

Division Director's Memorandum

NDA 20-498/s012
Applicant AstraZeneca Pharmaceuticals LP
PO Box 8355
Wilmington, DE 19803-8355

Submission Type Efficacy supplement

Drug
Established name Bicalutamide
Trade name Casodex®
Chemical name Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl) sulfonyl]-2-hydroxy-2-methyl-,(+)

Drug Class Nonsteroidal antiandrogen

Initial Proposed Indication
Immediate hormonal therapy, either alone or as adjuvant therapy to treatment of curative intent, in men with nonmetastatic prostate cancer

Revised Proposed Indications

1. Adjuvant therapy to radical prostatectomy and radiotherapy and radiotherapy of curative intent in patients with locally advanced non-metastatic prostate cancer who have a high risk for disease recurrence and
2. Immediate treatment (monotherapy) of non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated.

Route of Administration Oral
Dosage Form Tablet
Dosing Regimen One tablet daily
Dose 150 mg per day

Dates
Submitted 20 December 2001
CDER stamp date 20 December 2001
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Related IND IND 29,993
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1.0 BACKGROUND:

Treatment options for prostate cancer include radical prostatectomy, radiotherapy, androgen ablation or deprivation therapy (achieved by surgical castration, GnRH analogs, or nonsteroidal antiandrogens), and no active therapy (watchful waiting or surveillance). Selection of the most appropriate treatment depends on many factors that include the clinical stage of the tumor (localized to the prostate, local extension beyond the prostate, or distant or bony metastases), status of regional lymph nodes, degree of tumor

differentiation (generally assessed as Gleason grade), serum prostate specific antigen (PSA) concentration, and the patient's likely life expectancy due to the presence of other co-morbid conditions.

Patients with tumors that are localized to the prostate gland may be cured of their disease by a radical prostatectomy or radiation therapy. Patients with extensive local disease generally are not candidates for a curative procedure, particularly if the tumor is poorly differentiated and the serum PSA is > 10 ng/mL. Such patients are often managed by androgen ablation therapy alone or androgen ablation therapy plus radiotherapy. Patients with bony metastases or non-local soft tissue metastases are generally treated with androgen ablation therapy alone.

A minority of patients in the US (perhaps 10% of newly diagnosed cases) are initially managed by watchful waiting or surveillance. In the US, men who initially receive no active therapy tend to be older (generally > 75 years of age at diagnosis), have low grade and localized tumors, have no symptoms from their prostate cancer, and often have a life expectancy of < 10 years. The rationale for this approach is the expectation that prostate cancer will remain asymptomatic in the majority of these men and they will likely die from a disorder unrelated to prostate cancer.

Growth of prostate glandular tissue is regulated by a complex of growth factors of which androgens play a pivotal role. In most men, prostate cancer is at least in-part an androgen-dependent tumor at the time of initial presentation. Prostate cancer is also partially androgen-dependent in most men at the time of initial progression (either local or metastatic) if the patient has not been treated previously with androgen ablation therapy.

The mode of action of non-steroidal anti androgens (NSAAs) such as Casodex differs from that of medical (i.e. GnRH-induced) or surgical castration. Whereas castration causes a reduction in circulating levels of androgens, Casodex is a competitive antagonist of testosterone and dihydrotestosterone action at the level of the intracellular androgen receptor. Casodex binds competitively and reversibly to the androgen receptor without activating gene expression, and thus inhibits the stimulatory effect of androgens. This action of Casodex and other NSAAs markedly reduces the effects of circulating androgens on prostate cancer cells.

Nonsteroidal anti-androgens (NSAAs) currently available for clinical use in the US include flutamide, nilutamide, and bicalutamide (Casodex). All three are approved for use in the US in combined androgen blockade therapies: Casodex (50 mg per day) and flutamide in combination with a GnRH agonist and nilutamide in combination with surgical castration are approved for the treatment of advanced prostate cancer. No NSAAs is presently licensed in the US as a single agent monotherapy therapy.

In February 2000, AstraZeneca submitted an efficacy supplement (NDA 29-498/s6) for the treatment of locally advanced, non-metastatic (Stages T3-T4, NX, M0) prostate cancer with Casodex monotherapy (150 mg/d). Two pivotal trials (Studies 0306 and 0307) were submitted in support of the application. The trials were similar in design but

conducted in different geographic locales. Neither study was conducted in North America. Both were open-label, active comparator trials that compared Casodex monotherapy to medical or surgical castration. The studies originally included patients with metastatic disease (Stage M1) as well as non-metastatic (M0) disease. Based on an interim analysis of survival, the Data Safety Monitoring Board (DSMB) recommended that Casodex treatment be discontinued in M1 patients. The data at the time of this recommendation indicated that the risk of death was 25% and 31% higher in the Casodex M1 groups compared the castration M1 groups in Trails 0306 and 0307, respectively. The trial continued thereafter with only patients who had Stage M0 disease at the time of entry.

The results of Trials 0306 and 0307, in terms of survival, differed significantly based on the data submitted in the Sponsor's application. In Trial 0306 (n = 140 M0 patients), the risk of death was calculated as 36% lower in the Casodex group while in Trial 0307 (n = 352 M0 patients), the risk of death was calculated as 25% higher in the Casodex group. Both the primary medical reviewer and statistical reviewer recommended that the application not be approved for several reasons that included (1) the conflicting trials results with the larger trial demonstrating a survival disadvantage of the Casodex treatment group for M0 patients, (2) a survival disadvantage for M1 patients treated with Casodex in both treatment groups, and (3) a combined statistical analysis that (a) did not fully meet the Sponsor's original definition of noninferiority and (b) was considered to be statistically inappropriate. Upon learning that the application would not be approved, AstraZeneca withdrew the supplement in December 2000.

Based in part on some preliminary finding in men with prostate cancer and the demonstrated benefits of adjuvant anti-estrogen therapy in women with carcinoma of the breast, AstraZeneca initiated 3 clinical trials (the pivotal trials in support this supplemental NDA) in men with non-metastatic prostate cancer. In each of the trials, the potential benefit of adjuvant therapy with Casodex immediately following either radical prostatectomy or radiotherapy was compared to placebo. In 2 of the trials, the potential benefit of Casodex monotherapy (compared to placebo) was investigated in men with non-metastatic prostate cancer who were to be treated by watchful waiting or surveillance.

2.0 NDA INFORMATION

The clinical component of NDA 20-498/s12 consisted of 3 pivotal Phase III clinical trials (Trials 23, 24, and 25). Efficacy data from each of the Phase III clinical trials were reviewed separately and collectively. The 3 clinical trials were very similar in design. Efficacy assessments were identical across studies, and each trial had nearly identical primary and secondary efficacy endpoints; consequently, the 3 pivotal efficacy trials are presented, for the most part, in an integrated manner in the review that follows.

2.1 Conduct of Trials

The 3 Phase III clinical trials were comparative, multicenter, randomized, double-blind, parallel-group trials. The trials were conducted in (1) North America (Trial 23), (2) Europe (other than Scandinavia), South Africa, Israel, Mexico, and Australia (Trial 24),

and Scandinavia (Trial 25). All patients who qualified for enrollment were randomized in a 1:1 ratio to treatment with either Casodex 150 mg per day or matching placebo. Table 1 provides a comparison of the similarities and differences across the 3 trials. All trials excluded the enrollment of patients with metastatic disease beyond that of positive regional lymph nodes; however, in Trial 23, patients with positive regional lymph nodes also were not eligible. All 3 trials enrolled patients who had had previous therapy of curative intent (i.e., radical prostatectomy or radiation therapy). Trials 0024 and 0025 (but not Trial 23) also enrolled patients whose prostate cancer was being managed by watchful waiting. The maximal period of treatment with study drug varied in each of the studies. In Trial 23, treatment was limited to a maximum of 2 years or until objective disease progression (which ever occurred first). In Trial 25, patients were to be treated indefinitely or until progression of disease. In Study 24, patients with prior therapy of curative intent (adjuvant patients) were to be treated for a maximum of 5 years. Patients in each of the clinical trials were to have a bone scan at 2 years after enrollment unless objective progression of their disease had been confirmed prior to this time.

Table 1 Overview of Phase III Clinical Trials (Similarities and Differences)

Design Element	Trial 23 North America	Trial 24 Europe, South Africa, Israel, Mexico, Australia	Trial 25 Scandinavia
Double-blind, placebo controlled	Yes	Yes	Yes
Number of patients randomized	3292	3603	1218
Tumor staging criteria	T1b-T4, N0 or NX (N+ excluded), M0	T1b-T4, any N, M0	Same as 0024
Permitted standard care			
Radical prostatectomy or radiotherapy	Yes	Yes	Yes
Watchful waiting	No	Yes	Yes
Intended period of randomized treatment	2 yr.	5 yr. for adjuvant patients Until progression in non adjuvant patients	Until progression for all patients
2-yr. bone scan to determine progression	Yes	Yes	Yes
Follow-up for progression and survival	Yes ¹	Yes	Yes

1. Monitored only for survival and serum PSA. Bone scans to be obtained at discretion of investigator.

2.2 Population Disease Characteristics at Baseline

Baseline disease characteristics (other than serum PSA values) in each of the 3 trials are summarized in Table 2. The distribution of disease characteristics are expressed in terms of percentage of patients with the specific characteristic in each category. Within each of the individual trials, baseline disease characteristics were well balanced across the

Casodex and placebo treatment groups. In each of the trials, more than 50% of patients had Stage T1/T2 disease (localized disease) although a slightly greater percentage of patients in Trial 24 (approximately 35%) and Trial 25 (approximately 40%) had Stage T3/T4 disease (locally advanced disease) than in Trial 23 (less than 30%). Based on reported Gleason scores, a greater percentage of patients in Trial 23 (47-48%) had poorly differentiated tumors (Gleason scores of 7-10) than in either Trial 24 (26-27%) or Trial 25 (11-12%). In accordance with the inclusion criteria for Trial 23, all patients had received prior therapy of curative intent with 80% of patients having had a radical prostatectomy. In contrast, 35-37% of patients in Trial 24 and 80-83% of patients in Trial 25 were being managed by watchful waiting (i.e., had not had prior therapy of curative intent) prior to randomization.

Table 2 Disease Characteristics at Baseline (Percentage of Patients) *

Characteristic	Percentage of patients within each category					
	Study 23		Study 24		Study 25	
	Casodex (N=1647)	Placebo (N=1645)	Casodex (N=1798)	Placebo (N=1805)	Casodex (N=607)	Placebo (N=611)
Tumor stage: T category						
T1	9.6	9.7	25.5	25.2	19.8	22.4
T2	62.7	63.2	38.8	41.1	39.7	38.1
T3	27.4	26.9	33.2	31.2	38.9	37.0
T4	0.2	0.2	2.6	2.5	1.5	2.3
Gleason score						
Well differentiated (2,3,4)	4.2	4.8	31.0	31.2	42.7	43.2
Moderately differentiated (5,6)	47.9	48.5	40.5	41.1	43.7	45.2
Poorly differentiated (7,8,9,10)	47.9	46.7	26.7	26.1	11.9	11.1
Lymph node category						
N-	72.0	71.2	61.3	60.4	21.7	20.0
N+	0.1	0.0	2.6	2.7	4.6	4.3
NX	27.9	28.8	36.0	36.9	73.6	75.8
Previous therapy						
Radical prostatectomy	80.3	80.5	46.4	45.0	13.0	13.1
Radiotherapy only	19.7	19.5	18.6	18.0	6.4	4.3
Watchful waiting	0.0	0.0	34.9	36.9	80.1	82.7

* Characteristics are represented as the percentage of patients with the specific characteristic within each category.

Median serum PSA concentrations, both prior to prostatectomy or radiation therapy in patients who had had prior active therapy and at the time of randomization in all patients, are listed in Table 3 for each of the trials. Median serum PSA values prior to prostatectomy or radiation ranged from 7 µg/L in Trial 23 to 16-17 µg/L in Trial 25. Median pre-randomization serum PSA values were lowest in patients who had been treated by radical prostatectomy (median range: below the limit of detection [NQ] to 1.2 µg/L) and highest in patients managed by watchful waiting (median range: 11.0 to 17.8 µg/L). Within each initial treatment group (e.g., radical prostatectomy patients), median

serum PSA concentrations at randomization tended to be lowest in Trial 23 (or Trial 24 for watchful waiting patients) and highest in Trial 25.

Table 3 Serum PSA (Prior to Therapy of Curative Intent and/or at Randomization)

Time of Measurement or Pre-randomization Group	Trial 23		Trial 24		Trial 25	
	Casodex	Placebo	Casodex	Placebo	Casodex	Placebo
PSA ($\mu\text{g/L}$) prior to prostatectomy or radiation therapy						
Number patients ¹	1578	1581	1152	1122	109	99
Median PSA	7.1	7.1	12.0	11.5	17.0	16.0
PSA ($\mu\text{g/L}$) at time of randomization						
Prostatectomy patients						
Number patients	1312	1316	800	795	78	78
Median PSA	NQ ²	NQ	NQ	NQ	1.2	1.1
Radiotherapy patients						
Number patients	323	317	330	310	39	25
Median PSA	2.9	3.0	3.5	3.4	8.2	8.0
Watchful waiting patients						
Number patients	0	0	604	642	483	497
Median PSA	--	--	11.0	11.6	16.6	17.8
All treatments (all patients)						
Number patients	1635	1633	1734	1748	603	600
Median PSA	NQ	NQ	1.3	1.3	12.6	13.8

1. Number of patients for whom PSA values were available.

2. NQ = non quantifiable (i.e., below the minimal detectable value).

Director's Comments

There were significant incongruities between the trials. The most difficult was the low percentage of patients in Trials 24 and 25 with poorly differentiated tumors (Gleason grades of 7-10). Based on the observed incidence of positive bone scans at Study Year 2 (higher in Trials 24 and 25 than in Trial 23), one would have anticipated a higher percentage of poorly differentiated tumors in Trials 24 and 25 than in Trials 23.

Trials 24 and 25, but not Trial 23, allowed the enrollment of patients who were being managed by watchful waiting. Although it is estimated that less than 10% of men in the United States are managed by watchful waiting, this is a more frequently employed therapeutic option in other countries. In Trials 24 and 25, approximately 35% and 80% of patients, respectively, were initially managed by watchful waiting.

2.3 Efficacy

2.31 Endpoints

The protocol-defined primary efficacy endpoints were (1) time to objective disease progression defined as (a) local or distant progression of disease confirmed by bone scan, x-ray, CT scan, magnetic resonance imaging, ultrasonography, or biopsy and (b) death due to any cause in the absence of objectively confirmed progression and (2) time to death. The protocol-defined primary analysis was based on time to objective progression. Because of the potential for assessment bias (the side effects of Casodex treatment were likely to unblind patient treatment assignment and Casodex may independently lower PSA), the FDA (Division of Reproductive and Urologic Drug Products) requested that the primary efficacy endpoints be based only on events that occurred only within 2.5 years of randomization. Because bone scans were required of all patients within 2.5 years of beginning the study, the primary efficacy endpoints were bone scan documented disease progression and death due to any cause in the absence of bone scan confirmed progression

2.32 Efficacy Results

A total of 8,113 patients were randomized to therapy (the intent-to-treat population) in the trials with 3292, 3603, and 1216 patients randomized to Trials 23, 24, and 25, respectively. Patients enrolled into Trial 23 tended to be younger by several years, weighed slightly more, and had lower serum PSA values. Median patient years of follow up for disease progression and survival (efficacy analysis) were 3.2 years (Trial 23), 2.6 years (Trial 24) and 3.0 years (Trial 25). Within each of the individual trials, baseline demographic and disease characteristics were well balanced across the Casodex and placebo treatment groups.

Table 4 lists the number and percentage of patients with bone scan confirmed progression or death in the absence of progression within 2.5 years of randomization in each of the trials. In Trial 23, there was no evidence of a significant reduction in the proportion of patients with disease progression or death in the Casodex group. In each of Trials 24 and 25, the proportion of patients with disease progression or death was lower in the Casodex group compared to the placebo group.

Table 4 Bone Scan Confirmed Disease Progression or Death in the Absence of Progression within 2.5 Years after Randomization

Event	Number (Per Cent) of Patients					
	Study 23		Study 24		Study 25	
	Casodex (N = 1647)	Placebo (N = 1645)	Casodex (N = 1798)	Placebo (N = 1805)	Casodex (N = 607)	Placebo (N = 611)
Positive bone scan	14 (0.9)	11 (0.7)	42 (2.3)	98 (5.4)	22 (3.6)	72 (11.8)
Death in absence of progression	25 (1.5)	37 (2.2)	70 (3.9)	70 (3.9)	41 (6.8)	33 (5.4)
Total (%) of patients	39 (2.4)	48 (2.9)	112 (6.2)	168 (9.3)	63 (10.4)	105 (17.2)

Source: Table A4, pg. A56-A58, ISE

The estimates of the odds ratio (and 95% confidence limit) for disease progression in Casodex-treated patients compared to placebo-treated patients for each of Trials 23, 24, and 25, based on the requested FDA analysis, are listed in Table 5.

Table 5 Odds Ratios for Bone Scan Confirmed Progression or Death in Absence of Progression within 2.5 Years after Randomization

Trial	Treatment	No. of events	No. of patients	% patients with event	Estimate of Odds Ratio	95% confidence limit
23	Casodex	39	1647	2.4%		
	Placebo	48	1645	2.9%	0.81 ¹	0.52 to 1.24 ¹
24	Casodex	112	1798	6.2%		
	Placebo	168	1803	9.3%	0.645	0.500 to 0.832
25	Casodex	63	607	10.4%		
	Placebo	105	611	17.2%	0.515	0.365 to 0.729

¹ Values for Trial 23 calculated by FDA statistician. Values for Trials 24 and 25 calculated by Sponsor. Source: Submission of 17 May 2002, Appendix 2.

Director’s comments

Based on these analyses, it appears that the reductions in the proportion of patients with bone scan confirmed disease progression or death in the Casodex treatment groups in Trials 24 and 25 were statistically significant. However, The actual reductions in the proportion of patients with disease progression or death, however, were relatively small and were 3.1% (Trial 24) and 6.8% (Trial 25).

The differences between the treatment groups are a result of a reduction in bone scan confirmed disease progression and not improved survival as shown by the data in Table 4. .

Because the studies are immature relative to anticipated survival with a median follow up of approximately 3 years, the long-term clinical significance of these modest reductions in bone scan confirmed disease progression is unknown at this time.

To obtain a more complete picture of which treatment subgroup(s) may have derived benefit from treatment with Casodex, the Sponsor was asked to provide additional subgroup analyses based on the patient’s treatment prior to randomization (i.e., radical prostatectomy, radiotherapy, or management by watchful waiting). The descriptive analyses for each of the trials are summarized in Table 6, Table 7, and Table 8.

For each of the trials, the proportion of patients with bone scan confirmed disease progression or death from any cause in the absence of disease progression was numerically lower in Casodex-treated patients in each of the subgroups.

Table 6 Bone Scan Confirmed Disease Progression or Death within 2.5 Years after Randomization (Trial 23: Prior Treatment Subgroups)

Event	Number (per cent) of patients with event			
	Radical Prostatectomy		Radiotherapy	
	Casodex (N = 1322)	Placebo (N = 1325)	Casodex (N = 325)	Placebo (N = 320)
Positive bone scan	10 (0.8)	8 (0.6)	4 (1.2)	3 (0.9)
Death (any cause) in absence of progression	16 (1.2)	22 (1.7)	9 (2.8)	15 (4.7)
Total (%) Patients	26 (2.0)	30 (2.3)	13 (4.0)	18 (5.6)

1. Patients previously managed by watchful waiting were not eligible for this Trial.

Source: Submission of 3 April 2002, Appendix 3.

Table 7 Bone Scan Confirmed Disease Progression or Death within 2.5 Years after Randomization (Trial 24: Prior Treatment Subgroups)

Event	Number (per cent) of patients with event					
	Radical Prostatectomy		Radiotherapy		Watchful Waiting	
	Casodex (N = 835)	Placebo (N = 813)	Casodex (N = 335)	Placebo (N = 325)	Casodex (N = 628)	Placebo (N = 666)
Positive bone scan	12 (1.4)	27 (3.3)	11 (3.3)	28 (8.6)	19 (3.0)	43 (6.5)
Death (any cause) in absence of progression	17 (2.0)	16 (2.0)	13 (3.9)	8 (2.5)	40 (6.4)	46 (6.9)
Total (%) Patients	29 (3.5)	43 (5.3)	24 (7.2)	36 (11.1)	59 (9.4)	89 (13.4)

Source: Submission of 3 April 2002, Appendix 3.

Table 8 Bone Scan Confirmed Disease Progression or Death within 2.5 Years after Randomization (Trial 25: Prior Treatment Subgroups)

Event	Number (per cent) of patients with event					
	Radical Prostatectomy		Radiotherapy		Watchful Waiting	
	Casodex (N = 79) ¹	Placebo (N = 80)	Casodex (N = 39)	Placebo (N = 26)	Casodex (N = 486)	Placebo (N = 505)
Positive bone scan	1 (1.3) ²	7 (8.8)	3 (7.7)	6 (23.1)	17 (3.5)	59 (11.7)
Death (any cause) in absence of progression	5 (6.3)	1 (1.3)	4 (10.3)	3 (11.5)	32 (6.6)	29 (5.7)
Total (%) Patients	6 (7.6)	8 (10.0)	7 (17.9)	9 (34.6)	49 (10.1)	88 (17.4)

1. Does not include 3 patients who were initially treated by radical prostatectomy followed by local radiotherapy.

2. Does not include 1 patient who was initially treated by radical prostatectomy followed by local radiotherapy

Source: Submission of 3 April 2002, Appendix 3.

Director's Comments

The proportion of patients with bone scan confirmed disease progression in the placebo treatment groups in Trial 23 were < 1%; consequently, there was no opportunity for Casodex to be of benefit as these patients, at the time of data cutoff, were essentially free of metastatic disease. Therefore, Based on the findings in Trial 23, there were no data that suggested that patients with early or localized prostate cancer who were treated by either radical prostatectomy or radiation therapy would derive any benefit from adjuvant treatment with Casodex.

Each of the subgroups in Trial 24 had a sizable number of patients. In this Trial, the effect of treatment with Casodex was similar in each subgroup in that the proportion of patients with bone scan documented disease progression (excluding death in the absence of progression) was reduced by slightly more than 50%. The actual percent reductions in each subgroup, however, were relatively small and were 1.9% (radical prostatectomy), 3.5% (watchful waiting), and 5.3% (radiotherapy).

The radical prostatectomy and radiotherapy subgroups in Trial 25 contained only small numbers of patients and very few events. The subgroup of watchful waiting included almost 1000 patients. The proportion of patients with positive bone scans was reduced from 59 of 505 patients (11.7%) in the placebo group to 17 of 486 patients (3.5%) in the Casodex group, a reduction of 8.2%.

The estimate of the odds ratio (and 95% confidence interval) for the proportion of patients with bone scan confirmed disease progression or death in each of the subgroups is listed in Table 9. In all instances other than the subgroup of watchful waiting, the upper bound of the 95% confidence limit exceeded 1.000.

Table 9 Odds Ratios for Bone Scan Confirmed Progression or Death from Any Cause within 2.5 Years after Randomization in Treatment Subgroups

Trial Number	Previous Treatment	Randomized Treatment	Number of events	Number of patients	% patients with event	Estimate of Odds Ratio	95% confidence limits	
23	All treatments	Casodex	39	1647	2.4%	0.81 ¹	0.52 to 1.24 ¹	
		Placebo	48	1645	2.9%			
	Radical prostatectomy	Casodex	26	1322	2.0%	0.862	0.506 to 1.467	
		Placebo	30	1325	2.3%			
	Radiotherapy	Casodex	13	325	4.0%	0.672	0.321 to 1.408	
		Placebo	18	320	5.6%			
24	All treatments	Casodex	112	1798	6.2%	0.645	0.500 to 0.832	
		Placebo	168	1805	9.3%			
	Radical prostatectomy	Casodex	29	835	3.5%	0.616	0.379 to 1.003	
		Placebo	43	814	5.3%			
	Radiotherapy	Casodex	24	335	7.2%	0.625	0.361 to 1.081	
		Placebo	36	325	11.1%			
	Prostatectomy or Radiotherapy	Casodex	53	1170	4.5%	0.619	0.430 to 0.890	
		Placebo	79	1139	6.9%			
	Watchful waiting	Casodex	59	628	9.4%	0.674	0.471 to 0.964	
		Placebo	89	666	13.4%			
	25	All treatments	Casodex	63	607	10.4%	0.515	0.365 to 0.729
			Placebo	105	611	17.2%		
Radical prostatectomy		Casodex	7	82	8.5%	0.836	0.282 to 2.480	
		Placebo	8	80	10.0%			
Radiotherapy		Casodex	7	39	17.9%	0.397	0.123 to 1.285	
		Placebo	9	26	34.6%			
Prostatectomy or Radiotherapy		Casodex	14	121	11.6%	0.584	0.264 to 1.292	
		Placebo	17	106	16.0%			
Watchful waiting		Casodex	49	486	10.1%	0.498	0.338 to 0.734	
		Placebo	88	505	17.4%			

¹ Values calculated by FDA statistician. Other values calculated by Sponsor.

Source: Submission of 3 April 2002, Appendix 4 and Submission of 17 May 2002, Appendix 2.

Director's comment

Although these were exploratory analyses, they support the Sponsor's claim that treatment with Casodex is of some benefit to patients who would otherwise have their prostate cancer managed entirely by watchful waiting. However, it is not known at this time if this benefit (1) extends to the type of patients treated by watchful waiting in the US and (2) extends beyond that of delaying the development of osseous metastases. It also is not known if the benefit of treatment with Casodex in this population would be comparable to that of treatment with a GnRH agonist. GnRH therapy is often used in the US for patients who are not candidates for radical prostatectomy or who decline to have a radical prostatectomy or

radiotherapy. Data from Clinical Trials 0306 and 0307 previously submitted by the Sponsor in NDA 20-498/s006 suggested that Casodex treatment for locally advanced non-metastatic prostate cancer may have been less effective than medical or surgical castration.

The exploratory subset analyses presented in Table 9 also suggests that in Trial 24 adjuvant treatment with Casodex reduced bone scan confirmed disease progression or death in the absence of progression in patients previously treated by radical prostatectomy. However, in Trial 23 (the North American trial and the trial of most relevance to men with prostate cancer in the United State) there was no benefit of Casodex adjuvant therapy.

The proportion of placebo-treated patients with bone scan documented disease progression in the subgroups of radical prostatectomy and radiotherapy were several fold higher in Trial 24 compared to that in Trial 23. It thus appears that patients enrolled into Trial 24 for adjuvant therapy either had less favorable baseline disease characteristics or underwent less effective primary therapies, or both.

A meaningful comparison of baseline disease characteristics in Trial 23 to those in the non-North American trials (Trials 24 and 25) has not been possible, in part, because of failure by the Sponsor to require standardized criteria for assigning Gleason scores to tumor tissues. It is recommended that the Sponsor attempt to have the tumor specimens from the 3 clinical trials reread either centrally or by common criteria to facilitate meaningful cross study comparisons of the degree of tumor differentiation. Obtaining such information might help the Sponsor to identify the group of patients in the US who might benefit from adjuvant therapy with Casodex.

Based on the information in the present application, one can only identify those patients in the US who would not likely derive benefit from Casodex adjuvant therapy (i.e., those types of patients enrolled into Trial 23). The information in the present application does not identify patients with local or locally advanced prostate cancer in the US for whom adjuvant therapy might be of benefit.

2.321 Sponsor's Revised efficacy analysis

On 25 April 2002, a teleconference between the Sponsor and DRUDP was held. The purpose of the teleconference was to provide the Sponsor with an update as to the status of the review and to inform the Sponsor that there were several unresolved review issues. Prior to the teleconference, the Sponsor was provided with a list of questions that included the following:

1. How do you explain the disparity between the efficacy findings of Trial 23 (North American study) and those of Trials 24 and 25?
2. Based on the findings in Trial 23 as of 2 June 2000 (data cut-off date), it appears that Casodex does not offer a significant benefit for men with early prostate cancer who initially are treated by radical prostatectomy or radiation therapy with a curative

intent. In light of this observation, what population of patients with prostate cancer in the US, who are initially treated with radical prostatectomy or radiation therapy of curative intent, would benefit from adjuvant treatment with Casodex?

3. Since there was not a watchful waiting group in Trial 23, can you tell us how men treated by watchful waiting in Trials 24 and 25 compare to those that are likely to be treated by watchful waiting in the US. In particular, how do we know that such patients in the US would respond in a similar fashion as patients in Trials 24 and 25?
4. Please explain the criteria that were used to obtain Gleason scores for the tumors in each of the clinical trials. Did all pathologists use the same criteria?
5. There appears to be a lack of correlation between Gleason scores and pre-procedure PSA values. Patients in Trial 23 had higher Gleason scores (more severe disease) but lower PSA values. How do you explain this?

These questions initially were addressed by the Sponsor during the teleconference and subsequently more completely a written response of 10 May 2002. The Sponsor's written response included the following information and explanations regarding the 5 questions listed above.

1. "The disparity in efficacy findings between Trial 23 and Trials 24 and 25 is related to the immaturity of Trial 23. At data cut-off, only 5.2% of patients had objective progression, with the majority of progression events being non-prostate cancer related deaths."
2. "... on closer examination of the data, by means of the multivariate analysis, several groups of patients were identified in which a clear and consistent benefit for Casodex was found. These patients were as follows:
 - patients who underwent prostatectomy with locally advanced disease and detectable postsurgical PSA levels and
 - patients who underwent radiotherapy with locally advanced disease and elevated preradiation PSA levels

In other words, AstraZeneca believes that patients with locally advanced nonmetastatic prostate cancer who undergo radical prostatectomy but are at high risk for disease recurrence (eg, patients with detectable postsurgical PSA levels) would benefit from adjuvant treatment with Casodex."

3. "These data and guidelines [e.g., the American Urologic Association's Prostate Cancer Clinical Guidelines Panel Report] clearly show that watchful waiting is a well-recognized and practiced treatment option in the US, with the guidelines also recognizing this treatment for the types of patients represented in the watchful waiting cohorts in Trials 24 and 25."
4. "In the Casodex EPC program, the local pathologist assessed Gleason grade. In Trial 23, the actual numerical score was captured, but in Trials 24 and 25, the grade was captured only in terms of well, moderately, or poorly differentiated with guidance that 'well' represented a Gleason score of 2 to 4; moderate, a score of 5 or 6; and poorly, a grade of ≥ 7 ."

5. “The reason for the lack of correlation between Gleason grade and PSA is unclear, but may relate to the fact that they measure different aspects of the tumor. Therefore, as noted in Question 2, AZ does not believe that conclusions can be drawn in this program on the basis of Gleason grade.”

Director’s comment

The Sponsor’s responses to questions 1, 4, and 5 did not provide new information but rather confirmed this reviewer’s initial interpretation of previously submitted information. The Sponsor’s confirmation that Gleason grades or scores were not assigned in accordance with specific guidelines is problematic. Most US physicians consider the Gleason grade of the tumor an important prognostic indicator. The lack of concordance between the US and non-US Gleason grades further limits one’s ability to make comparisons between Trial 23 (the sole US study) and the 2 non-US trials.

2.3211 Casodex Adjuvant therapy;

The Sponsor provided additional information in support of their contention that patients who would benefit from adjuvant Casodex therapy included those with locally advanced disease (Stage T3/T4) prior to initial therapy and either (1) a serum PSA concentration > 0.2 ng/mL following radical prostatectomy or (2) a serum PSA concentration > 10 ng/mL prior to radiotherapy. Table 10 summarizes objective disease progression or death in the absence of progression for the subset of patients with Stage T3/T4 tumors and post prostatectomy PSA values > 0.2 ng/mL.

Director’s Comment

The sponsor initially provided data only for “total events” in each of the 3 trials. These data showed a numeric advantage for treatment with Casodex in terms of a reduction in the proportion of patients with objective disease progression or death. However, among the 3 trials, only the 95% confidence interval for the hazard ratio for Trial 24 did not cross 1.00 (Hazard ratio: 0.55 [95% CI: 0.32-0.96]). Upon request, the Sponsor provided further details regarding each of the trials (i.e., numbers of patients with (1) a positive bone scan, (2) other objective progression, and (3) death from any cause in the absence of objective progression). Review of these additional data (Table 10) indicated that the excess of events in the placebo-treated patients in Trial 23 was a result of (1) objective events other than positive bone scans and (2) deaths that were not due to prostate cancer. These data indicate that there is no substantial evidence Casodex is effective as Adjuvant therapy to radiotherapy (Table 9) or surgery (Table 9 and 10).

Table 10 Patients with Locally Advanced, Non-metastatic Prostate Cancer (Stage T3/T4) and Post Prostatectomy Serum PSA Values > 0.2 ng/mL

Event	Number (%) of patients with Event		Hazard Ratio (95% CL)
	Casodex Number (%)	Placebo Number (%)	
Trial 23			
Total Patients (158/2647 [6.0%]) ¹	83	75	
Total Events	8 (9.6%)	12 (16.0%)	0.53 (0.21, 1.37)
Bone Scan Positive	5	4	
Other Objective Events	2	4	
Deaths ²	1	4	
Trial 24			
Total Patients (277/1648 [16.8%])	133	144	
Total Events	20 (15.0%)	35 (24.3%)	0.55 (0.32, 0.96)
Bone Scan Positive	11	15	
Other Objective Events	4	16	
Deaths	5	4	
Trial 25			
Total Patients (74/159 [46.5%])	33	41	
Total Events	4 (12.1%)	11 (26.8%)	0.49 (0.15, 1.58)
Bone Scan Positive	2	8	
Other Objective Events	1	2	
Deaths	1	1	

1. The value expressed as [%] represents the percentage of all patients treated by radical prostatectomy who were clinical stage T3 or T4 and had a post surgical PSA value > 0.2 ng/mL.

2. All deaths other than 1 case in Trial 23 (placebo group) were due to causes other than prostate cancer. Listings (other than category of "Total Patients") compiled by medical reviewer from Submission of 22 May 2002.

Source: Submission of 10 May 2002, Table 2; Submission of 22 May 2002, Appendix 3.

Included with the written response of 10 May 2002, the Sponsor provided revised wording for the Casodex 150 mg label. The revised **indication** was:

“Casodex 150 mg is indicated as adjuvant therapy to radical prostatectomy and radiotherapy of curative intent in patients with locally advanced non-metastatic prostate cancer who have a high risk for disease recurrence **or** immediate treatment of non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated.”

2.3212 Casodex and Watchful Waiting

The Sponsor’s response regarding the applicability of the non-US watchful waiting patient data to US patients was not adequately addressed in the response of 10 May 2002. The sponsor was therefore asked to provide additional information about the disease characteristics of the watchful waiting patients. The data were to be provided in a manner that would allow the reviewer to determine if patients with minimal or early disease in the watchful waiting subgroups also derived benefit from treatment with Casodex. These data are provided in Table 11 (Trial 24) and Table 12 (Trial 25). Patients with bone scan confirmed progression or death from any cause in the absence of

progression are presented in terms of baseline disease characteristics (clinical stage, Gleason category, and prerandomization serum PSA value.

Director's comments

In each of Trials 24 and 25, approximately two thirds of the watchful waiting patients had localized disease (stage T1 or T2) as would be expected in a US population. However, the effect of treatment with Casodex in this subset was numerically small (e.g. Trial 24: 7.4% progression [Casodex group] vs. 10.0% progression [placebo group]) compared to that in patients with locally advanced disease (e.g. Trial 24: 15.7% progression [Casodex group] vs. 25.5% progression [placebo group]). Patients with locally advanced disease are not generally managed by watchful waiting in the US.

In Trials 24 and 25, 30% and 44% of patients had serum PSA values > 20 ng/mL at randomization. These values suggest more than minimal disease and it is not likely that many of these patients would be managed only by watchful waiting in the US.

The majority of patients had tumor Gleason categories of well differentiated or moderately differentiated. These categories would be compatible with those likely to be observed in a US population. However, because of the lack of standardized criteria for assigning Gleason category, Gleason scores or categories in these studies cannot be readily interpreted.

In summary, this exploratory analysis suggests that many of the patients enrolled into the watchful waiting subgroup would most likely have received active therapy in the US based on present standards of care. Because of this consideration, it is questionable if comparison of Casodex-treatment to that of placebo-treatment is meaningful in estimating the likely benefit of Casodex-therapy for patients presently managed by watchful waiting or surveillance in the US. To be of benefit to US patients with localized prostate cancer who are presently managed by watchful waiting or surveillance, the Sponsor would need to provide data demonstrating that prostate cancer-related morbidity or mortality in “watchful waiting” patients in the US occurs with a sufficiently high incidence that the potential benefits of Casodex treatment (a reduction in the incidence of objective disease progression) would outweigh the adverse effects of treatment with Casodex (e.g., liver toxicity and gynecomastia).

Table 11 Patients with Bone Scan Progression or Death within 2.5 Years of Randomization in Watchful Waiting Group (Trial 24)

Subgroup	Patients in Category		Patients with Event of Progression or Death			
			Casodex		Placebo	
	N	%	N	%	N	%
All Patients	1294	(100)	59/628	(9.4)	89/666	(13.4)
Tumor Stage						
Localized (T1/T2)	996	(77)	35/475	(7.4)	52/521	(10.0)
Locally advanced	298	(23)	24/153	(15.7)	37/145	(25.5)
Gleason category						
Well differentiated	560	(43)	22/272	(8.1)	22/288	(7.6)
Moderately differentiated	463	(36)	19/226	(8.4)	33/237	(13.9)
Poorly differentiated	239	(19)	18/115	(15.7)	31/124	(25.0)
Prerandomization PSA						
≤ 0.2 ng/mL	8	(<1)	0/4	(0.0)	0/4	(0.0)
> 0.2 to 4 ng/mL	252	(20)	6/122	(4.9)	10/130	(7.7)
> 4 to 10	298	(24)	8/156	(5.1)	16/142	(11.3)
> 10 to 20	316	(26)	20/150	(13.3)	16/166	(9.6)
>20	370	(30)	20/170	(11.8)	44/200	(22.0)

Source: Submission of 17 May 2002, Appendix 3.

Table 12 Patients with Bone Scan Confirmed Progression or Death within 2.5 Years of Randomization in Watchful Waiting Group (Trial 25)

Subgroup	All Patients		Patients with Event			
			Casodex		Placebo	
	N	%	N	%	N	%
All patients	991	(100)	49/486	(10.1)	88/505	(17.4)
Tumor Stage						
Localized (T1/T2)	631	(64)	29/304	(9.5)	39/327	(11.9)
Locally advanced	360	(36)	20/182	(11.0)	49/178	(27.5)
Gleason category						
Well differentiated	462	(47)	16/229	(7.0)	24/233	(10.3)
Moderately differentiated	415	(42)	15/198	(7.6)	44/217	(20.3)
Poorly differentiated	101	(10)	17/49	(34.7)	18/52	(34.6)
Prerandomization PSA						
≤ 0.2 ng/mL	2	(<1)	1/2	(50.0)	0/0	(0.0)
> 0.2 to 4 ng/mL	98	(10)	4/39	(10.3)	3/59	(5.1)
> 4 to 10	209	(21)	11/111	(9.9)	10/98	(10.2)
> 10 to 20	237	(24)	7/125	(5.6)	12/112	(10.7)
> 20	434	(44)	26/206	(12.6)	61/228	(26.8)

Source: Submission of 17 May 2002, Appendix 3.

3.0 Safety

The database from Trials 23, 24, and 25 supporting the safety of Casodex 150 mg per day was large. It included 4022 Casodex-treated patients, representing 9,387 patient-years of exposure. Patient exposure to Casodex in the controlled clinical trials was adequate to assess the likely safety profile of Casodex 150 per day in men with prostate cancer.

Most patients in the controlled clinical trials (97.4% Casodex group, 88.2% placebo group) had at least one adverse event. The number of patients with at least 1 drug-related adverse event was approximately 3-fold higher in the Casodex group (90.5%) than the placebo group (31.4%). A greater number of patients in the Casodex group also were withdrawn from treatment as a result of an adverse event (27.7% compared with 9.2% of placebo-treated patients). The number of patients who had at least 1 serious adverse event was similar across the treatment groups (33.6% Casodex group, 32.5% placebo group). Much of the difference between the Casodex and placebo treatment groups in each of the categories of (a) any adverse event, (b) drug-related adverse events, and (c) adverse events leading to withdrawal was due to the pharmacological (anti-androgenic and compensatory estrogenic) actions of Casodex.

Side effects associated with Casodex treatment can be classified for the most part into one of 2 categories: (1) those of a generally non-serious and non-life threatening nature that are due to the pharmacological actions of Casodex and which occur with a high incidence and (2) those that occur in a few percent of patients and which are occasionally serious or even fatal (primarily liver toxicity). The most commonly reported side effects which occurred more frequently in Casodex-treated patients and the percentage of Casodex-treated patients that experienced these side effects were breast pain (73%), gynecomastia (67%), asthenia (11%), vasodilatation (9%), impotence (9%), alopecia (8%), and weight gain (6%). All of these side effects (other than perhaps asthenia and weight gain) are likely to be due to the pharmacological actions of Casodex. Breast pain was reversible in > 90% of patients after cessation of Casodex therapy. Gynecomastia, however, resolved in only 50% of patients after discontinuation of treatment.

Treatment with all nonsteroidal anti-androgens is associated with hepatotoxicity that can be serious and occasionally fatal. Hepatotoxicity appears to occur more frequently in patients being treated with flutamide than other nonsteroidal anti-androgens. In the combined findings from Trials 23, 24, and 25, patients withdrawals due to increased serum ALT and AST values or bilirubin values were higher in Casodex-treated patients (1.2% and 0.4%, respectively) than in placebo-treated patients (0.5% and 0.2%, respectively). Similarly, adverse events classified as serious due to increased serum ALT and AST values or bilirubin values were more frequent in Casodex-treated patients (0.3% and 0.2%, respectively) than in placebo-treated patients (0.0% and <0.1%, respectively). However, the number of patients reported to have died from hepatic failure or a primary hepatic neoplasm was similar in the 2 treatment groups (5 of 4022 Casodex-treated patients and 5 or 6 of 4031 placebo-treated patients).

4.0 RISK BENEFIT ANALYSIS

The actual reduction in the incidence of disease progression or death from any cause in the absence of disease progression within 2.5 years after entry into Trial 24 or Trial 25 was modest. In Trial 24, the proportion of patients with disease progression or death within 2.5 years of study entry decreased from 9.3% (placebo group) to 6.2% (Casodex group). In Trial 25, the proportion of patients with disease progression or death within 2.5 years of study entry decreased from 17.2% (placebo group) to 10.4% (Casodex group). Based on the information presented by the Sponsor, the short term clinical significance of this decrease in Casodex-treated patients is not known as quality of life data (e.g., the proportion of symptomatic versus asymptomatic metastases) were not provided.

There was no evidence of increased disease-specific survival or overall survival for Casodex-treated men in any of the 3 clinical trials. Median follow up time for disease progression was approximately 3 years, a short period for assessing the long term potential benefits of a medical therapy for men with non-metastatic prostate cancer

No medical therapy is presently approved by the FDA as monotherapy for non-metastatic prostate cancer. However, concomitant treatment with a GnRH analog plus flutamide (maximal androgen blockade) and radiotherapy for locally advanced prostate cancer, compared to radiotherapy alone, has been reported to increase survival and has been approved by the FDA.³ In a relatively small study, treatment with a GnRH analog or surgical castration following radical prostatectomy in men with positive regional lymph nodes was reported to increase survival. Thus it is possible, but entirely unproved at this time, that treatment with Casodex (a non-steroidal antiandrogen) might improve disease-specific survival compared to placebo treatment. However the trend seems to indicate a survival disadvantage in Trial 23 for Casodex treated patients. (See Table 13) Long term follow-up of patients in Trials 23, 24, and 25 would be required to investigate this possible benefit.

Table 13 Number and percentages of Deaths in Trials 23, 24, and 25

Cause of Death	Study 23		Study 24		Study 25	
	Casodex N= 1647	Placebo N=1645	Casodex N= 1798	Placebo N=1805	Casodex N= 607	Placebo N= 611
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Prostate cancer	8 (0.5)	3 (0.2)	26 (1.4)	38 (2.1)	24 (4.0)	28 (4.6)
Other	54 (3.3)	58 (3.5)	97 (5.4)	99 (5.5)	45 (7.4)	42 (6.9)
Total¹	62 (3.8)	61 (3.7)	123 (6.8)	137 (7.6)	69 (11.4)	70 (11.5)
Prostate cancer	9 (0.6)	4 (0.2)	47 (2.6)	53 (2.9)	35 (5.8)	42 (6.9)
Other	74 (4.6)	83 (5.1)	132 (7.3)	131 (7.3)	54 (8.9)	43 (7.1)
Total²	83 (5.1)	87 (5.3)	179 (10.0)	184 (10.3)	89 (14.7)	85 (14.0)
Prostate cancer	14 (0.9)	6 (0.4)	56 (3.1)	66 (3.7)	49 (8.1)	56 (9.2)
Other	91 (5.6)	93 (5.7)	168 (9.4)	161 (9.0)	67 (11.1)	50 (8.2)
Total³	105 (6.5)	99 (6.1)	224 (12.5)	227 (12.6)	116 (19.2)	106 (17.4)

1. Data cutoff date of June 2, 2000. Data based on efficacy population.

2. Data cutoff date of 23 February, 2001. Data based on safety population. (Calculated by medical reviewer).

3. Data cutoff date of 28 September, 2001. Data based on safety population. (Calculated by medical reviewer).

Source: Table T5.1, ISE; Table T8.2 Safety Addendum for each of Trials 23, 24, and 25; Submission of 17 May 2002, Appendix 1.

Division director's comment

The proportion of patients who died from prostate cancer (Casodex and placebo treatment groups combined) was approximately 5-fold and more than 10-fold greater in Trial 24 and Trial 25, respectively, compared to that in Trial 23. These observations are consistent with the higher proportions of patients with positive bone scans in Trials 24 and 25.

There is no evidence that treatment with Casodex had a beneficial effect on overall survival in any of the trials based on presently available data.

There is a suggestion that the percentage of deaths due to prostate cancer may be reduced in the Casodex treatment arm in Trial 25. However, there is an opposite trend in deaths due to other causes in this Trial.

Adjuvant therapy or monotherapy with Casodex for men with non-metastatic prostate cancer may be equivalent (perhaps inferior, see supplement 006) but not superior, to treatment with a GnRH analog in terms of reducing disease progression. Both classes of drug (nonsteroidal anti-androgens or GnRH analogs) are thought to be effective in the management of prostate cancer by reducing androgen stimulation of cancer cells. However, non-steroidal anti-androgens compared to GnRH analogs are likely to be less effective *in vivo* in blocking the effects of testosterone as there is a compensatory increase in serum testosterone concentrations during treatment. In some situation, (e.g., men with metastatic prostate cancer), this difference in pharmacological activity may be have clinical consequences such as reduced survival as shown in NDA 20-498/s006 for patients with M1 disease. In other situations, efficacy may be similar and the difference in side effect profiles may be an important consideration in choice of drug. Men treated with a GnRH analog are likely to have more severe and more frequent vasomotor symptoms (e.g., hot flashes), bone loss, and possibly more sexual dysfunction (impotence

and decreased libido). Conversely, a very high proportion of men receiving 150 mg Casodex per day will develop gynecomastia and/or breast pain and are at a slightly greater risk for clinically significant hepatotoxicity.

The risk of serious hepatotoxicity in Casodex-treated patients with prostate cancer is not sufficient to preclude approval of the drug if the benefits of therapy are clinically and statistical significant, such as seen in patients in Trials 24 and 25. The sponsor's proposed labeling is appropriate and appears to be adequate based on spontaneous post marketing safety reports for cases of serious hepatic toxicity in patients receiving 50 mg per day (the presently approved dose). It is possible, however, that hepatotoxicity will be increased in patients receiving 150 mg Casodex per day.

4.1 Risk Benefit Conclusions

The relevance of the findings in Trials 24 and 25 supporting the efficacy of Casodex 150 mg per day treatment to men with prostate cancer in the US who would be treated with Casodex (either adjuvant therapy or monotherapy) is uncertain. Based on the data submitted by the Sponsor, patients similar to those enrolled in Trial 23 who are initially treated by radical prostatectomy or radiotherapy, would derive **no benefit from Casodex adjuvant therapy**. Such patients exhibited too few events of disease progression to warrant treatment with Casodex.

Whether patients who would be treated by **Casodex monotherapy, instead of watchful waiting** in accordance with current medical practices in the US, would derive significant benefit also **is uncertain**. A watchful waiting subgroup was not included in Trial 23. Review of the baseline disease characteristics of the watchful waiting subgroups in Trials 24 and 25 indicated that many of these patients had more advanced stages of prostate cancer than would likely be managed by watchful waiting alone in the US. The Sponsor has not show that patients presently managed by watchful waiting in the US would experience disease progression of sufficient magnitude to warrant treatment with Casodex and the associated side effects.

In summary, the risks of treatment with Casodex 150 mg per day may be justified and acceptable in patients who would derive significant benefit from treatment with Casodex, i.e., patients similar to those enrolled in Trials 24 and 25. However, based on data submitted to date by the Sponsor, it is not clear as to which patients in the US would derive significant clinical benefit from either adjuvant therapy or monotherapy with Casodex. In the absence of such data, the risks of treatment with Casodex for men with non-metastatic in the US are not warranted.

5.0 SUGGESTED REGULATORY ACTION AND RECOMMENDATION TO SPONSOR

The following letter text provides my regulatory action and recommendations:

In your May 10, 2002 communication, you changed your original proposed indication from “immediate hormonal therapy, either alone or as adjuvant therapy to treatment of curative intent, in men with nonmetastatic prostate cancer” to the two revised indications described below:

1. Adjuvant therapy to radical prostatectomy and radiotherapy of curative intent in patients with locally advanced non-metastatic prostate cancer who have a high risk of disease recurrence or
2. Immediate treatment of non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated.

The data supporting both the original and revised indications were reviewed and we have determined that Casodex 150 mg tablets (NDA 20-498) /s012) is not approvable for either the original or revised indications.

Adjuvant Therapy Indication

The adjuvant therapy indication is not approvable because of the lack of demonstrated efficacy of Casodex as adjuvant therapy for patients in the U.S. Trial #23 including absence of efficacy for the U.S. high-risk subset. There was no difference in the proportion of patients with objective progression of disease between the placebo and Casodex treatment groups.

In addition, we were unable to adequately characterize the patients in Trials #24 and #25, both non-U.S. trials, who benefited from Casodex adjuvant treatment because of lack of standardized Gleason scores.

To resolve these deficiencies (1) provide a revised subset analysis based on standardized Gleason scores, as well as clinical stage and serum PSA, and other relevant parameters, to identify the common subset of patients in the non-U.S. and U.S. trials that benefited from Casodex therapy and (2) provide updated 4-year efficacy data that demonstrate that the high risk patient subset [identified in (1)] on Casodex has lower disease progression and no survival disadvantage based on mandatory bone scans and clinical outcome data.

You must study Casodex as an adjuvant therapy in U.S. patients who are at high risk for recurrence using survival and objective progression (i.e. protocol mandated bone scans) as co-primary endpoints.

Immediate Treatment

Localized. The immediate treatment indication for localized prostate cancer is not approvable because the relevance of the efficacy findings in Trials #24 and #25 to patients in the U.S. who would otherwise be managed by watchful waiting according to present standards of care has not been demonstrated. The comparability of the non-U.S. study population and the U.S. study population who would otherwise undergo watchful waiting has not been established.

To resolve this deficiency, provide data that demonstrate that the non-U.S. watchful waiting groups in Trials #24 and #25 are comparable to patients who are treated by watchful waiting in the US. In addition, provide standardized Gleason scores and updated 4- year efficacy data that demonstrate that the watchful waiting subsets from #24 and #25 on Casodex have lower disease progression based on the additional mandatory bone scans. Provide survival data from these subsets.

In addition, you must study Casodex monotherapy compared to placebo in U.S. patients who are appropriate for watchful waiting. This study must demonstrate efficacy using objective disease progression (i.e. protocol mandated bone scans). Survival data must be obtained.

Locally Advanced Disease. Patients with locally advanced non-metastatic prostate cancer treated with immediate Casodex monotherapy may incur a survival disadvantage compared to patients treated with current U.S. standard of care as evidenced by NDA 20-498/006. Therefore, comparison of the efficacy of Casodex therapy for disease progression and survival to that of placebo is not sufficient.

You must study Casodex monotherapy against castration in locally advanced ,non-metastatic U.S. patients to demonstrate efficacy of Casodex using objective progression (i.e. protocol mandated bone scans) and survival as co-primary endpoints.

Please submit all protocols for comment to the Division prior to initiation.

Daniel A Shames MD
Director,
DRUDP/ CDER/FDA