

Overview for Oncology Drugs Advisory Committee
December 18, 2002 Meeting
NDA 20-498/s012

Drug

Established name Bicalutamide
Trade name Casodex

Applicant AstraZeneca Pharmaceuticals LP
PO Box 8355
Wilmington, DE 19803-8355

Proposed Indication *Original Indication (Submitted 20 December 2001 with NDA)*
Immediate hormonal therapy or adjuvant therapy to treatment of curative intent in patients with non-metastatic prostate cancer

First Revision of Indication (Submitted 10 May 2002)
Part 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 for disease recurrence or
Part 2: Immediate treatment of non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated

Second Revision of Indication (Submitted 10 May 2002)
Part 1: (Unchanged from 10 May 2002 submission)
Part 2: Immediate treatment of localized non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated

Dosing Regimen One 150 mg tablet daily

1 Background

Casodex at a daily dose of 50 mg in combination with medical or surgical castration is registered world-wide for the palliative treatment of advanced prostate cancer. In some markets, the mode of castration is limited to one or the other method. The product was approved in the US in 1995 for the treatment of metastatic prostate cancer (Stage D2) in combination with GnRH analog therapy.

In February 2000, AstraZeneca submitted an efficacy supplement (NDA 20-498/s006) for the treatment of locally advanced, non-metastatic (Stages T3-T4, NX, M0) prostate cancer with Casodex monotherapy (150 mg/d). Two pivotal trials were submitted in support of the application. The trials were similar in design but conducted in different geographic locales. 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 their recommendation indicated that the risk of death was 25% and 31% higher in the Casodex M1 groups compared to the castration M1 groups in Trails 0306 and 0307,

respectively. The trials continued thereafter with only patients who had Stage M0 disease at the time of entry.

Survival in the M0 Casodex-treated patients, compared to that in the patients treated by castration, differed across the Trials. 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 trial results with the larger trial demonstrating a survival disadvantage in the Casodex treatment group for M0 patients, and (2) 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 supplemental NDA in December 2000.

2 Regulatory History of NDA 20-498/s012

AstraZeneca first met with the FDA in 1995 to discuss their proposed clinical program for the use of Casodex monotherapy (150 mg/d) for the treatment of patients with "early prostate cancer (the EPC Program)." The Sponsor indicated that several clinical trials would be conducted under the EPC Program. Efficacy of Casodex monotherapy would be assessed in terms of time-to-progression (TTP) and survival. A combined analysis, based on the findings across all of the studies also was proposed. At the meeting, the FDA concurred with the overall design of the clinical program but raised concerns for potential unblinding due to anticipated differences in the incidence of gynecomastia and reduced PSA levels in the Casodex treatment groups relative to the placebo groups. The FDA agreed with the Sponsor that a meta-analysis for survival was acceptable; however, if a time-to-progression endpoint was the only endpoint, 2 trials would be required.

The differences between the Sponsor and the FDA regarding the choice of primary efficacy endpoints and the primary efficacy analyses persisted. The Sponsor's preferred, protocol-defined primary endpoints continued to be (1) *objective disease progression* defined as local or distant progression of disease *confirmed by bone scan, x-ray, CT scan, magnetic resonance imaging, ultrasonography, or biopsy* and (2) *death* due to any cause in the absence of objectively confirmed progression. The Sponsor's preferred, protocol-defined primary efficacy analyses were time to objective progression or death. Because of continuing concern about the potential for assessment bias due to the adverse effects of Casodex treatment, the FDA requested that the primary efficacy endpoints be limited to (1) the events of (a) *bone scan documented disease progression* and (b) *death* due to any cause in the absence of bone scan confirmed progression and (2) *events that occurred within 2 years of randomization*. The 2-year endpoint was selected because all study protocols required that a bone scan be performed at Year 2 unless objective progression had previously been documented. Minutes from the final communication between the sponsor and the Division of Reproductive and Urologic Drug Products in May 2001 stated: "... disagreements remain between the sponsor and the Agency; the Division will need to review the data to determine approvability of the sNDA." NDA 20-498 was submitted on 20 December 2001 and was assigned priority review status.

3 Overview of the Clinical Trials

The Sponsor submitted data from 3 placebo-controlled, randomized, double-blind, parallel-group clinical trials that enrolled men with local or locally advanced non-metastatic prostate cancer. The trials were conducted in (1) North America, predominantly the US [Trial 23], (2) Europe (other than Scandinavia), South Africa, Israel, Mexico, and Australia [Trial 24], and

(3) Scandinavia [Trial 25]. Patients were randomized in a 1:1 ratio to treatment with either Casodex 150 mg per day or matching placebo. In all 3 trials, Casodex was investigated as adjuvant therapy in patients who had had previous therapy for their prostate cancer (i.e., radical prostatectomy or radiation therapy). In Trials 24 and 25 (but not Trial 23), Casodex also was investigated as monotherapy (i.e., in patients who had had no prior therapy and whose prostate cancer would otherwise be managed by watchful waiting or surveillance).

A total of 8,113 patients were randomized to therapy (the intent-to-treat population) with 3292, 3603, and 1218 patients randomized to Trials 23, 24, and 25, respectively. Median patient-years of follow up for disease progression and survival (efficacy analyses) were 3.2 years (Trial 23), 2.6 years (Trial 24) and 3.0 years (Trial 25). In general, baseline patient characteristics across Trials 24 and 25 were similar but differed somewhat from those in Trial 23 in that patients in Trial 23 tended to be younger by several years, weighed slightly more, and had lower serum PSA values.

4 Overview of Efficacy Findings

The percentages of patients with disease progression or death in the absence of disease progression in each of the trials (based on the Sponsor's preferred protocol-defined endpoints) are summarized in Table A.). There was no evidence of benefit from Casodex treatment in Trial 23 (the only trial conducted in the US).

Table A Disease Progression or Death (Based on Sponsor's Preferred Endpoints)

Event	Number (per cent) of patients with event					
	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	21 (1.3)	15 (0.9)	60 (3.3)	116 (6.4)	32 (5.3)	95 (15.5)
Other objective events ¹	10 (0.6)	17 (1.0)	25 (1.4)	85 (4.7)	19 (3.1)	40 (6.5)
Death in absence of progression	52 (3.2)	55 (3.3)	96 (5.3)	92 (5.1)	48 (7.9)	44 (7.2)
Total (%) Patients	83 (5.0)	87 (5.3)	181 (10.1)	293 (16.2)	99 (16.3)	179 (29.3)

¹ Documented by magnetic resonance imaging, computerized tomography, sonography, or biopsy.

The percentages of patients with objective disease progression or death in the absence of objective progression within 2.5 years of randomization (FDA-requested endpoints) are presented in Table B.

Table B Disease Progression or Death (Based on FDA Requested Endpoints)

Event	Number (per cent) of patients with event within 2.5 yr. of randomization					
	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)

The total number and percentage of deaths due to prostate cancer or other causes in each of the trials at the data cutoff for the efficacy analyses (2 June 2000) and the data cutoff for the safety update (28 September 2001) are listed in Table C. There were no significant differences in the percentage of patients who died, either of prostate cancer or of other causes, in the Casodex and placebo groups within each of the trials.

Table C Total Number and (%) of Deaths due to Prostate Cancer or Other Causes

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	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)
Total²	105 (6.5)	99 (6.1)	224 (12.5)	227 (12.7)	116 (19.2)	106 (17.4)

1. Data cutoff of 2 June 2000 (efficacy population). 2. Data cutoff of 28 September 2001 (safety population).

Summary of Efficacy Findings. The Sponsor has provided statistically significant evidence in two non-US clinical trials (Trials 24 and 25) that treatment with Casodex 150 mg per day, compared to treatment with placebo, in men with non-metastatic prostate cancer at entry delayed progression of disease as assessed by the appearance of new bone scan confirmed metastases or death in the absence of objective disease progression. In Trial 23 (the only trial conducted in the US and the trial most relevant to patients in the US), there was no evidence that treatment with Casodex delayed disease progression. The relevance of benefit from treatment with Casodex in the 2 non-US trials for men with prostate cancer in the US who might be treated with Casodex adjuvant therapy or Casodex monotherapy is unknown. There was no evidence that treatment with Casodex improved survival in any of the trials or in the combined analysis. Evidence of improved survival, however, was not anticipated as the survival data were expected to be immature.

5 Unresolved Review Issues

5.1 General Issues

The following issues were identified during the review of this NDA. Input from the Oncology Drugs Advisory Committee is sought regarding these unresolved issues.

Across ongoing Trials 24 and 25, only 15.6% of patients (Sponsor-preferred endpoints) and 9.3% of patients (FDA-requested endpoints) had objective progression of prostate cancer or died from any cause in the absence of disease progression. At the time of data cutoff (June 2000), median follow up was 2.6 years (Trial 24) and 3.0 years (Trial 25). In the absence of meaningful survival data or quality of life benefits, are these studies sufficiently mature to conclude with a reasonable level of confidence that patients treated with Casodex will derive clinically significant long-term benefit?

There was a lack of correlation between Gleason scores and preprocedure PSA values. Patients in Trial 23 had higher Gleason scores (more severe disease) than patients in Trials 24 and 25 but lower PSA values. Patients in Trial 23 also had less progression of disease (unexpected with higher Gleason scores) than patients in Trials 24 and 25. Due to the failure to standardize

Gleason scores (and the questionable validity of the Gleason scores in Trials 24 and 25), it was not possible to adequately characterize the patients in Trials 24 and 25. This deficiency contributed to the Division's inability to identify those patients in the US who might derive significant benefit from Casodex treatment.

The relevance of the findings in Trials 24 and 25 to men with prostate cancer in the US who would be treated with Casodex (either adjuvant therapy or monotherapy) was not clear to the Division.

5.2 Issues Related to Casodex Adjuvant Therapy

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 in the US would derive no benefit from Casodex adjuvant therapy. A supplemental analysis by the Sponsor, based on a subset of patients in Trial 23, also did not show convincing evidence of efficacy for Casodex adjuvant therapy. As described previously, it was not possible (1) to adequately characterize the patients in Trials 24 and 25 because of lack of standardized Gleason scores and (2) to extrapolate the data from patients in Trials 24 and 25 to Trial 23 to identify US patients who might benefit from Casodex adjuvant therapy.

5.3 Issues Related to Casodex Immediate Treatment or Monotherapy.

A watchful waiting (immediate treatment) subgroup was not included in Trial 23. The proposed indication did not adequately identify the population of prostate cancer patients in the US who might derive sufficient benefit from Casodex monotherapy to warrant the risks of treatment.

For local or early disease. The Sponsor did not provide sufficient evidence that the findings in Trials 24 and 25 are relevant to prostate cancer patients in the US who are currently managed by watchful waiting or surveillance. In particular, the Sponsor did not provide data demonstrating that prostate cancer-related morbidity or mortality in patients with localized prostate cancer occurs with a sufficiently high incidence that the potential benefits of Casodex treatment will outweigh the adverse effects of treatment (e.g., gynecomastia, breast pain, and possible liver toxicity).

For locally advanced disease. Trials 24 and 25 were not conducted in accordance with present standards of care for patients with locally advanced, non-metastatic prostate cancer in the US. Since the comparator in these trials was placebo and not active therapy (i.e., medical or surgical castration), it was not possible to adequately address the efficacy of Casodex monotherapy. This is a critical issue since survival may be shortened in patients with locally advanced prostate cancer treated with Casodex monotherapy instead of by medical or surgical castration (the present standard of care in the US for such patients). This concern has been addressed, in part, by the Sponsor's second revision to the proposed indication for Casodex immediate therapy that was submitted on 22 October 2002. The second revision states that Casodex immediate treatment is indicated for the treatment of "localized non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated."