits (n = 3/sex) received 10 applications of 500 mg bicalutamide in saline(days 1-5 and 8-12). On each day drug was applied to one abraded and one intact skin site. Bicalutamide application produced erythema of the skin in all rabbits, however in 2 rabbits (1/sex) this response was only observed on 1 day out of 10. In general, abraded skin was more sensitive to bicalutamide. Bicalutamide had a mean irritation score of 0.17 (very low). Edema was never observed at the application sites.

Conclusion - Bicalutamide produced very slight irritation of rabbit skin. Skin irritation in humans would not be expected.

Ocular Tolerance Study in Rabbits (TIB/268)

Bicalutamide (10 mg) was applied to the conjunctival sac of rabbits (n = 3/sex). Eyes were examined for an irritation reaction immediately after, 1-2 hours and 1, 2, 3, 4 and 7 days after application of drug. No ocular changes were observed in any animal at any time point.

Conclusion- Application of 10 mg of bicalutamide into the conjunctival sac of rabbits was not associated with pain or irritation.

LABELLING REVISIONS

1. page 4, paragraph 2, line 4

The sentence beginning " The male offspring of rats..." should be changed as follows-

The male offspring of rats receiving doses of 10 mg/kg/day (plasma drug concentrations in rats equal to drug concentrations in men receiving the 50 mg/day dose) and above, ...

The reference to "no effects in rabbits" should be omitted since rabbits were not dosed during the critical period for development of male external genitalia.

2. pg 4, paragraph 2, line 8

The sentence should be revise to read as follows:

No other teratogenic effects were observed in rabbits receiving doses up to 200 mg/kg/day (plasma drug concentrations in rabbits 1/3 human therapeutic concentrations with 50 mg/day) or rats receiving doses up to 250 mg/kg/day (2 times human therapeutic concentrations).

3. Carcinogenesis, Mutagenesis, Impairment of Fertility

page 6 - no changes

page 7 -

paragraph 1- In male rats dosed with 250 mg/kg/day (3 times human therapeutic concentrations), the precoital ...

paragraph 2 - No effects on female rats dosed at 10, 50 and 250 mg/kg/day (1, 2, and 3 times human therapeutic concentrations) or their female offspring were observed. Administration of bicalutamide to pregnant females resulted in feminization of the male offspring leading to hypospadias at all dose levels. Affected offspring were also impotent.

SUMMARY AND EVALUATION

Casodex is a nonsteroidal anti-androgen that competitively binds with cytosolic androgen receptors in target tissues. It is a racemate with anti-androgenic activity exhibited almost entirely by the R-enantiomer. Casodex is unique among the anti-androgens in its ability to inhibit growth of androgen-sensitive tumors in vitro and in vivo.

Casodex had no hormonal, CNS, renal, respiratory, anti-inflammatory, analgesic, or immunosuppressant effects in general pharmacology screens. Casodex decreases P-R interval and increases heart rate in dogs at doses ≥ 2.5 mg/kg/day (NOEL = 1 mg/kg/day). No changes in blood pressure were observed in bicalutamide-treated dogs.

Casodex is well absorbed after oral dosing but saturation of absorption is observed in rats and dogs. The saturation of absorption leads to plateauing of plasma drug levels with the high doses utilized in the toxicology studies in rats and mice, but not in dogs. A comparison of single dose pharmacokinetics of Casodex in the species studied is provided below. Protein binding of Casodex is extensive (95-95%) and comparable in all species.

<u>Species</u>	<u>Dose</u> (mg/kg)	<u>C_{max}</u> (ug/ml)	<u>T_{1/2}</u>	<u>AUC</u> (ug.hr/ml)	<u>Excretion</u>	
					Feces	Urine
Mouse	8			200	64%	25%
Rat	25	11	17 hrs	250	62%	22%
Dog	10	5.8	5.7 days	1802	69%	
Man	1	0.85	6.3days	216	42%	36%

Casodex is widely distributed in rats. Drug concentrations in several tissues exceed blood drug levels (6-fold higher in liver, 3-fold higher in GI tract, kidney, 2-fold higher in lungs). Casodex is extensively metabolized prior to excretion in bile and urine. Glucuronide conjugates of bicalutamide and hydroxylated bicalutamide are major metabolites in the bile of rats and dogs. The polar acid and amino-sulphate metabolites are the major urinary metabolites (see page 10A) in animals.

Administration of Casodex to rats consistently produced the following drug-related changes :

1. **Changes reflecting the desired anti-androgenic effects,** namely, prostate, seminal vesicle, testicular atrophy and pituitary castration cells in male rats at all dose levels (≥ 5 mg/kg/day).

2. **Changes secondary to drug-induced hormonal imbalance**, such as
 - a. increased adrenal weights and adrenal cortical hypertrophy and vacuolization
 - b. testicular leydig cell hyperplasia secondary to inhibition of testosterone/DHT feedback at the pituitary progressing to adenomas in rats treated for ≥ 1 year.
 - c. ovarian granulosa-thecal cell hyperplasia
 - d. uterine adenocarcinoma
3. **Changes secondary to liver enzyme induction**
 - a. hepatocyte basophilia and hypertrophy
 - b. thyroid follicular epithelial hyperplasia progressing to adenomas in the 2 year rat carcinogenicity study.
4. Mild decreases in hemoglobin and increases in total protein/albumin were observed at doses ≥ 75 mg/kg/day .

Administration of Casodex to mice produced effects almost identical to those observed in rats. Decreased hemoglobin and increased total protein were observed at doses ≥ 500 mg/kg/day (AUC exposures 11 times therapeutic exposures). Increases in liver weights and hepatocyte hyperplasia, hypertrophy and polyploidy were observed at ≥ 75 mg/kg/day (5 times human exposures), increases in ALT and alkaline phosphatase were observed at ≥ 500 mkd, and hepatocyte necrosis was observed at doses ≥ 1000 mkd. Increased adrenal weights and adrenal cortical hypertrophy and vacuolization were observed with doses ≥ 500 mkd. Prostatic and seminal vesicle atrophy were observed at all dose levels (≥ 5 mkd) and testicular leydig cell hyperplasia was observed at doses ≥ 100 mkd. An increased frequency of malignant hepatocellular tumors and deaths due to liver tumors were observed in male mice receiving 75 mg/kg/day in the 2 year carcinogenicity study.

Administration of Casodex (≥ 2.5 mkd) to beagle dogs produced drug-related effects similar to those noted in rodents, namely prostate/testicular atrophy, leydig cell hyperplasia, adrenal cortical hypertrophy and vacuolization, and increased liver weights and enzymes (alkaline phosphatase, ALT). Drug-related changes not previously observed in rodents included increased heart rate, decreased white blood cells and marked neutrophil depletion, and increased cholesterol levels. Some dogs dosed with 100 mg/kg/day for 6 months (50 times therapeutic AUC exposures with the 50mg/day dose) displayed inappetance, weight loss, and infections probably secondary to WBC, neutrophil depletion (1 HD male was killed in extremis). No drug-related signs or mortality were observed in dogs treated with 50 mg/kg/day (20 times human exposure) for 1 year.

Administration of bicalutamide (≥ 5 mkd) to male rats for 11 weeks prior to mating increased the time until successful mating but had no other effects on fertility. Administration of

bicalutamide (≥ 10 mkd) to pregnant rats feminized the male fetuses producing decreased anogenital distance, hypospadias, abnormal scrotums and nipple development in male offspring of all treated dams. Male fetuses of dams receiving 250 mkd (2 times human exposure) also displayed vaginal openings. Casodex produced no other teratogenic effects in rats. Administration of bicalutamide (10, 50, 200 mkd) to pregnant rabbits produced no teratogenic effects in rabbit fetuses. However, Casodex was not administered during the period of development of male external genitalia in rabbit fetuses and, therefore, feminizing effects in male rabbits were not assessed.

Casodex was not genotoxic in a battery of in vitro and in vivo mutagenicity assays. Bicalutamide (5, 15, 75 mkd = 0.5, 1, 2 times human AUC exposures) was administered to Alpk Wistar rats for 2 years to assess carcinogenic potential. The high dose utilized in the study was not the maximum tolerated dose. Bicalutamide increased the incidence of thyroid follicular cell adenomas in rats of both sexes, testicular leydig cell adenomas in males and uterine adenocarcinoma in female rats. These tumors most probably result from drug-induced hormonal imbalances and not direct carcinogenic effects. Testicular benign leydig cell adenomas have been observed in the carcinogenicity studies with all anti-androgens (flutamide and nilutamide) and 5 α -reductase inhibitors (finasteride and epristeride). These compounds inhibit testosterone/DHT feedback at the pituitary and/or hypothalamus resulting in increased LH secretion and consequent leydig cell hyperplasia. A similar mechanism would be expected with bicalutamide and may also be involved in the induction of uterine tumors.

Bicalutamide (5, 15, 75 mkd = 0.5, 1.5, and 5 times human AUC exposure) was administered to CD-1 mice for 2 years to assess carcinogenic potential. The high dose utilized in this study was not the maximum-tolerated dose in mice. As was observed in rats, bicalutamide treatment increased the incidence of thyroid follicular adenomas in mice of both sexes (see data below taken from statistical review).

<u>Male</u> <u>Organ/Tumor</u>	<u>Tumor rate</u>				<u>P-values</u>	
	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>	<u>Trend</u>	<u>Pairwise</u>
Liver/ Hepatocellular adenoma	3	0	0	4	.0260	.1307 (C,H)
Liver/ Hepatocellular carcinoma	2	1	1	8	.0002	.0023 (C,H)
Liver/ Histiocytic sarcoma	2	0	3	4	.0257	.0926 (C,H)
Thyroid gland/ Follicular adenoma	8	0	0	7	.0133	.1475 (C,H)
<u>Female</u>						
Pituitary gland/Adenoma	6	7	4	8	.0452	.0392 (C,H)
Thyroid gland/ Follicular adenoma	0	1	1	2	.0450	.0937 (C,H)

The sponsor suggests that the thyroid hyperplasia/adenomas observed in rats and mice are secondary to drug-related liver enzyme induction and a consequent increase in thyroid hormone metabolism by the liver. The sponsor has demonstrated liver enzyme induction in bicalutamide-treated rats and mice.

Bicalutamide (75 mkd) administration to mice for 2 years significantly increased the incidence of malignant hepatocellular carcinoma in high dose male mice. Hepatocyte cytomegaly and polyploidy were also observed in mice at doses \geq 15 mkd. The carcinogenic potency of Casodex in mice was probably underestimated since the study was not performed at the MTD.

The carcinogenicity study data are adequate to permit approval of NDA 20-498. However, the studies were conducted utilizing high dose levels which are not the maximum tolerated doses and are low multiples of human exposure with the 50 mg/day dose. I am concerned about the adequacy of the carcinogenicity studies to support other indications and dose levels. Zeneca is currently conducting Phase III studies with 150 mg/day for treatment of earlier stages of prostate cancer and benign prostatic hyperplasia (BPH). In addition, hepatocyte polyploidy was observed in rats treated with high doses of Casodex. Casodex may also produce liver tumors in rats if the MTD is utilized.

The carcinogenicity data for Casodex will be presented to the Pharmacology/Toxicology Carcinogenicity Assessment Committee to obtain their recommendation regarding the acceptability of the studies for other indications.

Table 15 : 176,334 : Two year oncogenicity study in rats : dietary administration.
Study number TCR/1296. Overall incidence of tumours.

GROUP	TUMOUR TABLE											
	MALES						FEMALES					
	I	II	III	IV	I	II	III	IV	I	II	III	IV
mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day
NUMBER OF ANIMALS:	102	51	51	51	104	52	52	52	52	52	52	52
NO. OF ANIMALS WITH TUMOURS	71	37	44	50	100	48	48	47	47	48	47	47
NO. OF ANIMALS WITH SINGLE TUMOURS	36	12	17	13	28	25	20	12	12	20	12	12
NO. OF ANIMALS WITH MULTIPLE TUMOURS	35	25	27	37	72	23	28	35	35	28	35	35
NO. OF ANIMALS WITH BENIGN TUMOURS	67	33	44	50	98	47	48	44	44	47	44	44
NO. OF ANIMALS WITH MALIGNANT TUMOURS	16	9	7	8	23	5	5	12	12	5	12	12
NO. OF ANIMALS WITH METASTASISING TUMOURS												
TOTAL NUMBER OF TUMOURS	126	84	92	136	215	87	95	100	100	95	100	100
TOTAL NUMBER OF BENIGN TUMOURS	109	75	85	127	191	80	90	88	88	90	88	88
TOTAL NUMBER OF MALIGNANT TUMOURS	17	9	7	9	24	7	5	12	12	5	12	12
TOTAL NUMBER OF METASTASISING TUMOURS												

Benign - 1%
Malignant - 17%
25% 29%
18% 24%
Continued 2.7%
2.4%

% of animals with benign tumors in males, no change in frequency of malignant tumors
% of animals with multiple tumors

Table 15 (contd) : 176,334 : Two year oncogenicity study in rats : dietary administration.
 Study number TCR/1296. Overall incidence of tumours.

		TUMOUR TABLE							
		MALES				FEMALES			
GROUP		I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
% ANIMALS WITH TUMOURS		70	73	86	98	96	92	92	90
% ANIMALS WITH SINGLE TUMOUR		35	24	33	25	27	48	38	23
% ANIMALS WITH MULTIPLE TUMOURS	✓	34	49	53	73	69	44	54	67
% ANIMALS WITH BENIGN TUMOURS		66	65	86	98	94	90	92	85
% ANIMALS WITH MALIGNANT TUMOURS		16	18	14	16	22	10	10	23
% ANIMALS WITH METASTASISING TUMOURS									

Table 16 : 176,334 : Two year oncogenicity study in rats : dietary administration.

Study number TCR/1296. Group incidence of tumours by organ.

TUMOURS	INCIDENCE OF TUMOURS (NUMERIC)								
	GROUP	MALES				FEMALES			
		I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
ABDOMINAL CAVITY:									
Malignant fibrohistiocytic sarcoma [M]	(4)	(1)			(9)	(4)	(2)	(5)	
ADRENAL GLANDS:									
Benign pheochromocytoma [B]									
Malignant pheochromocytoma [M]	(102)	(51)	(51)	(51)	(104)	(52)	(50)	(52)	
Cortical adenoma [B]	3	4	1	3	1	1		1	
BONE AND MARROW - STERNUM:									
Adjacent muscle fibrosarcoma [M]	(102)	(51)	(51)	(51)	(104)	(52)	(51)	(52)	
BRAIN:									
Benign meningioma [B]	(102)	(51)	(51)	(51)	(104)	(52)	(51)	(52)	
Malignant meningioma [M]	1	2	1	3			1		
Astrocytoma [B]	2	2							
Malignant oligodendroglioma [M]	1							2	

Continued ...

270

Table 16 (contd) : 176,334 : Two year oncogenicity study in rats : dietary administration.

Study number TCR/1296. Group incidence of tumours by organ.

TUMOURS	INCIDENCE OF TUMOURS (NUMERIC)								
	GROUP	MALES				FEMALES			
		I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
CERVIX:									
Benign fibrous histiocytoma [B]									
Malignant fibrohistiocytic sarcoma [M]									
Polyp (stromal) [B]									
Granular cell myoblastoma [B]									
Histiocytic sarcoma [M]									
EARS:									
Squamous papilloma [B]	(7)	(2)	(1)	(5)	(4)	(2)	(1)	(2)	
EPIDIDYMIDES:									
Adjacent tissue anglioma [B]									
Benign mesothelioma [B]	(101)	(51)	(51)	(51)					
INTESTINE - CAECUM:									
Lelomyoma [B]	(94)	(50)	(48)	(50)	(100)	(49)	(48)	(51)	

Continued ...

Table 16 (contd) : 176,334 : Two year oncogenicity study in rats : dietary administration.

Study number TCR/1296. Group incidence of tumours by organ.

TUMOURS	GROUP	INCIDENCE OF TUMOURS (NUMERIC)							
		MALES				FEMALES			
		1 0 mg/kg /day	11 5 mg/kg /day	111 15 mg/kg /day	IV 75 mg/kg /day	1 0 mg/kg /day	11 5 mg/kg /day	111 15 mg/kg /day	IV 75 mg/kg /day
INTESTINE - DUODENUM:		(101)	(51)	(51)	(51)	(104)	(51)	(51)	(52)
Adenocarcinoma (M)	1		1	1	1				
INTESTINE - ILEUM:		(96)	(46)	(44)	(48)	(101)	(49)	(46)	(51)
Malignant fibrohistiocytic sarcoma (M)						1			
INTESTINE - JEJUNUM:		(99)	(49)	(47)	(50)	(101)	(50)	(49)	(51)
Adenocarcinoma (M)		(102)	(51)	(51)	(51)	(104)	(52)	(51)	1 (52)
KIDNEYS:			1		1		1		
Tubular adenoma (B)									
Tubular cystadenoma (B)									
Nephroblastoma (M)								1	
LIMBS AND TAIL:		(57)	(32)	(33)	(28)	(41)	(21)	(28)	(15)
Squamous papilloma (B)	2								
Keratoacanthoma (B)	1								1
Osteosarcoma (M)	1								

Continued ...

Table 16 (contd) : 176,334 : Two year oncogenicity study in rats : dietary administration.

Study number TCR/1296. Group incidence of tumours by organ.

TUMOURS	GROUP	INCIDENCE OF TUMOURS (NUMERIC)												
		MALES				FEMALES								
		1 0 mg/kg /day	11 5 mg/kg /day	111 15 mg/kg /day	IV 75 mg/kg /day	1 0 mg/kg /day	11 5 mg/kg /day	111 15 mg/kg /day	IV 75 mg/kg /day					
LIMBS AND TAIL:														
Angioma (B)		(57)	(32)	(33)	(26)	(41)	(21)	(26)	(15)					
LIVER:														
Hepatocellular adenoma (B)		(102)	(51)	(51)	(51)	(104)	(52)	(51)	(52)					
Hepatocellular carcinoma (M)		1	1	1	1	1	1	1	1					
LUNGS:														
Cystic adenoma (B)		(102)	(51)	(51)	(51)	(104)	(51)	(50)	(52)					
LYMPH. NODE - MANDIBULAR:		(102)	(50)	(51)	(51)	(103)	(49)	(46)	(52)					
Malignant lymphoma - lymphoblastic (M)			2			1								
Malignant fibrohistiocytic sarcoma (M)		(102)	(51)	(51)	(51)	(104)	(52)	(51)	(52)					
LYMPH NODE - MESENTERIC:														
Angioma (B)		1	1	1	1	1	1	1	1					
Malignant lymphoma - lymphoblastic (M)		1	2											

Continued ...

Table 16 (contd) : 176,334 : Two year oncogenicity study in rats : dietary administration.

Study number TCR/1296. Group incidence of tumours by organ.

TUMOURS	INCIDENCE OF TUMOURS (NUMERIC)								
	GROUP	MALES				FEMALES			
		I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
LYMPH NODES - NON-PROTICOLLED:	(53)	(25)	(26)	(34)	(37)	(11)	(20)	(21)	
Pancreatic node malignant lymphoma - lymphoblastic [M]	1								
MAMMARY GLANDS:	(102)	(51)	(51)	(51)	(104)	(52)	(52)	(50)	
Fibroadenoma [B]	2				29	6	6	3	
Adenoma [B]					6	2	2		
Adenocarcinoma [M]	1				8	2			
Fibroma [B]					2				
histiocytic sarcoma [M]			1						
MASSES AT NECROPSY:					(1)				
Histiocytic sarcoma [M]					1				
MUSCLE - SKELETAL:	(102)	(51)	(51)	(51)	(104)	(52)	(52)	(52)	
Neurofibroma [B]	1								

Continued ...

Table 16 (contd) : 176,334 : Two year oncogenicity study in rats : dietary administration.

Study number TCR/1296. Group incidence of tumours by organ.

TUMOURS	INCIDENCE OF TUMOURS (NUMERIC)								
	GROUP	MALES				FEMALES			
		1 0 mg/kg /day	11 5 mg/kg /day	111 15 mg/kg /day	1V 75 mg/kg /day	1 0 mg/kg /day	11 5 mg/kg /day	111 15 mg/kg /day	1V 75 mg/kg /day
ORAL CAVITY:									
Squamous papilloma [B]	(4)		(2)	(1)	(5)			(1)	
Squamous carcinoma [M]			1	1	1			1	
Basal cell carcinoma [M]	1				(104)			(52)	
OVARIES:									
Arrhenoblastoma [B]					2	1		2	
Granulosa cell adenoma [B]					1	2			
Granulosa cell carcinoma [M]					1	1			
PANCREAS:									
Exocrine adenoma [B]	(102)	(51)	(51)	(51)	(104)	(52)	(51)	(52)	
Exocrine adenocarcinoma [M]	8	4	2	6	1		4	1	
Islet cell adenoma [B]	1	1		1	1		2		
PARATHYROID GLANDS:	(92)	(46)	(45)	(38)	(87)	(43)	(42)	(41)	
Adenoma [B]			1						

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2121

Table 16 (contd) : 176,334 : Two year oncogenicity study in rats : dietary administration.

Study number TCR/1296. Group incidence of tumours by organ.

TUMOURS	GROUP	INCIDENCE OF TUMOURS (NUMERIC)							
		MALES				FEMALES			
		I mg/kg /day	II mg/kg /day	III mg/kg /day	IV mg/kg /day	I mg/kg /day	II mg/kg /day	III mg/kg /day	IV mg/kg /day
PITUITARY GLAND:		(100)	(51)	(50)	(51)	(104)	(52)	(52)	(52)
Adenoma - angiomatous [B]		15	12	9	13	66	33	34	33
Adenoma - solid [B]		$\frac{25}{40}$	$\frac{10}{22}$	$\frac{9}{18}$	$\frac{7}{20}$	$\frac{26}{42}$	$\frac{10}{43}$	$\frac{10}{44}$	$\frac{5}{38}$
PROSTATE GLAND:		(102)	(49)	(47)	(47)				
Adenoma [B]		1							
SALIVARY GLANDS - PAROTID:		(102)	(49)	(51)	(51)	(102)	(49)	(47)	(52)
Acinar adenoma [B]		2			1			1	
SALIVARY GLANDS - SUBMAXILLARY:		(102)	(50)	(51)	(51)	(103)	(49)	(48)	(52)
Adenocarcinoma [M]						1			
SEMINAL VESICLES:		(102)	(51)	(51)	(51)				
Adenocarcinoma [M]		2							

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CASODEX

3 OF 3

Table 16 (contd) : 176,334 : Two year oncogenicity study in rats : dietary administration.

Study number TCR/1296. Group incidence of tumours by organ.

TUMOURS	INCIDENCE OF TUMOURS (NUMERIC)							
	MALES				FEMALES			
	GROUP	1 mg/kg /day	11 5 mg/kg /day	111 15 mg/kg /day	IV 75 mg/kg /day	1 mg/kg /day	11 5 mg/kg /day	111 15 mg/kg /day
SKIN - NON-PROTOCOLLED:	(65)	(29)	(28)	(33)	(66)	(31)	(37)	(31)
Squamous papilloma [B]	7	1	1	1	1		1	1
Squamous carcinoma [M]					1	1		
Benign fibrous histiocytoma [B]	1	1	2	3	1	1	1	
Malignant fibrohistiocytic sarcoma [M]	2	1		1	1			
Fibroma [B]	1							
Lipoma [B]	1							
Angioma [B]	1							
Basal cell adenoma [B]	1							
Basal cell carcinoma [M]	1							
SKIN - NON-PROTOCOLLED:	(65)	(29)	(28)	(33)	(66)	(31)	(37)	(31)
Sebaceous adenoma [B]	1							

Continued ...

Table 16 (cont'd) : 176,334 : Two year oncogenicity study in rats : dietary administration.

Study number TCR/1296. Group incidence of tumours by organ.

TUMOURS	GROUP	INCIDENCE OF TUMOURS (NUMERIC)							
		MALES				FEMALES			
		I mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
SPLEEN:	(102)	(51)	(51)	(51)	(51)	(104)	(52)	(50)	(52)
Malignant lymphoma - lymphoblastic (M)						1			1
Malignant lymphoma - lymphocytic (M)			1						
Monocyclic leukaemia (M)					1				1
Histiocytic sarcoma (M)							1		
Angiosarcoma (M)									
STOMACH:	(102)	(51)	(51)	(51)	(51)	(104)	(52)	(51)	(52)
Squamous papilloma (B)									
TESTES:	(102)	(51)	(51)	(51)	(51)				
Benign Leydig cell tumour (B)	3	19	32	48					
Benign mesothelioma (B)	7	1	3	1					
Mesothelioma (M)									

Continued ...

Table 16 (cont'd) : 176,334 : Two year oncogenicity study in rats : dietary administration.

Study number TCR/1296. Group incidence of tumours by organ.

TUMOURS	GROUP	INCIDENCE OF TUMOURS (NUMERIC)											
		MALES				FEMALES							
		I mg/kg /day	II mg/kg /day	III mg/kg /day	IV mg/kg /day	I mg/kg /day	II mg/kg /day	III mg/kg /day	IV mg/kg /day				
TESTES:													
Histiocytic sarcoma [M]	(102)	(51)	(51)	(51)	(51)	(102)	(51)	(48)	(51)				
THYMUS:													
Benign mixed thymoma [B]	1					(100)	(50)	(51)	(50)				
Adenoma [B]	2	5	5	5	3	1	1	1	1	7	6	5	5
Malignant thymic lymphoma - lymphoblastic [M]	2	1	1	1	1					1			1
Adenocarcinoma [M]													
Malignant thymic lymphoma - lymphocytic [M]													
Adjacent tissue fibrosarcoma [M]													
THYROID GLAND:													
Adenoma - follicular [B]	(101)	(50)	(51)	(51)	(51)	(103)	(49)	(49)	(52)				
Parafollicular adenoma [B]	4	9	15	29	2	2	8	22	1	1	1	1	1
Parafollicular cell carcinoma [M]	4	1	1	4	1	7	1	1	1	2	1	1	1
Parafollicular cell carcinoma [M]	2	1	1	1	1	1	1	1	1	2	1	1	1

Continued ...

Thymoma 18, 24, 22 16%

0.9
22
51

Table 16 (contd) : 176,334 : Two year oncogenicity study in rats : dietary administration.

Study number TCR/1296. Group incidence of tumours by organ.

TUMOURS	GROUP	INCIDENCE OF TUMOURS (NUMERIC)							
		MALES				FEMALES			
		I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
TONGUE:		(102)	(51)	(51)	(51)	(103)	(50)	(49)	(52)
Squamous papilloma [B]									
UTERUS:						(104)	(52)	(52)	(52)
Polyp (stromal) [B]						18	6	7	7
Polyp (adenomatous) [B]							1	1	1
Adenocarcinoma [M]								1	5
Squamous carcinoma [M]									1
VAGINA:						(104)	(52)	(52)	(52)
Malignant fibrohistiocytic sarcoma [M]						1		2	

Figures in brackets represent the number of animals from which this tissue was examined microscopically. The absence of a numeral indicates that the lesion specified was not identified. [M] = malignant, [B] = benign.

Table 17 : 176,334 : Two year oncogenicity study in rats :
dietary administration. Study number TCR/1296. Males -
tumours with increasing incidence with dose statistically
significant at 5% level.

	Incidence of tumours			
	Control	5 mg/kg	15 mg/kg	75 mg/kg
<u>Testes: benign leydig</u> <u>cell tumour (B)</u>				
Prevalence context				
Days 1 - 420	0/10	1/7	0/3	-
Days 421 - 532	0/14	1/6	2/6	5/5
Days 533 - 616	0/12	0/5	2/10	7/9
Days 617 - 672	1/15	5/10	6/6	6/6
Days 673 - terminal necropsy	1/17	7/11	5/6	6/6
Terminal necropsy	1/34	5/12	17/20	24/25
P-values				
trend		p<0.0001		
multiplicity corrected trend		p<0.0001		
pairwise versus control	-	p<0.0001	p<0.0001	p<0.0001
<u>Thyroids: adenoma -</u> <u>follicular (B)</u>				
Prevalence context				
Days 421 - 532	0/14	1/6	0/6	0/5
Days 533 - 616	0/12	0/5	4/10	5/9
Days 617 - 672	1/15	3/10	1/6	3/6
Days 673 - terminal necropsy	1/17	1/11	3/6	4/6
Terminal necropsy	2/34	4/12	8/20	17/25
P-values				
trend		p<0.0001		
multiplicity corrected trend,		p<0.0001		
pairwise versus control	-	p=0.0038	p<0.0001	p<0.0001

Table 18 : 176,334 : Two year oncogenicity study in rats : dietary administration. Study number TCR/1296. Females - tumours with increasing incidence with dose statistically significant at 5% level.

	Incidence of tumours			
	Control	5 mg/kg	15 mg/kg	75 mg/kg
<u>Brain : astrocytoma (B)</u>				
Fatal context	0	0	0	2
P-values				
trend		p=0.036		
multiplicity corrected trend		NS		
<u>Thyroids : adenoma - follicular (B)</u>				
Prevalence context				
Days 421 - 532	0/7	0/1	0/1	1/6
Days 533 - 616	0/11	0/5	1/6	0/3
Days 617 - 672	0/12	1/4	1/6	6/8
Days 673 - terminal necropsy	0/20	0/8	1/9	7/11
Terminal necropsy	0/46	1/30	5/24	8/19
P-values				
trend		p<0.0001		
multiplicity corrected trend		p<0.0001		
pairwise versus control	-	NS	p=0.0001	p<0.0001
<u>Uterus : adenocarcinoma (M)</u>				
Fatal context	0	0	0	3
Prevalence context				
days 673 - terminal necropsy	0/20	0/8	1/11	0/8
Terminal necropsy	0/46	0/30	0/24	2/19
P-values				
trend		p=0.0002		
multiplicity corrected trend		p=0.0026		
pairwise versus control	-	-	NS	p=0.0016

Note to table:

NS = Not statistically significant (p>0.05)

Table 19 : 176,334 : Two year oncogenicity study in rats :
dietary administration. Study number TCR/1296. Tumours
with decreasing incidence with dose statistically
significant at 5% level.

	Incidence of tumours				P-value Trend test
	Control	5 mg/kg	15 mg/kg	75 mg/kg	
<u>Males</u>					
Pituitary gland: adenoma - solid (B)	25/100	10/51	9/50	7/51	0.015
Skin non-protocolled*: squamous papilloma (B)	7/102	1/51	0/51	1/51	0.042
<u>Females</u>					
Mammary glands: fibroadenoma (B)	29/104	6/52	6/52	3/50	0.0002
Mammary glands: adenocarcinoma (M)	8/104	2/52	0/52	0/50	0.0054
Pituitary gland: adenoma - solid (B)	26/104	10/52	10/52	5/52	0.023

* = all animals are regarded as at risk for non-protocolled tissues

Table 14 : 176,334 : Two year oncogenicity study in mice: dietary administration.

Study number TCN/634. Total incidence of tumours.

GROUP	TUMOUR TABLE											
	MALES						FEMALES					
	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
NUMBER OF ANIMALS:	100	50	50	50	100	50	50	50	100	50	50	50
NO. OF ANIMALS WITH TUMOURS	70	39	38	40	77	41	45	37	77	41	45	37
NO. OF ANIMALS WITH SINGLE TUMOURS	56	34	33	25	58	30	31	25	58	31	31	25
NO. OF ANIMALS WITH MULTIPLE TUMOURS	14	5	5	15	19	11	14	12	19	11	14	12
NO. OF ANIMALS WITH BENIGN TUMOURS	20	5	8	14	16	12	10	12	16	10	10	12
NO. OF ANIMALS WITH MALIGNANT TUMOURS	62	37	33	33	72	35	43	32	72	35	43	32
NO. OF ANIMALS WITH METASTASISING TUMOURS				1				1			1	
TOTAL NUMBER OF TUMOURS	85	45	43	57	99	56	62	53	99	56	62	53
TOTAL NUMBER OF BENIGN TUMOURS	21	5	8	19	18	14	11	14	18	14	11	14
TOTAL NUMBER OF MALIGNANT TUMOURS	64	40	35	38	81	42	51	39	81	42	51	39
TOTAL NUMBER OF METASTASISING TUMOURS				1			1				1	
% ANIMALS WITH TUMOURS	70	78	76	80	77	82	90	74	77	82	90	74
% ANIMALS WITH SINGLE TUMOUR	56	68	66	50	58	60	52	50	58	60	52	50
% ANIMALS WITH MULTIPLE TUMOURS	14	10	10	30	19	22	28	24	19	22	28	24
% ANIMALS WITH BENIGN TUMOURS	20	10	16	28	16	24	26	24	16	24	26	24
% ANIMALS WITH MALIGNANT TUMOURS	62	74	66	66	72	70	86	64	72	70	86	64
% ANIMALS WITH METASTASISING TUMOURS				2			2				2	

NDA 20-49E
Appendix 2 - Mouse
Carcinogenicity

Table 15 : 176,334 : Two year oncogenicity study in mice: dietary administration.

Study number TCM/634. Group based listing of tumours.

TUMOURS	GROUP	INCIDENCE OF TUMOURS (NUMERIC)							
		MALES				FEMALES			
		I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
ADRENAL GLANDS:		(100)	(49)	(50)	(50)	(100)	(50)	(49)	(49)
Benign pheochromocytoma [B]		(100)	(50)	(50)	(49)	(98)	(50)	(49)	(50)
BONE AND MARROW - STERNUM:									
Histiocytic sarcoma [M]				1	1	1			1
Angiosarcoma [M]		(100)	(50)	(50)	(50)	(99)	(50)	(50)	(50)
BRAIN:			1			1			
Meningeal composite lymphoma [M]									
Benign meningioma [B]									
CERVIX:									
Histiocytic sarcoma [M]		(100)	(50)	(50)	(50)	(92)	(48)	(49)	(48)
EPIDIDYMIDES:		4	2	1				4	1
Histiocytic sarcoma [M]									

Continued ...

070

Table 15 (cont'd) : 176,334 : Two year oncogenicity study in mice: dietary administration.
 Study number TCM/634. Group based listing of tumours. 1 1

TUMOURS	GROUP	INCIDENCE OF TUMOURS (NUMERIC)							
		MALES				FEMALES			
		I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
GALL BLADDER:		(85)	(44)	(40)	(43)	(84)	(42)	(38)	(37)
Papilloma [B]						1			
HARDERIAN GLANDS:		(100)	(50)	(50)	(50)	(100)	(50)	(50)	(50)
Cystadenoma [B]		5	1	1	3		2	1	
Adenoma [B]									
INTESTINE - DUODENUM:		(93)	(44)	(47)	(44)	(91)	(46)	(44)	(45)
Polyp [B]		1				1			2
INTESTINE - JEJUNUM:		(95)	(42)	(46)	(43)	(90)	(46)	(43)	(46)
Polyp [B]						1			
Composite lymphoma [M]				2		1	1		
INTESTINE - ILEUM:		(90)	(42)	(42)	(41)	(87)	(44)	(39)	(41)
Composite lymphoma [M]		3				1	1		

Continued ...

Table 15 (contd) : 176,334 : Two year oncogenicity study in mice: dietary administration.

Study number TCM/634. Group based listing of tumours.

TUMOURS	INCIDENCE OF TUMOURS (NUMERIC)								
	GROUP	MALES				FEMALES			
		I mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
LIVER:	(100)	(50)	(50)	(50)	(100)	(50)	(50)	(50)	
Hepatocellular adenoma [H]	3			4					
Hepatocellular carcinoma [M]	2	1	1	8		1			
Histiocytic sarcoma [M]	2		3	4	3	1	3	1	
Angioma [H]					1				
Angiosarcoma [M]		3	1		1				
LUNGS:	(100)	(50)	(50)	(50)	(100)	(50)	(50)	(50)	
Adenocarcinoma [M]					2			2	
LYMPH NODE - MANDIBULAR:	(99)	(49)	(50)	(49)	(99)	(50)	(50)	(50)	
Composite lymphoma [M]	1		2		1			1	

Continued ...

Table 15 (contd) : 176,334 : Two year oncogenicity study in mice: dietary administration.

Study number TCM/634. Group based listing of tumours.

TUMOURS	GROUP	INCIDENCE OF TUMOURS (NUMERIC)							
		MALES				FEMALES			
		I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
LYMPH NODE - MESENTERIC:		(98)	(50)	(50)	(49)	(99)	(50)	(50)	(49)
Composite lymphoma [M]		40	24	18	19	47	27	25	20
Histiocytic sarcoma [M]		1	1	1	1	1	1	1	1
Angioma [B]									
LYMPH NODES - NON-PROTOCOLLED:		(49)	(26)	(28)	(22)	(57)	(29)	(31)	(26)
Composite lymphoma [M]		1	1	1	1	4	1	2	2
Histiocytic sarcoma [M]						1			
OVARIES:						(96)	(50)	(50)	(49)
Granulosa cell adenoma [B]						1		1	
Arrhenoblastoma [B]						1			
PITUITARY GLAND:		(96)	(48)	(49)	(48)	(91)	(48)	(49)	(49)
Adenoma [B]				2		6	7	4	8
SALIVARY GLANDS - SUBMAXILLARY:		(99)	(49)	(50)	(49)	(100)	(50)	(50)	(50)
Histiocytic sarcoma [M]		1	1	1	1				1

Continued ...

073

Table 15 (cont'd) 176,334 : Two year oncogenicity study in mice: dietary administration.

Study number TCH/634. Group based listing of tumours.

TUMOURS	INCIDENCE OF TUMOURS (NUMERIC)								
	GROUP	MALES				FEMALES			
		1 0 mg/kg /day	11 5 mg/kg /day	111 15 mg/kg /day	1V 75 mg/kg /day	1 0 mg/kg /day	11 5 mg/kg /day	111 15 mg/kg /day	1V 75 mg/kg /day
SEMINAL VESICLES:									
Histiocytic sarcoma (M)	(100)	(49)	(78)	(45)	(100)	(49)	(50)	(50)	
SPINAL CORD:									
Histiocytic sarcoma (R)	1 (100)	(50)	(50)	(50)	(99)	(50)	(50)	(50)	
SPLEEN:									
Composite lymphoma (M)	2	2	3	2	3	6	3	3	
Mast cell sarcoma (M)	1								
Myeloid leukaemia (myeloblastic) (M)	3	1	2	1	2	1	2		
Angiosarcoma (M)	2								
Angioma (R)									
STOMACH:	(98)	(47)	(50)	(48)	(98)	(49)	(50)	(49)	
Squamous carcinoma (M)									
Squamous papilloma (R)	1				1			1	

Continued ...

Table 15 (contd) : 176,334 : Two year oncogenicity study in mice: dietary administration.

Study number TCM/634 Group based listing of tumours.

1

TUMOURS	GROUP	INCIDENCE OF TUMOURS (NUMERIC)							
		MALES				FEMALES			
		I 0 mg/kg /d.y	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
TESTES:		(100)	(50)	(50)	(50)	(98)	(49)	(48)	(50)
Malignant Leydig cell tumour [M]			1						
Benign Leydig cell tumour [B]			1	2	1				
Histiocytic sarcoma [M]			2		1				
Angioma [B]									
THYROID GLAND:		(99)	(48)	(50)	(50)	(98)	(50)	(50)	(50)
Adenoma - follicular [B]		8			7				2
UTERUS:		(11)				(98)	(50)	(50)	(50)
Histiocytic sarcoma [M]						9	4	7	4
Angioma [B]						1	1	2	
VERTEBRAL COLUMN:						(3)			
Osteosarcoma [M]						1			
Histiocytic sarcoma [M]						1			

Continued ...

Table 15 (contd) : 176,334 : Two year oncogenicity study in mice: dietary administration.

Study number TCH/634. Group based listing of tumours.

TUMOURS	INCIDENCE OF TUMOURS (NUMERIC)														
	GROUP	MALES					FEMALES								
		10 mg/kg /day	5 mg/kg /day	11 mg/kg /day	15 mg/kg /day	1V 75 mg/kg /day	10 mg/kg /day	5 mg/kg /day	11 mg/kg /day	15 mg/kg /day	1V 75 mg/kg /day				
ABDOMINAL CAVITY:															
Angioma [H]	(2)	(1)	(1)	(1)	(2)	(1)	(1)	(1)	(2)	(1)	(1)	(2)	(1)	(1)	(1)
BONE AND MARROW - FIBRO:															
Mast cell tumour [M]	(100)	(50)	(49)	(50)	(50)	(49)	(50)	(50)	(49)	(50)	(50)	(49)	(50)	(50)	(50)
Histiocytic sarcoma [M]	2				1						1				
Angiosarcoma [M]	(9)	(4)	(7)	(3)	(3)	(7)	(3)	(3)	(3)	(8)	(5)	(5)	(1)	(1)	(1)
LIMB AND TAIL:															
Angiosarcoma [M]										2					
ORAL CAVITY:															
Osteosarcoma [M]	(17)					(1)									
PREPUTIAL GLAND:															
Histiocytic sarcoma [M]	1					(3)				(1)					(1)

Continued ...

Table 15 (cont'd) : 176,334 : Two year oncogenecity study in mice: dietary administration.

Study number TCM/634. Group based listing of tumours.

TUMOURS	INCIDENCE OF TUMOURS (NUMERIC)								
	GROUP	MALES				FEMALES			
		I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
SKIN - NON-PROLIFERATED: Composite lymphoma [M] Histiocytic sarcoma [M] Squamous papilloma [B] Angioma [B] Fibroma [B] Benign mastocytoma [B]	(42)	(21)	(16)	(16)	(48)	(24)	(24)	(27)	
	1	1	1	1	1	1	1	1	
	0	2	1	1	0	1	1	1	

Figures in brackets represent the number of animals from which this tissue was examined microscopically. The absence of a numeral indicates that the lesion specified was not identified. [M] = malignant, [B] = benign.

Table 16 : 176.334 : Two year oncogenicity study in mice:
 dietary administration. Study number TCM/634.
 Statistical analysis of hepatocellular carcinomas.
 Increasing trend with dose statistically significant at 5%
 level - males.

Group	Incidence of tumours			
	I 0 mg/kg /day	II 5 mg/kg /day	III 15 mg/kg /day	IV 75 mg/kg /day
<u>LIVER</u>				
<u>Hepatocellular carcinoma</u> (M)	(100)	(50)	(50)	(50)
Fatal context	2	0	0	3
Prevalence context				
Days 421 - 616	0/14	0/12	1/10	0/6
Days 617 - 672	0/11	0/7	0/7	1/5
Days 673 - terminal necropsy	0/22	1/10	0/10	0/11
Terminal necropsy	0/47	0/20	0/21	4/21
Overall				
Observed incidence (expected)	2 (4.9)	1 (2.4)	1 (2.4)	8 (2.3)
Ratio observed: expected	0.41	0.41	0.41	3.52
P-values				
Trend		p = 0.0009		
Multiplicity corrected trend		p = 0.0082		
Pairwise versus control	-	NS	NS	p = .0016

Note to table:

Fatal context - animals dying prior to terminal necropsy where liver tumour has been designated cause of death.

NS - not statistically significant at the 5% level.

Expected incidences are those to have been anticipated if there was no compound effect. They reflect survival differences between the groups.

Kee

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DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 20-498

AUG 25 1995

CHEMISTRY REVIEW #: 2

DATE REVIEWED: 8-25-95

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
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ORIGINAL	9-14-94	9-15-94	9-16-94
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AMENDMENT	8-22-95		8-23-95
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NAME & ADDRESS OF APPLICANT:

Zeneca Pharmaceuticals Group
1800 Concord Pike
Wilmington, Delaware 19897

DRUG PRODUCT NAME

<u>Proprietary:</u>	Casodex
<u>Nonproprietary/Established/USAN:</u>	Bicalutamide tablets
<u>Code Name/#:</u>	176,334
<u>Chem.Type/Ther.Class:</u>	1 C

PHARMACOLOGICAL CATEGORY/INDICATION: Antiandrogen agent/Prostate cancer

DOSAGE FORM:

Tablets

STRENGTHS:

50mg

ROUTE OF ADMINISTRATION:

Oral

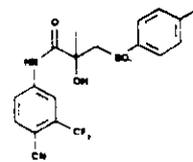
DISPENSED:

Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[[4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl, (+-)

C₁₈H₁₄N₂O₄F₄S
MW = 430.37



CONCLUSIONS & RECOMMENDATIONS:

The deficiencies communicated to the firm on August 8, 1995 were satisfactorily resolved in this Amendment. This NDA is approvable from chemistry point of view pending satisfactory review of EA. Summary of Review is attached. For the container and blister package labels, the word 'Tablets' should be part of either Trade name or established name, and the name of manufacturer should be spelled out as the way specified in 21 CFR 201.1(h)(5)

cc:

Org. NDA 20-498

HFD-510/Division File

HFD-510/MRhee/YChiu/LPaul

R/D Init by: SUPERVISOR

filename: NL-1.206

YChiu
8/25/95

Moo-Jhong Rhee, Ph.D.
Review Chemist

SUPPORTING DOCUMENTS:

Chem Rev #1 dated 8-8-95.

Related Document:

See Chem Rev #1

REMARKS/COMMENTS:

The 8-22-94 amendment was submitted in response to the deficiencies noted in the Chem Rev #1 dated 8-8-95. By this Amendment, all the CMC issues, except for EA, are resolved.

quantitatively demonstrate the amount of R and S forms, but rather to demonstrate clear separation of each enantiomer under the specified HPLC condition. Therefore, the amount of each enantiomer weighed was not exactly the same in the preparation resulting in different peak area from each other. Satisfactory.

B. Drug Product:

1. Container:

Question 5: *Please provide schematic diagram and specifications of dimension of containers for tablets.*

Response: As requested, detailed schematic diagrams and physical specifications for the HDPE bottle (75cc, white, square, and wide mouth w/M33-sp-400 finish) and blister pack were provided. Satisfactory.

Question 6: *Please clarify as to whether the blister package and plastic bottles used in the stability studies are the same as the proposed package in terms of container size and the number of tablets per container.*

Response: The firm confirmed that the stability samples have the same packaging configuration as proposed packaging in terms of container size and the number of tablets (100 tablets per 75cc bottle and 10 tablets per blister strip). Satisfactory.

7. Stability:

Question 7: *Please submit chiral HPLC chromatograms of samples subjected to 40oC/80% in blister package and bottles for 1, 3, and 6 months.*

Response: Chiral HPLC chromatograms of stability samples (25oC for 12 months, 30oC/80%RH for 12 months, and 40oC/80%RH for 6 months) in blister package as well as bottles were submitted. The chromatographic profiles look almost identical confirming their argument made in the response to **Question 4**. Satisfactory.

C. Labeling:

Question 8: *In package insert, dosage form (tablets) should be indicated in the heading right after tradename or established name.*

Response: As requested dosage form will be indicated in the heading of package insert as follows: Casodex (bicalutamide) tablets. Satisfactory.

Question 9: *Please provide draft labels for cartons.*

Response: Draft labels of cartons for bottle (100 tablets per bottle) and blister packages (3 packs per carton) were submitted. Also submitted is draft label for blister package and bulk container. They all have adequate information. The only comment is that to be consistent with package insert, dosage form should be specified in the tradename and the manufacturer should be spelled out in accordance with 21 CFR 201.1 (h)(5). Satisfactory.

Summary of Chemistry Review

A. Drug Substance:

1. Other Firm: Satisfactory. See Chem Rev #1
2. Synthesis: Satisfactory. See Chem Rev #2
3. Raw Material Controls: Satisfactory. See Chem Rev #1
4. Specifications and Analytical Method: Satisfactory. See Chem Rev #2

B. Drug Products:

1. Components and Composition: Satisfactory. See Chem Rev #1
2. Raw Material Controls: Satisfactory. See Chem Rev #1
3. Manufacturer: Satisfactory. See Chem Rev #1
4. Manufacturing and Processing: Satisfactory. See Chem Rev #1
5. Packaging and Labeling: Satisfactory. See Chem Rev #1
6. Laboratory Controls: Satisfactory. See Chem Rev #1
7. Containers: Satisfactory. See Chem Rev #2
8. Stability: Satisfactory. See Chem Rev #2

C. Investigational Formulations: Satisfactory. See Chem Rev #1

D. Environmental Impact Analysis Report: Pending.

E. Samples and Results: Method Validation will be requested.

F. Labeling: Satisfactory. See Chem Rev #2. Minor comments to be communicated to firm.

G. Established Inspection: Satisfactory. See Chem Rev #1

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

AUG - 8 1995

NDA #: 20-498
CHEMISTRY REVIEW #: 1

DATE REVIEWED: 8-8-95

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	9-14-94	9-15-94	9-16-94
AMENDMENT	10-28-94	10-31-94	
	2-17-95	2-21-95	
	4-10-95	4-12-95	
	7-5-95	7-6-95	

NAME & ADDRESS OF APPLICANT: Zeneca Pharmaceuticals Group
1800 Concord Pike
Wilmington, Delaware 19897

DRUG PRODUCT NAME

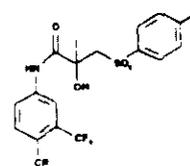
<u>Proprietary:</u>	Casodex
<u>Nonproprietary/Established/USAN:</u>	Bicalutamide tablets
<u>Code Name/#:</u>	176,334
<u>Chem. Type/Ther. Class:</u>	1 C

PHARMACOLOGICAL CATEGORY/INDICATION: Antiandrogen agent/Prostate cancer

DOSAGE FORM: Tablets
STRENGTHS: 50mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl, (+-)



$C_{18}H_{14}N_2O_4F_4S$
MW = 430.37

CONCLUSIONS & RECOMMENDATIONS:

CMC information provided is considered to be adequate with minor deficiencies identified. EER returned with acceptable rating (7-26-95). The tradename was cleared by the Labeling and Nomenclature Committee on 2-6-95. Therefore, from chemistry point of view, this NDA is approvable pending satisfactory review of EA and submission of draft carton labels. In addition, the deficiencies delineated in the draft letter should be clarified (see draft letter).

cc:
Org. NDA 20-498
HFD-510/Division File
HFD-510/MRhee/YChiu/LPaul

R/D Init by: SUPERVISOR
filename: NL.206

Moo-Jhong Rhee, Ph.D.
Review Chemist

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-498

CASODEX®

REVIEW DIVISION: HFD-510

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-004

DATE COMPLETED: August 20, 1995

ENVIRONMENTAL ASSESSMENT

1. Date:

NDA submitted: 14 September 1994
EA #1 dated: January 1992
EA #2 dated: November 1994
EA revision #1: 17 February 1995
EA revision #2: 5 July 1995
EA revision: August 1995*

Consult to HFD-004: August 17, 1995

*Information reviewed.

CSO: Lana L. Pauls

2. Name of Applicant/Petitioner:

ZENECA Limited
Macclesfield Cheshire, England
ZENECA Pharmaceuticals Group, a business unit of
ZENECA, Inc., is authorized U.S. agent for ZENECA
Limited for the subject NDA.

Adequate.

3. Address:

Administrative Headquarters

ZENECA Limited
Alderly Park
Macclesfield Cheshire
SK10 4TF England

RESPONSE TO DEFICIENCY FAX OF AUGUST 10, 1995:

The FOI'able EA should be revised as follows:

1. The statement in section 8.3 that the material is strongly absorbed to soil is not consistent with the conclusion in the sorption/desorption test report which states that the material is likely to be moderately mobile. Please revise as appropriate.

RESPONSE: The Company has clarified that section of the document. **ADEQUATE**

2. The acute toxicity *Daphnia magna* test results should be included into the EA (section 7 and 15.1).

RESPONSE: Testing was not performed due to the limited solubility due to solubility problems. The LC₅₀ of > 5.3 ppm quoted in the report is the best estimate of acute toxicity. They have included this information in the EA. **ADEQUATE**

3. Section 14 is not a confidential section. All that is required in Section 14 is a list of documents used in the preparation of the EA. Listed documents might include chemical handbooks, published reports, FDA EATAD's or other such documents. The information currently listed in this section are appendices which should be listed by name in section 15 and designated as confidential. The MSDS for Casodex should be included as a non-confidential appendix and attached to the FOI'able EA. Please revise sections 14 and 15 and provide the MSDS as noted above.

RESPONSE: Section 14 and 15 have been revised appropriately.
ADEQUATE

SUMMARY

A FONSI may be written. The MEEC terrestrial is estimated at 1.1 ppm and the MEEC aquatic as 1.1 ppm (based on 1.1 kg/year). Chronic toxicity testing in *Daphnia* is reported as LC₅₀ 3.2 ppm (NOEC 5.6 ppm) and acute toxicity is estimated at LC₅₀ > 5.3 ppm. Toxicity to both blue green and green algae is reported as EC₅₀ >1.1 ppm and NOEC 1.1 ppm

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT

CASODEX®

(bicalutamide tablets)

50 mg

NDA 20-498

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM and ENDOCRINE
DRUG PRODUCTS (HFD-510)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-498

CASODEX®

(bicalutamide tablets)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for CASODEX®, Zeneca Limited has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Bicalutamide is a synthetic drug which is administered as an oral tablet in the treatment of advanced prostrate cancer. The drug substance will be manufactured by Zeneca Limited, Cheshire, England, the drug product will be manufactured by Zeneca GmbH, Plankstadt, Germany and the drug product will be packaged by Zeneca Pharmaceuticals Group, Newark, Delaware. The finished drug product could be used in hospitals, clinics and by patients in their homes.

Bicalutamide may enter the environment from excretion by patients, as emissions from manufacturing sites or from disposal of pharmaceutical wastes. Chemical and physical test results indicate that the drug substance will most likely enter the aquatic or terrestrial environment. No rapid environmental depletion mechanism has been identified.

As the drug would be expected to persist in the environment for some time, the toxicity of the material to organisms was characterized. Chronic toxicity studies in water fleas (*Daphnia magna*) and testing of blue green algae (*Microcystis aeruginosa*) and green algae (*S. capricornutum*) indicate that the drug substance is not toxic to organisms at the expected environmental concentrations.

Disposal of the drug may result from manufacturing waste, rejected, returned or expired drug product and user disposal of empty or partly used product and packaging. Manufacturing waste will be disposed of at a licensed facility. Rejected, returned or expired drug product will be disposed of by high temperature incineration at a licensed facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

8/21/95
DATE

Nancy B. Sager
PREPARED BY
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

8/21/95
DATE

R. A. Jerussi
CONCURRED
Robert A. Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

ENVIRONMENTAL ASSESSMENT FOR CASODEX

NON CONFIDENTIAL

**REDACTIONS MADE
BY APPLICANT**

**REDACTIONS MADE
BY APPLICANT**

CONTENTS

SECTION ONE	(PAGE 3)	Introduction
SECTION TWO	(PAGE 4)	Applicant
SECTION THREE	(PAGE 5)	Addresses
SECTION FOUR	(PAGE 6)	Description of Proposed Action
SECTION FIVE	(PAGE 11)	Identification of Substances
SECTION SIX	(PAGE 12)	Introduction of Substances into the Environment
SECTION SEVEN	(PAGE 18)	Fate of Emitted Substances in the Environment
SECTION EIGHT	(PAGE 21)	Environmental Effects of Released Substances
SECTION NINE	(PAGE 24)	Use of Resources and Energy
SECTION TEN	(PAGE 25)	Mitigation Measures
SECTION ELEVEN	(PAGE 27)	Alternatives to Proposed Action
SECTION TWELVE	(PAGE 28)	Preparers
SECTION THIRTEEN	(PAGE 29)	Certification
SECTION FOURTEEN	(PAGE 30)	References
SECTION FIFTEEN	(PAGE 31)	Appendices
15.1	(PAGE 31)	Data Summary Charts
15.2		Estimate of Yearly Market Volume
15.3	(PAGE 32)	Material Safety Data Sheet for Casodex
15.4		Materials Used in the Synthesis of ICI 176334
15.5		Site Authorisations and Permits
15.6		Results of Physical Testing
15.7		Results of Biological Testing
15.8		Certificates of Analysis

CASODEX ENVIRONMENTAL ASSESSMENT

SECTION 1.

DATE: AUGUST 1995

REDACTIONS MADE
BY APPLICANT

SECTION 2. APPLICANT

ZENECA Limited,
Macclesfield, Cheshire, England

ZENECA Pharmaceuticals Group a business unit of ZENECA Inc is the
authorised US agent for ZENECA Limited for the subject NDA

**REDACTIONS MADE
BY APPLICANT**

SECTION 3. ADDRESSES

Administrative Headquarters.

ZENECA Limited
Alderley Park
Macclesfield Cheshire
SK10 4TF England

Site for Manufacture of Active Material

ZENECA Limited
Macclesfield Cheshire
SK10 4TF England

Site for Formulation of Drug Product

ZENECA GmbH
Otto-Hahn Strasse
68723 Plankstadt
Germany

US Distribution Centre
ZENECA Pharmaceuticals Group
587 Old Baltimore Pike
Newark, Delaware 19711

REDACTIONS MADE
BY APPLICANT

SECTION 4. DESCRIPTION OF THE PROPOSED ACTION

REDACTIONS MADE
BY APPLICANT

4.1 Describe the requested action

ZENECA Limited is filing a new drug application for approval to manufacture and formulate, package and distribute CASODEX.

The US agent is: ZENECA Pharmaceuticals
P.O. Box 751
Wilmington
Delaware

The NDA number is 20-498

CASODEX is a tablet containing 50 mg of bicalutamide; the active drug substance is also known as ICI 176334.

4.2 Describe the need for the proposed action

CASODEX is a drug for the treatment of advanced prostate cancer. It will be used chronically in elderly male patients. ICI 176334 is a non-steroidal antiandrogen.

4.3 Locations where the products are to be :-

(1) Produced

The active material will be produced at the ZENECA manufacturing site at Macclesfield

The address of the facility is:-

ZENECA Limited
Charter Way,
Hurdsfield Industrial Estate
Macclesfield,
Cheshire,
SK10 4TF.
England

REDACTIONS MADE
BY APPLICANT

(2) Formulated

The active drug substance will be formulated at the ZENECA facility at Plankstadt in Germany.

The address of the facility is:-

ZENECA GmbH
Otto-Hahn Strasse
68723 Plankstadt
Germany

(3) Final Packaging

Final packing will take place at Macclesfield and Plankstadt and at Newark, Delaware in the USA.

The address of the Newark facility is:-

ZENECA Pharmaceuticals Group
587 Old Baltimore Pike
Newark, Delaware 19711

The latter facility will be the distribution centre for the USA.

(4) Used

Casodex is indicated for the treatment of advanced prostrate cancer. The product will be used in hospitals and in home care therapy.

(3) Disposed

The product is used in hospitals and homes for treating patients with advanced prostrate cancer. It is administered in tablet form. The packaging would be disposed of by the normal methods used for disposing of the packaging of medicinal products.

Any rejected, returned or time expired product will be disposed of by high temperature incineration in facilities approved by the local authorities having jurisdiction in the area in which disposal is taking place.

made up of a three-fold division:

- Keuper Marl;
- Waterstone;
- Keuper Sandstone (bottom).

REDACTIONS MADE
BY APPLICANT

All three groups merge into one another becoming progressively finer in grain until the clay of the Keuper Marl, with its evaporitic beds, overspread the other Triassic rocks. In the Alderley Edge area, the Keuper Sandstone basal beds are noted as being coarse grained and conglomeratic. The Waterstones are an alternating series of thin bedded marly brown sandstones and soft sandy marls and variegated shales. They represent a transitional depositional phase between the underlying Keuper Sandstone and the overlying Keuper Marl. In the Cheshire Basin the Keuper Marl attains its fullest development in Britain. The Keuper Marl comprises a relatively homogeneous sequence silty red clay (Marl) with thin intercalations of dolomitic substance.

In the vicinity of the ZENECA Macclesfield site the Triassic Sandstone lithologies comprise Upper Mottled Sandstone and Bunter Pebble Beds of the Bunter Formation, and no impermeable Keuper lithologies are present.

Overlying the Triassic Sandstone Formations are a sedimentary succession of Pleistocene and recent deposits, which are 50-60m in thickness in the vicinity of the ZENECA Macclesfield facility. These drift deposits are generally differentiated as boulder clay or sands and gravels. This is somewhat misleading as they are characteristically intricately intercalated with both vertical and lateral gradation and discontinuity.

The site has been developed over the last 20 years to provide a comprehensive facility for the development, manufacture, formulation and distribution of pharmaceuticals together with associated laboratories and administration areas. The buildings are of modern design and construction.

4.4.2 Site of Formulation Facilities

The site at Plankstadt is located in an area designated as an industrial zone. The area of the site is approximately 95,000 m². It stands on a plain just to the west of a range of hills which run north to south. The predominant wind direction is from the west. The site stands on alluvial deposits from the rivers Rhine and Necker. The soil is sandy with many small pebbles. It is bounded by other industrial property and farmland.

The site has been developed over the past 20 years to provide facilities for the purification of active materials and the formulation and packing of pharmaceuticals products. The buildings are of modern design and construction.

4.4.3 Sites for Final packing and Distribution

REDACTIONS MADE
BY APPLICANT

Geographically the ZENECA Pharmaceuticals Group facility is on the Delaware Peninsula where the weather is moderated by both the Chesapeake Bay to the west and the Delaware River and Bay and Atlantic Ocean to the east. The area of the plant site is a plain just south of hills which extend from northern Delaware into Pennsylvania.

The environment of the site itself is 87 acres of relatively flat second growth woodlands. The soils are a thin layer of organic soils over heavy clay and occasional sand or glacial till. The sedimentary rock beneath the soils is deeply buried at the plant site and nearby area. Development of the site is about 405,000 square feet of buildings which supports the pharmaceuticals business, substantial grass lawn areas and decorative plantings, paved walkways, paved and unpaved access roads, and paved parking lots. The buildings are of modern construction, designs and materials and have been built specifically for pharmaceuticals production since 1971. Site drainage improvements have been made by installing a pond to slow rainwater run-off from buildings and paved areas.

The environment adjacent to the site is to the north, US interstate 95; to the west a casement for an interchange to US interstate 95; to the south, Old Baltimore Pike and a residential area; and to the east, Salem Church Road and a residential area.

The potable water is supplied by Wilmington Suburban Company and the waste water from the site is treated in the New Castle County Municipal Sewer System at the Wilmington Treatment Facility.

SECTION 5. IDENTIFICATION OF CHEMICALS SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION

5.1 Drug Substance

The active drug substance is also known as ICI 176334

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BY APPLICANT

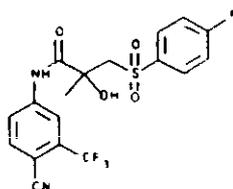
5.1.1 Complete Nomenclature

N-(4-Cyano-3-(trifluoromethyl)phenyl)-3-(4-fluorophenyl)sulphonyl)-2-hydroxy-2-methylpropamide

5.1.2 CAS Registration Number

CAS 090357-06-5

5.1.3 Molecular Structure



Molecular weight 430.37 g/mol

5.1.4 Physical Description

CASODEX is a white crystalline powder.

5.2 Materials used in the Synthesis

A list of materials used in the synthesis is included in Section 15

is included in Section 15. This agreement relates to the total discharge of aqueous effluent from the site, which includes but is not limited to the manufacture of CASODEX.

North West Water PLC have been informed of the intention to manufacture CASODEX and have not seen it necessary to impose any specific limits for emissions from the CASODEX process.

6.1.2 Major Requirements of the Agreement

Flow	1.2 million gallons/day up to a maximum of 7 million gallons /week.
COD	88,200 lbs / week
Total Solids	500mg/litre
pH	6.0 - 9.5

REDACTIONS MADE
BY APPLICANT

6.1.3 Non-aqueous Liquid Wastes

Non-aqueous liquid wastes are segregated, where possible, into separate components. These components are transported to specialised operators for recovery for non-pharmaceutical use. Where segregation and recovery is not feasible the streams are collected together in a common site system for high temperature incineration in a licensed facility off-site.

In this facility a destruction efficiency of >99.99% is assumed for all organic species. The flue gasses are treated to remove pollutants prior to discharge to atmosphere. The treatment consists of rapid quenching of the stream to minimise secondary reactions followed by wet scrubbing and particulate removal. The facility meets all relevant operating and discharge permits.

The facility currently used by ZENECA is

Cleanaway Ltd
Bridges Road
Ellesmere Port
Cheshire
L65 4EQ

Cleanaway Ltd is authorised by Her Majesty's Inspector of Pollution. The authorisation number is AG 8233

All contractors are regularly audited by ZENECA.

6.1.4 Air Emissions

All air emissions from the manufacturing facilities are in compliance with local and national legislation. Limits applied by Her Majesty's Inspector Of Pollution are contained in the site's authorisation, number AK 4079 appended in Section 15

6.1.5 Control of Air Emissions

Emissions from ICI 176334 production are discharged in such a manner as to comply with local legislation. Where appropriate emissions are discharged through scrubbers or are controlled by installing cooled condensers on reactors.

Monitoring to ensure compliance is carried out where specified in the site's Authorization for operation or where deemed appropriate by the site's management.

6.1.6 Treatment of Solid Waste Arisings from Production of ICI 176334

All solid wastes are collected as part of a site-wide system and stored temporarily, in appropriate containers, in a specially designated area. The storage and treatment of the wastes are controlled by a licence from the local waste disposal authority. The licence is numbered 60909 and has been renewed in 1992. The site is regularly inspected for compliance by the Waste Disposal Authority and permission for continuing operation is dependant on full compliance with the terms of the licence. A copy of the licence is included in Section 15.

All organic wastes are transported, by licensed carriers, to an off-site facility for high temperature incineration.

In this facility a destruction efficiency of >99.99% is assumed for all organic species. The flue gasses are treated to remove pollutants prior to discharge to atmosphere. The treatment consists of rapid quenching of the stream to minimise secondary reactions followed by wet scrubbing and particulate removal. The facility meets all relevant operating and discharge permits.

The facility currently used by ZENECA is

Cleanaway Ltd
Bridges Road
Ellesmere Port
Cheshire
L65 4EQ

REDACTIONS MADE
BY APPLICANT

Cleanaway Ltd is authorised by Her Majesty's Inspector of Pollution. The authorisation number is AG 8233

All contractors are regularly audited by ZENECA.

6.1.7 Emissions due to the manufacture of ICI 176334

It is estimated that less than 2.0 Kg/year of ICI 176334 will be emitted to waste water systems as a result of production of the active material. Emissions of other materials will be controlled so as to ensure that discharges remain within existing permitted levels and have no effect on either the treatment processes or the wider environment.

6.1.8 Effect of Approval on Compliance with Current Limits at the Production Site

The production of ICI 176334 will be controlled so as to ensure the site continues to meet all the relevant Agreements, Authorisations and Permits. There will be a minimal increase in the amount of materials discharged from the site which will be controlled using existing systems. The nature and amounts of these materials is such that they will be accommodated within the terms of the existing permits and authorisations. The relevant authorities have been informed of the proposals to manufacture ICI 176334 and have raised no objection.

6.2 Formulation of Drug Product

All emissions from the processing facilities at Plankstadt are treated in accordance with local legislation.

6.2.1 Aqueous waste

All aqueous wastes from the formulation of CASODEX are transferred to the sites effluent system. The total effluent from the site is settled to remove solids and the pH adjusted to between 6.5-8.5 before being discharged to the local sewerage treatment plant. All discharges to the treatment plant are made under an agreement between ZENECA and both the Landratsamt Heidelberg and Gemeinde Plankstadt.

It is estimated that less than 20kg/year of CASODEX is discharged to the sewage system.

6.2.2 The Major requirements of the Agreement are:-

Flow	7763 cubic meters/week
TOD	2058 mg/l
pH	6.5-8.5
Temperature	< 35°C
Heavy metals (Cu Zn Pb)	each less than 1ppm
Hg	0.05 ppm

REDACTIONS MADE
BY APPLICANT

6.2.3 Air Emissions

All discharges from the plant are either filtered or passed through wet scrubbers to prevent the discharge of Casodex. The aqueous effluent from the scrubbers is passed to the site effluent system for treatment. Used filters are sent for incineration at a facility approved by the Authorities as part of the site's system for disposing of solid wastes.

6.2.4 Solid Wastes

All solid wastes are collected as part of a site wide system and stored temporarily, in appropriate containers, in a specially designated area. The disposal of solid wastes is controlled by a licence from the Regierungspraesedeum Koeln.

All wastes are transported by licensed contractors to an approved incineration facility. This facility operates under a licence from the local authority and meets all relevant operating and discharge consents.

The contractors currently used by ZENECA are:

GVS Gmbh and Company KG
Otto Hahn Strasse 50
68168 Mannheim

GVS Gmbh and Company KG is authorised by the Bezirksregierung Munster. The permit number is 0000619.

All contractors are audited by ZENECA.

6.2.5 Effect of Approval on Compliance with Current Limits at the Production Site

The production of the CASODEX drug product will be controlled so as to ensure the site continues to meet all the relevant Agreements, Authorisations and Permits. There will be a minimal increase in the amount of materials discharged from the site which will be controlled using existing systems. The nature and amounts of these materials is such that they will be accommodated within the terms of the existing permits and authorisations. will have no impact on compliance with current environmental legislation and permits.

REDACTIONS MADE
BY APPLICANT

6.3 Final Packing and Distribution

All wastes are collected into a centralised system for disposal by licensed contractors. Where appropriate materials are incinerated in a facility approved by the local authorities.

The only discharges to water result from cleaning operations and these will not cause the breach of an existing permits and consents.

The contractors currently used by ZENECA are:

Lancaster County Solid Waste
Management Authority Resource
Recovery Facility
Route 441 South
Bainbridge, PA 17502

No discharges of materials to air will result from the proposed activity.

6.4 Compliance Statements

ZENECA Pharmaceuticals Group, a Business Unit of ZENECA Inc., states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Casodex at its facilities in Newark, Delaware, as well as emission requirements set forth in applicable Federal, State and local statutes, and regulations.

Compliance statements for the Macclesfield and Plankstadt facilities are appended.

**REDACTIONS MADE
BY APPLICANT**

SECTION 7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

7.1 Summary of Results of Physical Testing

7.1.1 Water Solubility

Mean solubility in water at 25°C = 2.77ppm (SD = 0.06)

A graph plotted of mean concentration (ppm) against time (days) shows that equilibrium was reached after 3 days.

7.1.2 Hydrolysis

After 5 days at 50°C, less than 10% hydrolysis occurred at pH 5, 7 and 9. CASODEX bulk drug is, therefore, considered to have a half-life equal to or greater than one year at 25°C.

Hydrolysis Rate Constant $K = 2.2 \times 10^{-8} \text{S}^{-1}$

7.1.3 Dissociation Constant

CASODEX bulk drug has a solubility of $6.4 \times 10^{-6} \text{M}$ in water.

The Environmental Assessment Technical Assistance Handbook states that chemicals with a water solubility below 10^{-5}M need not be tested. No further work is required for the estimation of the dissociation constant.

7.1.4 n-Octanol/Water Partition Coefficient (log P)

	Sample Concentration (ppm) 1000	100
log P	2.35	2.54
Std. Dev	0.02	0.08

REDACTIONS MADE
BY APPLICANT

7.1.5 Vapour Pressure

CASODEX melts at 191-193°C. The structure of the material is such that it would not be expected to sublime therefore ZENECA believes that the vapour pressure will be very low and therefore not relevant to the environmental assessment.

7.2 Summary of Biological Testing

7.2.1 Biodegradability

Biological Oxygen Demand (28days) = 0
Carbon Loss = 97%
Test Substance Loss = 23%

REDACTIONS MADE
BY APPLICANT

Note: The carbon loss (from solution) is attributed to the insoluble nature of CASODEX and not to biodegradation.

7.2.2 Anaerobic Biodegradability

Anaerobic Biodegradation = 0
Test Substance Loss < 8%

Note: The carbon loss (from solution) is attributed to the insoluble nature of CASODEX and not to biodegradation.

7.2.3 Chronic Toxicity to Daphnia Magna

TIME (days)	LC 50 (mg/l)	95% Confidence Interval	Calculation Method
1	>5.3	-	-
2	>5.3	-	-
4	>5.3	-	-
7	>5.3	-	-
14	4.0	3.5-4.6	Moving angle method
21	3.2	2.9-3.6	Moving angle method

No observed effect concentration (NOEC) = 5.6 mg/l (Mean measured)

Acute testing for toxicity to Daphnia Magna was not performed due to limited solubility of CASODEX. The highest concentration tested (5.6 mg/l) being higher than the aqueous solubility level of 2.77mg/l. It is therefore judged that the 48hr LC50 of >5.3 mg/l quoted in the report is the best estimation of the acute toxicity of CASODEX.

7.2.4 Toxicity to Blue Green Algae *Microcystis aeruginosa*

No observed effect (P=0.05) concentration (NOEC) = 1.1mg/ml

Median effective Concentration, (EC 50) > 1.1 mg/l

REDACTIONS MADE
BY APPLICANT

7.2.5 Toxicity to Green Algae *Selenastrum capricornutum*

No observed effect (P=0.05) concentration (NOEC) = 1.1mg/ml

Median effective Concentration, (EC 50) > 1.1 mg/l

7.2.6 Soil Sorbtion and Desorbtion

Results based upon mean measured concentrations as mg. CASODEX per litre

SOIL	pH	Koc
1	5	561
2	5.8	612
3	7.7	420

7.3 Metabolites

CASODEX is a racemate (50:50) with its antiandrogenic activity being almost exclusively exhibited by the R-enantiomer; the S-enantiomer is essentially inactive. CASODEX is extensively absorbed and is excreted almost equally in urine (36%) and faeces (43%) over a 9 day collection period; the incomplete recovery (15%) is a consequence of the slow elimination of (R)-CASODEX from the plasma. No measurable concentrations of metabolites have been detected in the systemic circulation, but two polar metabolites of CASODEX were detected in urine with virtually no parent compound present. The two urinary metabolites are the glucoronide conjugates of CASODEX and hydroxy-CASODEX, the latter being hydroxylated in the monofluorophenyl ring. CASODEX and hydroxy- CASODEX are recovered in the faeces, probably as a result of enzyme cleavage of the corresponding glucoronide conjugates by gut flora. Hydroxy-CASODEX has no significant antiandrogenic activity.

Toxicology studies of the metabolites have not been performed.

SECTION 8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1 Maximum Expected Environmental Concentration (MEEC) of Drug Substance

8.1.1 Assumptions in Calculation of MEEC

Fraction of US Population using Waste Water Treatment Plants $F_{(sewered)}$	0.74
Annual US Sewage Flow (SF_{annual})	$3.7 \cdot 10^{13}$ L/yr
Annual Yield of Dry Sludge from WWTP (DS_{annual})	$5.9 \cdot 10^9$ kg/yr
Dilution Rate of Application of Sludge to Agricultural Land (DR_{annual})	0.025
Estimated Annual Volume of Drug Substance (MV_{total})	2000 kg
Fraction of Drug Substance not excreted.	0
Average K_p Casodex	285

The MEEC of Casodex into the environment from use of the drug product is calculated as follows, assuming 100% excretion of the drug and its metabolites.

REDACTIONS MADE
BY APPLICANT

8.2 Calculation of MEEC for Drug Substance

$$\begin{aligned}
 \text{Quantity emitted into WWTPs} &= MV_{(total)} \cdot F_{(sewered)} \\
 &= 2000 \cdot 0.74 \\
 &= 1480 \text{ kg/yr}
 \end{aligned}$$

Based on the distribution between sludge and water

$$K_p = \frac{\text{Concentration in sludge } (C_2)}{\text{Concentration in water } (C_1)}$$

$$285 = \frac{C_2}{C_1}$$

$$C_2 = 285 \cdot C_1 \text{ (equation 1)}$$

Since the total quantity emitted is distributed between the sludge and the effluent the material balance between the compartments is

$$C_1 \cdot SF_{annual} + C_2 \cdot DS_{annual} = 1480 \text{ kg (equation 2)}$$

Substitution for C_2 (equation 1) into equation 2 gives

$$(C_1 * 3.7 * 10^{13}) + (C_1 * 285 * 5.9 * 10^9) = 1480$$

$$C_1 * 3.9 * 10^{13} = 1480$$

$$C_1 = 3.8 * 10^{-11} \text{ kg/kg or } 3.8 * 10^{-5} \text{ mg/kg}$$

$$C_2 = 285 * C_1$$

$$C_2 = 285 * 3.8 * 10^{-5}$$

$$C_2 = 1.1 * 10^{-2} \text{ mg/kg}$$

REDACTIONS MADE
BY APPLICANT

Since the maximum dilution rate resulting from land application of sludge is 0.025 the maximum expected concentration of drug substance assuming 100% land application of all sludge is:

$$\begin{aligned} \text{MEEC}_{(\text{terrestrial})} &= \text{DR}_{\text{annual}} * C_2 \\ &= 0.025 * 1.1 * 10^{-2} \\ &= 2.8 * 10^{-4} \text{ mg/kg} \end{aligned}$$

$$\begin{aligned} \text{MEEC}_{(\text{aquatic})} &= C_1 \\ &= 3.8 * 10^{-5} \text{ mg/L} \end{aligned}$$

8.3 Effect of Drug Substance on the Environment

The lowest "no effect" level of the drug substance on aquatic organisms is 1.1 mg/L. and the MEEC for aquatic systems is $3.8 * 10^{-5}$ mg/L the drug substance is not expected to have any adverse effect on the environment.

The material has a low solubility (2.77 ppm) and whilst mobility could be expected in groundwater it is strongly absorbed to the clay component of soil. Therefore even if low levels are discharged to the environment little will be available to affect biological systems and therefore it is not relevant to carry out further testing.

The total world-wide production is expected to be below 2000 Kg /year therefore although the hydrolysis rate is low it is anticipated that this will provide an effective method of depletion and provide an adequate margin of safety to the environment

8.4 Effect of Other Releases on the Environment

All emissions released during the production of Casodex are made in accordance with the levels set in local permits. Compliance with these levels ensures that any effect on the environment is minimised.

8.5 Effect of Releases on the Workforce.

8.5.1 Standards of control

All emissions of materials into the workplace are controlled with the limits set by the relevant authorities. Where no official limits exist Zeneca establishes internal control values.

Workplace exposures are kept below these levels.

REDACTIONS MADE
BY APPLICANT

SECTION 9. USE OF RESOURCES AND ENERGY

9.1 Energy

The incremental increase of the use in energy as a result of the manufacture of CASODEX is estimated to be less than 2% of the current energy used by the manufacturing facilities. Therefore this increase is not deemed to be significant.

9.2 Effect on Threatened Species and Property of Historic Interest

Each of the manufacturing sites have conducted surveys to identify any threatened or endangered species on or adjacent to their property. None have been identified. There are no properties of historic in the immediate area of the sites.

Given the controls on the manufacturing process and disposal of waste materials there will be no effect on threatened species or property of historic interest.

REDACTIONS MADE
BY APPLICANT

SECTION 10. MITIGATION MEASURES

The measures for controlling emissions from the manufacturing processes are described in Section 6.

ZENECA Pharmaceuticals has a policy of minimising the environmental effects of the manufacture of its products by assessing the environmental impact of new and proposed processes at an early stage in their development. The impact of each process step is evaluated and efforts are made to minimise both waste and energy use. Each new process is subject to a series of hazard studies which evaluate the potential risks to both people and the environment and put in place suitable controls to ensure the risks are minimised.

10.1 Emergency and Spillage Procedures

At each site there is an emergency plan covering all aspects of the site's activities. Plans are in place to contain and remove any spillages or other loss of containment. In the event of a spill or other loss of containment, immediate measures are implemented to control the spill and prevent materials being released off-site, while the relevant supervisor is contacted to assess the situation. Following this assessment the site emergency response coordinator is also notified to further evaluate the situation. If necessary a spillage control team would be requested to respond and implement additional measures if necessary. In all situations the spill is cleaned up and the material disposed of as specified in the Material Safety Data Sheets in such a manner as to minimise risks both to people and the environment. The manufacture of CASODEX will be covered by these arrangements.

10.2 Control of Workplace Exposure

10.2.1 Control Procedures

REDACTIONS MADE
BY APPLICANT

On each site primary control of workplace exposure is by containment within the manufacturing plants. This is supplemented, where appropriate, by local exhaust ventilation. Where necessary personal protective equipment is used to prevent workplace exposure.

10.2.2 Monitoring

Monitoring programmes are in place at each site to ensure that the controls remain effective. These programmes include monitoring both the performance of equipment and sampling the atmosphere in the workplace.

10.2.3 Information and Training

Safety Data Sheets are available at each site for all materials used in the manufacture of Casodex.

All operators are fully trained to understand the hazards of the materials and the procedures in place to prevent emissions to the environment.

10.3 Waste Minimisation

ZENECA Pharmaceuticals has a policy of minimising waste and developing routes of manufacture which have the minimum impact to the environment. The Company's management have programmes in place to ensure these policies are progressed.

REDACTIONS MADE
BY APPLICANT

SECTION 11. ALTERNATIVES TO PROPOSED ACTION

There are no alternatives to the proposed action. Failure to approve the proposed action will result in denying patients with prostate cancer the potential benefits of a novel therapy.

No adverse environmental effects resulting from use of the product have been identified. The actions taken in controlling emissions and disposing of waste materials arising from manufacture will ensure that there are no adverse effects on the environment arising from these activities.

REDACTIONS MADE
BY APPLICANT

SECTION 12. PREPARERS

This assessment was prepared by Martin Rackham, Occupational Hygiene and Environmental Affairs Manager for ZENECA PHARMACEUTICALS. He has a Bachelors Degree in Chemistry and Physiology and a Masters Degree in Occupational Hygiene.

REDACTIONS MADE
BY APPLICANT

SECTION 13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the firm or agency responsible for the preparation of the environmental assessment.



**Martin Rackham MSc BSc MIOH
Occupational Hygiene and Environmental Affairs Manager
International Safety, Health and Environment Department
ZENECA Pharmaceuticals**

REDACTIONS MADE
BY APPLICANT

SECTION 14. REFERENCES

14.1 Methodology for Physical Testing

Test Protocols US Food and Drug Administration Technical Assistance Handbook.

14.2 Methodology for Biological Testing

Aerobic Biodegradability (BOD₂₈)

Test Protocol Organisation for Economic Co-operation and Development Guideline 301 C (UK Version)

Anaerobic Degradation

Test Protocol ISO Committee Draft CD11734

Chronic Toxicity to Daphnia magna

Test Protocol: US Food and Drug Administration Technical Assistance Document 4.09

Algal Tests

Test Protocol US Food and Drug Administration Technical Assistance Document 4.01

REDACTIONS MADE
BY APPLICANT

15. APPENDICES

15.1 Summary Data Charts ICI 176334

Water Solubility	2.77ppm
log p Octanol/Water	2.49
Vapour pressure	Not relevant
Hydrolysis Rate Constant	$2.2 \times 10^{-8} \text{ S}^{-1}$
BOD (28 day)	0
Anaerobic Degradation	0
NOEC daphnea	5.6mg/l
EC50 algae	>1.1mg/l
Soil sorbtion Koc (average)	531

15.2 Estimate of Maximum Yearly Market Volume

Confidential

REDACTION
BY APPLICANT

15.3 Material Safety Data Sheet for CASODEX

These are appended (See pages 32 to 35).

15.4 Materials used in the synthesis of ICI 176334

Confidential

15.5 Other Material Safety Data Sheets

Confidential

15.6 Site Permits, Authorisations & Agreements

Confidential

15.7 Results of Physical Testing

Confidential

15.8 Results of Biological Testing

Confidential

15.9 Certificates of Analysis

Confidential

HAZARD DATA SHEET**ZENECA**

ZENECA Pharmaceuticals

1. IDENTIFICATION

CASODEX

2. PRODUCT DESCRIPTIONAlternative Names

ICI 176,334

N-(4-Cyano-3-(trifluoromethyl)phenyl)-3-((4-fluorophenyl)sulphonyl)-2-hydroxy-2-methylpropanamide

2(RS)-4'-Cyano-3-(fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide

CAS No. : 030357-06-5
 Form : crystalline solid or powder
 Colour : white
 Use : treatment of prostate cancer

3. SUMMARY

May cause reproductive effects in males and females.

Health Hazard Category : A

REDACTIONS MADE
BY APPLICANTOccupational Exposure Limits- Company Internal - 0.01 mg/m³ (8hr TWA)**4. PHYSICO CHEMICAL DATA**

Melting Point (Deg C) : 191-193
 Flammable Powder Class : Group A
 Minimum Ignition Temperature (Deg C) : 500-550
 Minimum Ignition Energy (mJ) : 100-250
 Solubility (Water) : practically insoluble
 Solubility (Other) : soluble in: ethanol acetone and DMSO
 Dissociation constant: >12

5. STABILITY AND REACTIVITY

Hazardous Decomposition Product(s) : None known.

Hazardous Reactions : None known.

(02 Revision: 03)
ZENECA LIMITED(Date: 0293)
(0193 REV03) (Page: 1 -continued)

HAZARD DATA SHEET**ZENECA**

CASODEX

ZENECA Pharmaceuticals

6. STORAGE

Keep container tightly closed.

7. HANDLING

Do not breathe dust. Avoid contact with skin and eyes.
 Atmospheric levels should be controlled in compliance with the occupational exposure limit.

8. PERSONAL PROTECTION

Wear suitable respiratory protective equipment if exposure to levels above the occupational exposure limit is likely. Wear suitable protective clothing, gloves and eye/face protection.

9. SPILLAGE/ACCIDENTAL RELEASE

Moisten spillages with water.
 Ensure suitable personal protection (including respiratory protection) during removal of spillages.
 Transfer to a container for disposal.

REDACTIONS
 BY APPLICANT

10. WASTE DISPOSAL

Disposal should be in accordance with local, state or national legislation.

11. FIRST-AID MEASURES

- Inhalation** : Remove patient from exposure, keep warm and at rest. Obtain medical attention.
- Skin Contact** : Remove contaminated clothing. Wash skin with soap and water.
- Eye Contact** : Irrigate with eyewash solution or clean water, holding the eyelids apart, for at least 10 minutes. Obtain medical attention.
- Ingestion** : Wash out mouth with water. Obtain medical attention.

Further Medical Treatment

Symptomatic treatment and supportive therapy as indicated.

(02 Revision: 03)
 ZENECA LIMITED

(Date: 0293)
 (0193 REV03) (Page: 2 -continued)

HAZARD DATA SHEET**ZENECA**

CASODEX

ZENECA Pharmaceuticals

12. FIRE AND EXPLOSION

The material can form flammable dust clouds in air.
Thermal decomposition will evolve flammable vapours.

Extinguishing Media : water spray, foam, dry powder or
CO₂.

13. HEALTH HAZARD : TOXICITY DATA

Inhalation : Unlikely to be hazardous by acute inhalation.

Skin Contact : Non-irritant following repeated applications to
rabbit skin. Unlikely to cause skin irritation in
man.
It is not a skin sensitiser in animal tests.
Unlikely to cause skin sensitisation.

Eye Contact : Non-irritant to rabbit eyes causing ~~practically no~~
initial pain. **PREDICTIONS MADE**
Unlikely to cause eye irritation in man. **BY APPLICANT**

Ingestion : Unlikely to be hazardous if swallowed.

Long Term Exposure : Short term tests have shown that it is unlikely to
be a carcinogenic hazard to man.

Studies in animals have shown that repeated
ingestion produces adverse reproductive effects. In
male rats reproductive performance was reduced but
was reversible after cessation of dosing. Evidence
of suppressed sexual development was observed in
the male offspring of female rats.
None of these effects are likely to occur in
humans, provided exposure is maintained at or below
the occupational exposure limit.

14. ENVIRONMENTAL INFORMATIONEnvironmental Fate and Distribution

The substance is essentially insoluble in water.
The substance has moderate mobility in groundwater.
In soils of a high clay content, Casodex may be retained, and rendered
immobile.

(02 Revision: 03)
ZENECA LIMITED

(Date: 0293)
(0193 REV03) (Page: 3 -continued)

ZENECA

CASODEX

ZENECA Pharmaceuticals

Persistence and DegradationChemical Oxygen Demand (COD) 1.47gO₂/g.

Biological Oxygen Demand (BOD 28 DAY) zero

The substance shows no evidence for biodegradability in water.

There is no evidence of degradation in water.

Toxicity

LC50 (rainbow trout) (96 hour) (static) >100mg/l.

EC50 (Daphnia magna) (48 hour) >1.0mg/l.

EC50 (bacteria, aerobic) >100mg/l.

EC50 (bacteria, anaerobic) >100mg/l.

EC50 (nitrifying bacteria) >100mg/l.

EC50 (blue-green algae) >1.1mg/l. The no effect concentration was 1.1mg/l.

EC50 (green algae) >1.1mg/l. The no effect concentration was 1.1mg/l.

A study in daphnia has shown that repeated doses produce no adverse reproductive effects up to the concentration of 0.96mg/l.

A study in daphnia has shown that repeated doses produce no adverse effects on length up to the concentration of 0.56mg/l.

WGK 2 (self classification)

15. REGULATORY INFORMATION
USER

Not Classified as Dangerous for Supply.

REDACTIONS MADE
BY APPLICANT

Users should ensure that they comply with any relevant local, state or national legislation.

TRANSPORT

Not Classified as Dangerous for Conveyance.

NDA 20-498
Casodex® (bicalutamide) Tablets
Zeneca Pharmaceuticals, Inc.

Microbiology Review

No microbiology review is required per discussion with the reviewing chemist,
Dr. Moo-Jhong Rhee (product is in tablet form).

NDA 20-498

MAY 26 1995

Zeneca Pharmaceuticals
Attention: Frances Kelleher, Ph.D.
Regulatory Products Manager
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

Dear Dr. Kelleher:

Please refer to your pending September 14, 1994, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Casodex (bicalutamide).

We have completed our review of the Environmental Assessment (EA) section of your submission and have identified the following deficiencies:

General:

The entire environmental assessment document is marked as Confidential. Confidential data and information that are pertinent to the environmental review of a proposed action should be submitted separately as a confidential section (Appendix) to the environmental assessment, however, this information must be summarized in the environmental assessment document to the extent possible. Please note that the environmental assessment document will be releasable under the Freedom of Information Act.

Section 4 - Description of the Proposed Action:

1. Requested approval
 - a. The description of action should also reference your intent to package and distribute product.
 - b. The description of the requested approval should include the applicant's name, drug product application number (if available), drug product name, dosage form, strength, a brief description of the drug product packaging, whether an EA or abbreviated EA is provided and, if applicable, the basis for the abbreviated EA [e.g., Zeneca Pharmaceuticals has filed an NDA pursuant to Section 505(b) of the Food, Drug, and Cosmetic Act for Casodex (bicalutamide) oral tablet 50mg, or an EA has been submitted in accordance with 21 CFR § 25.31a(a)].

- c. The EA should briefly describe the drug's use in the diagnosis, cure, mitigation, treatment or prevention of disease. It should also indicate if the drug is for acute or chronic use, the current and/or expected patient population and Orphan Drug Status, if applicable.

2. **Production Locations:**

- a. Section 5.3 lists four intermediates of the synthesis of the drug substance. The EA should confirm that any isolatable intermediates used in the synthesis of the drug substance are not synthesized at another location. If they are, the name and address of the facility and pertinent information relating to that facility's operations must be provided.
- b. Please explain why the street address where the substance will be formulated is not the same as that provided in Section 3.
- c. The EA indicates that the address given for final packaging in the USA is also a distribution center in the USA. Please explain why this address is not the same address as that provided in Section 3.

3. **Disposal Locations:**

It is not clear whether the reference to "relevant local authorities" refers to authorities with respect to the addresses identified in this section or other unspecified locations. Specific locations of product disposal should be clearly stated, and relevant incineration permit numbers should be provided.

4. **Types of environments at and adjacent to above locations:**

This section will need to be expanded if intended product disposal locations are other than those listed in this section of the EA.

Section 5 - Identification of Chemical Substances that are Subject to the Proposed Action:

1. Please provide the molecular weight for the substance.
2. The EA lists synthesis starting materials, intermediates and other reagents but does not list additives. If additives are "not applicable," it should be specified as such in the EA. In addition, starting materials and intermediates should be identified by CAN registration number.
3. Impurities are not listed in this section of the EA. Appendix 3 to the EA, Certificate of Analysis, says "Complies" with regard to "Related Impurities." Any impurities associated with the product should be listed in Section 5, identified by CAN registration number. In addition, the percentage of each impurity must also be included.

Section 6 - Introduction of Substances into the Environment:

1. Specific makeup of waste streams should be identified for all parts of the process.
2. The EA should indicate the identification number of the agreement with the privately owned sewage treatment plant and information on emissions related specifically to production of Casodex. The total amount of Casodex emitted in this waste stream is said to be less than _____ per year, however, no concentration data are provided.
3. Non-aqueous liquids are said to be separated into components and transported to "specialized operators" for recovery for non-pharmaceutical use. Precise composition and disposition of these components should be provided. Those components that cannot be separated are mixed in a common system for high temperature incineration at an off-site facility. The EA should provide the location of this facility either in Section 6 or in Section 4 and should provide applicable license or permit numbers.
4. Air emissions are said to be subject to scrubbing to maintain compliance, however, information concerning specific permit identification or emission rates was not provided.
5. Solid wastes from production are stored at a "specially designated area" but no details of specific storage conditions are provided. The EA indicates that "storage and treatment of the wastes are controlled by a license from the local waste disposal authority", however, no license identification or terms of agreement are provided. Organic wastes are transported off-site for incineration as described above. This same type of discussion is provided regarding the formulation of Casodex, however, no details regarding the waste stream quantities or license identification is provided.
6. EA should include copies of specific permits, consent decrees and administrative orders currently in place and reference to specific applicable Federal, State, and local statutes and regulations. Statement of compliance in UK should be from regulating agency rather than from Zeneca. Statement regarding German compliance should be provided in English (certified copy) to facilitate review.
7. Although occupational exposures (in general) are discussed in Section 10 - Mitigating Measures, no occupational exposures are discussed for any specific location in this Section as required.
8. The discussion of the effects of the action on current emissions requirements is adequate only if information on specific statutes, regulations and permits is included.
9. Other than the expected emission of Casodex itself (less than _____ year for production and less than _____ year for formulation), no emissions estimates are provided.

Section 7 - Fate of Emitted Substances in the Environment:

1. Please include the form that the active ingredient exists *in vivo*. In addition, the metabolites and their relative toxicity to the parent compound and the percentage of dose excreted as unmetabolized Casodex or metabolites should be provided, if known.
2. The relevant physical properties of the drug substance or its excreted metabolites should be provided. These should be used to predict which environmental compartments (air, soil, or water) will be likely to contain the emitted drug substance or metabolites as a result of patient use of the drug substance.
3. Please explain the reason why vapor pressure is considered "not relevant."
4. Methods used to measure physical constants should be referenced in the EA. Any significant deviations from EATAD methods cited in the EA should be described and discussed as to any impact on the conclusions regarding the environmental fate of the drug substance.

Section 8 - Environmental Effects of Released Substances:

1. The source of the K_p of 1,930 should be given. In addition, the relatively low water solubility and the high ratio of sludge-bound drug substance to its water concentration requires more information about the fate and effects in the terrestrial compartment. At a minimum, soil biodegradation should be measured and the expected environmental concentration compared with terrestrial toxicity data.
2. The EA includes a statement that effects on the environment from production of Casodex will be minimized by compliance with local permits. This statement would be adequate except that the discussions of relevant laws, regulations, and permits in EA Section 6 are also deficient. See comments on that section of the document.

Section 9 - Use of Resources and Energy:

1. The EA includes a statement that the incremental increase in energy use resulting from the manufacture of Casodex is expected to be insignificant. While this statement is likely true (given the small amount of Casodex being produced), some indication of actual current or future energy use should be given to allow an independent assessment.
2. The EA includes a statement that there will be no effect due to controls on manufacturing process and waste disposal. While this statement may be true, no inventory of potentially impacted species or properties is provided to allow independent assessment. Alternatively, if the deficiencies identified in Section 6 of the EA are corrected, concerning introduction of substances into the environment and controls exercised, and if the estimated emitted concentrations

due to patient use are shown to be significantly lower than appropriate No Observed Effects Concentrations in both terrestrial and aqueous compartments, then the above statement may be rendered "adequate."

Section 10 - Mitigation Measures:

1. The EA should provide at least some details of emergency plan.
2. The EA should contain a list of measures routinely used in the production to mitigate the release of materials into the environment (e.g., compliance with Federal, State and local environmental laws, spill prevention plans). If applicable, a brief description of special measures which are taken to mitigate the release of toxic or potentially toxic materials into the environment should be provided [e.g., special handling information in the product labeling, Occupational Safety and Health Administration (OSHA) requirements, incineration, containment procedures]. If there is a discussion of any of these mitigation measures in another section of the EA, reference to that information is adequate. Actual copies of mitigation measures [e.g., standard operating procedures (SOP's), plans, corporate policies, OSHA regulations] are not necessary.

Section 11 - Alternatives to the Proposed Action:

1. This Section should be revised to include an alternative to the proposed action (e.g., one alternative is "no action").
2. If the data generated indicate that there should be no potential adverse environmental impact from the proposed action, the EA should so state.
3. If potential adverse environmental impacts have been identified for the proposed action, the EA should contain a detailed description of the environmental impact including all reasonable alternatives to the proposed action (e.g., no action, measures that FDA or another government agency could undertake, or those the applicant/petitioner would undertake). In addition, the EA should include a description of those alternatives that will enhance the quality of the environment and avoid some or all of the adverse environmental impacts of the proposed action. Furthermore, the environmental benefits and risks of the proposed action and the environmental benefits and risks of each alternative should be discussed.

Section 13 - Certifications:

This section is reversed with Section 12 in the EA. The information provided in the EA for this section, however, relates to environmental compliance. This information is more appropriately discussed in Section 6 of the EA. This section should include a date, signature, and title of the official responsible for certifying that the information presented in the EA is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for the preparation of the EA.

Section 14 - References:

A reference section should be included in the EA listing complete citations for all referenced material. Copies of referenced articles not generally available should be attached.

Section 15 - Appendices:

Both confidential and non-confidential appendices may be included. A list of the appendices should be included in the EA summary document. Typically, the non-confidential appendices should include Material Safety Data Sheet(s) for the drug substance and, if appropriate, drug product and/or proprietary drug substance intermediate, certification and compliance statements, data summary tables, and copies of referenced articles that are not generally available or which were used in support of specific claims in the EA. Proprietary/confidential information and test reports should be included in the confidential appendices.

Data Summary Table:

To facilitate review, the EA should include a data summary table in a non-confidential appendix (EA format item 15).

Test Methods and Report Formats:

Test methods and report formats are provided in the FDA EA Technical Assistance Handbook (FDA, 1987). Equivalent tests, such as those provided by the EPA (40 CFR § 796 and 797), the American Society for Testing and Materials (ASTM), the Organization for Economic Co-operation and Development (OECD) or other validated, peer reviewed methods may be used. Test reports should be provided and should fulfill the FDA reporting requirements included in the FDA EA Technical Assistance Handbook. The expected minimum level of test performance and test reporting should meet the standards of FDA's Good Laboratory Practice (GLP) regulations. Raw test data (e.g., copies of notebook pages, all HPLC chromatograms) should not be included.

Confidential/Non-Confidential Information:

Some of the information that is normally submitted in an EA is available elsewhere in an application. This information may be cross-referenced in the EA, if the information is publicly available. However, the EA should be a stand-alone document, summarizing information that is available elsewhere. The non-confidential parts of the EA will be made public by the FDA in accordance with regulations proscribed by the Council on Environmental Quality, 40 CFR 1508.9 (see 21 CFR 25.31). Therefore, the EA should contain three distinct parts:

- 1) the EA summary document;
- 2) non-confidential appendices; and
- 3) confidential appendices.

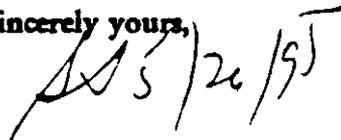
References to non-confidential and confidential appendices may be included in the EA summary document, as appropriate. Confidential data and information that are pertinent to the environmental review of a proposed action and which are submitted in confidential appendices should be summarized in the EA summary document to the extent possible. The EA summary document, non-confidential appendices and finding of no significant impact or environmental impact statement will be made available for public inspection.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Lana L. Pauls, M.P.H.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,



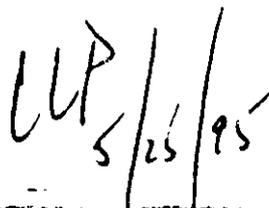
Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-498
HFD-510
DISTRICT OFFICE
HFD-004/PVincent
HFD-510/MRhee/YYChiu
Concurrences: MRhee5.18.95/Chiu5.22.95

drafted: LLPauls/May 18, 1995/N20498IR.EA/ft/dj/5.24.95

INFORMATION REQUEST (IR)



NDA 20-498

OCT 31 1994

Zeneca Pharmaceuticals Group
Attention: Frances Kelleher, Ph.D.
Manager, Drug Registration
Drug Regulatory Affairs Department
P.O. Box 751
Wilmington, DE 19897

Dear Dr. Kelleher:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Casodex® (bicalutamide), 50 mg tablet.

We have determined that your application will be filed on November 14, 1994. However, in order to complete our review of the sections of your application cited below, we request the following information:

Chemistry/ Manufacturing Controls

1. FDA policy states that any racemic mixture must have a chiral specific identification test and assay for both the drug substance and the drug product. Your submission contains IR and regular HPLC tests only. Are the chiral specific tests available?
1. Please provide a proposed expiration date, based on the available stability data, for your product.
2. In accordance with 21 CFR 314.50(d)(1)(ii)(b), please submit the batch production records for the batches used in the bioavailability and stability studies.

Biopharmaceutics

Please provide individual plasma profiles for Casodex® in all studies performed.

Environmental Assessment

1. Please provide a non-confidential version of the environmental assessment (EA).
2. Please provide the CAS numbers for emissions, and the substances used in manufacturing.
3. Please provide the permit numbers, the authorities who issued them, and the emissions limits.

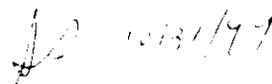
4. Please provide a discussion on the effect of approval on compliance - saying "none" is inadequate.
5. Please provide additional information in regard to the toxicity and the rate of degradation. A depletion mechanism should be established, otherwise, additional effects testing must be conducted.
6. Please provide additional information in regard to the energy and natural resources section (Item 11). In this same section, you must also provide a statement regarding the alternative of "no action".
7. Please provide additional information regarding the percent (%) of energy use, and whether any threatened or endangered species reside in the area of manufacture.
8. Please complete Items 14 and 15 in the EA.
9. Please provide a signature of either the preparer and/or responsible official certifying that the information provided in the EA is true and accurate.
10. Please provide a summary chart containing data on both fate and effects.
11. Please provide a letter from the respective Governmental authorities (England and Germany) stating that the manufacturing facilities and the manufacture of the specific drug are in compliance with their respective environmental laws.

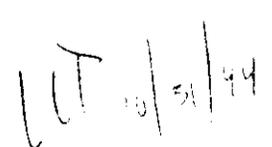
Please provide a prompt written response (with review copies in the appropriately colored jackets) so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Lana L. Pauls, M.P.H.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,


Solomon Sobel, M.D.
Director
Division of Metabolism
and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research



NDA 20-498

SEP 20 1994

Zeneca Pharmaceuticals Group
Attention: Frances Kelleher, Ph.D.
Manager, Drug Registration
Drug Regulatory Affairs Department
P.O. Box 751
Wilmington, DE 19897

Dear Dr. Kelleher:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Casodex® (bicalutamide), 50 mg tablet
Therapeutic Classification: S
Date of Application: September 14, 1994
Date of Receipt: September 14, 1994
Our Reference Number: NDA 20-498

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 13, 1994, in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Should you have any questions concerning this NDA, please contact:

Lana L. Pauls, M.P.H.
Consumer Safety Officer
(301) 43-3510

Sincerely yours,

 9-20-94
Enid Galliers
Chief, Project Management Staff
Division of Metabolism
and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

NDA 20-498
Casodex® (bicalutamide) Tablets
Zeneca Pharmaceuticals, Inc.

Advisory Committee Meeting

No Advisory Committee Meeting was held for this product.

END

MD

J.H.M. RESEARCH & DEVELOPMENT, INC. 5776 SECOND STREET, N.E. WASH. DC 20011