

BACKGROUND INFORMATION ONLY
NOT THE PRIMARY SUBJECT OF PRESENT ODAC MEETING
(REVIEW OF EARLIER SUPPLEMENTAL NDA SUBMISSION)

Deputy Division Director/ Team Leader Memorandum

NDA 20-498 SE1-006

Date NDA submitted: February 25, 2000

Date NDA received: February 25, 2000

Draft review completed: December 15, 2000

Revisions completed:

Sponsor: AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850

Drug: **Generic:** Bicalutamide
Proposed Trade: CASODEX
Chemical: propanamide, N-[4-cyano-3-(trifluoromethyl)-phenyl]-
3- [(4-fluorophenyl)sulfonyl-2-hydroxy-2-methyl-, (+-)]

Route: Oral

Dosage form: Tablets

Strength: 150 milligrams

Proposed indication: Treatment in locally advanced, non-metastatic (Stages T3-T4, NX, M0) prostate cancer

REGULATORY BACKGROUND

On October 18, 1989, Zeneca met with the Division of Metabolic and Endocrine Drug Products and presented the concepts for two "pivotal" clinical trials. These trials would compare CASODEX 50 mg daily monotherapy with castration (medical or surgical) in patients with locally advanced (M0) or known bone metastases (M1). The two trials would be conducted outside the United States.

On July 1, 1992, the sponsor returned for an interim guidance meeting and informed the Division that they had concluded that the 50 mg dose "did not produce the expected efficacy" as monotherapy. Therefore, trials had begun testing doses of 100 mg and 150 mg. Several months after the trials began, the sponsor decided that 150 mg was the more efficacious dose because of a robust PSA reduction with the higher dose. Thereafter the trials (0306,0307) were conducted with the higher dose.

In addition, at the July 1, 1992 meeting, the sponsor informed the Division of their plan to move ahead with a “combination” therapy program, comparing LHRH agonist + CASODEX 50 mg to LHRH agonist + flutamide 250 mg TID. On October 4, 1995, CASODEX received accelerated approval as “combination therapy” for advanced prostate cancer. On December 12, 1997, CASODEX 50 mg received full approval.

During the conduct of these trials, it became apparent to the Data Monitoring Safety Committee that there was a qualitative interaction between survival and stage of disease (reduced survival of M1 patients in the CASODEX group compared to the castration group). Accordingly, all M1 patients were withdrawn from both trials on April 1995. The trials continued with M0 patients only.

On June 16, 1997, the sponsor met with DRUDP in a Pre-sNDA meeting for the 150 mg monotherapy indication. The survival data in the M0 patients from 0306 and 0307 indicated disparate results. At that time, the Division informed the sponsor that “**the inconsistencies in the results between the two studies in the M0 subgroup presents a major review challenge**”. The Division recommended that the sponsor should allow the data to mature and “perhaps, the data would become more consistent over time.

On September 23, 1997, the Division again met with the sponsor to discuss the 150 mg monotherapy program. At that time, the Division stated that “**the study results for trials 0306 and 0307 for M0 patients should not be combined if the results are in opposite directions (cannot pool the results).**”

On November 16, 1999, the sponsor met again with DRUDP and informed the Division of their continued desire to submit this data as an sNDA. The application was submitted on February 25, 2000.

NDA CLINICAL BACKGROUND AND INFORMATION

Scientific Rational: Currently, the approved treatment for patients with advanced prostate cancer is medical castration using an LHRH agonist alone or in combination with an antiandrogen. Medical castration at this time is approved only as “palliative” treatment in these patients. However, there is evidence that early testosterone ablation of patients with advanced prostate cancer provides clinical benefit, including a survival benefit.

However, castration (whether medical or surgical) is associated with several well-recognized adverse effects. These include the development of hot flashes, reduced libido, impotence, asthenia, bone demineralization and the potential for bony fracture. Chronic injections of LHRH agonists can be inconvenient. Surgical castration is often rejected by patients due to concerns related to bodily disfigurement and self-image.

The sponsor’s hypothesis was that CASODEX monotherapy would be as efficacious in the treatment of advanced prostate cancer as castration but that it would obviate many of the recognized adverse effects. The sponsor intended to prove this hypothesis by conducting two identical trials (0306 and 0307) in the appropriate patient population.

Conduct of Clinical Trials (0306 and 0307): They were multicenter, randomized, open-label trials which compared castration with CASODEX monotherapy in terms of time to death, time to treatment failure and time to objective progression. In addition, a comparison of quality-of-life questionnaires and adverse events were also undertaken. Although the trials would be conducted in different geographic locales, (Trial 0306 in Scandinavian countries only and Trial 0307 in other European countries, South Africa and Australia) they were otherwise identical.

The majority of patients in the castration group selected medical castration with ZOLADEX. The initial phase of each trial was designed to compare the “PSA response” of 100 mg and 150 mg doses. The sponsor selected the 150 mg dose after it was recognized that the percent PSA reduction was significantly less with 100 mg than with the 150 mg dose. Once the 150 mg dose was selected, the trials continued with the long-term endpoints. Trial 0306 began recruitment in May 1992 and the last patient entered the trial in June 1993. Trial 0307 began recruitment in January 1992 and the last patient entered the trial in June 1993. Both trials are ongoing. However, the data cutoff for this NDA was June 1, 1999.

The sample size was selected to demonstrate that CASODEX was no more than 25% worse than castration in terms of time to death. The sponsor believed that they could demonstrate “equivalent “efficacy and improved “quality of life”. A total of 1453 patients were randomized in both trials and of those, 492 were classified as M0. Trial 0307 contained 352 M0 patients and Trial 0306 contained 140 M0 patients.

Efficacy Results: As previously mentioned, the results reported for each trial demonstrated a statistically significant disadvantage for time to death in the CASODEX group compared to castration in M1 patients. The data submitted by the sponsor indicated that the risk of death was 25% and 31% higher in the CASODEX M1 groups compared with the castration M1 groups, in Trials 0306 and 0307, respectively.

In the M0 groups, the results of Trials 0306 and 030 were disparate. In **0306** (N=140, M0 patients), the hazard ratio (HR) for risk of death in the CASODEX group compared to castration group was calculated as being 0.65 (upper bound 1-sided 95% CI **0.96**), while the HR in **0307** (N=352, M0 patients) was 1.25 (upper bound 1-sided 95% CI **1.63**). When the M0 subgroups from both trials are combined, the results reveal a hazard ratio of 1.05, with an upper one-sided confidence interval of **1.31**. The sponsor concluded that in the pooled M0 population, survival was not meaningfully different between CASODEX and castration, although they acknowledged that 1.31 was outside the pre-determined limit of 1.25.

The sponsor also argues that data from a quality-of-life questionnaire from approximately one third of the M0 patients who successfully submitted a questionnaire at baseline and at Week 52 demonstrate a benefit for CASODEX in terms of preservation of libido and “physical capacity”.

Finally, the sponsor argues that a single assessment of bone mineral density in 29 patients at a median follow-up of 5.5 years demonstrated significant differences between the CASODEX and the castration groups.

Safety Results: Over 4800 patients received CASODEX at doses of 100 mg daily or greater. The majority of these received 150 mg daily. Approximately 200 patients received doses of at least 200 mg daily. In the “pivotal trials”, 570 patients received at least 6 months of therapy, 435 patients received at least one year of therapy, 326 patients received at least 2 years of therapy, and 127 patients received at least 4 years of therapy. Overall, the total exposure in the pivotal trial alone was estimated as 1924 patient-years. The sponsor studied an appropriate population for the proposed indication as documented by the mean age, weight, and concomitant medical conditions.

The major risks are those related to male breast enlargement and breast pain, several episodes of jaundice or hepatic dysfunction, and the potential for interactions with drugs metabolized by the cytochrome P450 3A4, 2C9, 2C19 and 2D6 enzymes. This drug/drug interaction potential would be particularly important for concomitantly administered drugs with a narrow therapeutic index.

INTERGRATED COMMENTS ON SAFETY AND EFFICACY

1. The sponsor failed to provide substantial evidence that CASODEX 150 monotherapy provides an equivalent survival advantage compared to castration in M0 patients with prostate cancer.

- The individual trials (0306,0307) indicate disparate results with the larger trial demonstrating a survival disadvantage for CASODEX.
- The pooled results do not demonstrate statistical equivalence between the CASODEX and castration groups but the sponsor claims they are “clinically” equivalent. The sponsor had been informed in September 1997 that that pooling is inappropriate when the results are in opposite directions. In addition, the statistical reviewer makes a compelling argument against using the combined results as evidence of efficacy.

2. It is of great concern that the M1 patients who took CASODEX had a significant survival disadvantage. It is difficult to imagine a mechanism whereby M1 patients who take CASODEX have a survival disadvantage while M0 patients have an advantage. In addition, the diagnosis of M0 and M1 patients is not precise in these trials. Because of the high PSA levels in the M0 patients, one can conclude that many of them actually were M1.

3. There was insufficient QOL, adverse event or bone density data to conclude that CASODEX would provide an improved quality of life to prostate cancer patients even if survival benefit had been demonstrated to be equivalent to castration.

4. The adverse effects to the breast and liver might prove to be of significant concern in larger populations as well as the for drug/drug interactions. In fact, it is of great concern that the adverse event of death was more common in the CASODEX treated patients and the cause of this increased mortality is unknown.

Therefore, I agree with the primary medical reviewer's recommendation of non-approval of this supplemental NDA.

NDA PHARMACOTOXICOLOGY INFORMATION

CASODEX is an approved drug. Therefore, the only action that would be required is modification of the label in the carcinogenesis and pregnancy sections to reflect lower multiples of the animal/human exposure ratios.

Reviewer's comment: Since no label will be finalized, these changes are not required at the time of this action. I agree with the comments of the Pharmtox. team.

NDA CHEMISTRY INFORMATION

From A CMC point of view, the supplement may be approved. The EER was found to be acceptable on 12/12/00. The tradename CASODEX 150 mg is acceptable.

Reviewer's comment: I agree with the recommendation of the chemistry team.

NDA CLINICAL PHARMACOLOGY INFORMATION

The biopharmaceutics reviewer recommended approval of this supplement. Recommendations regarding dissolution specifications should be conveyed to the sponsor at the appropriate time. Labeling modifications regarding potential drug/drug interactions should be conveyed at the sponsor.

Reviewer's comment: I agree with the recommendations of the biopharmaceutics team.

DSI INSPECTIONS

Two sites were inspected. At both sites, there were similar findings including deviations from protocol, failure to maintain adequate records and inadequate informed consent procedures. The DSI reviewer believed these problems were unlikely to significantly impact on the data generated. The primary clinical reviewer concurs with this opinion.

Reviewer's comment: I agree with opinion of the DSI and medical reviewer that the deficiencies observed at the clinical sites probably do not have a significant effect on the clinical (especially mortality) evaluation.

REGULATORY RECOMMENDATION

I recommend **non-approval** of NDA 20-498 SE1-006.

The following reasons (deficiencies) for non-approval should be conveyed in a regulatory letter:

1. The sponsor failed to provide substantial evidence that CASODEX 150 monotherapy provides an equivalent survival advantage compared to castration in M0 patients with prostate cancer.

- The individual trials (0306,0307) indicate disparate results with the larger trial demonstrating a survival disadvantage for CASODEX.
- The pooled results do not demonstrate statistical equivalence between the CASODEX and castration groups but the sponsor claims they are “clinically” equivalent. The sponsor had been informed in September 1997 that that pooling is inappropriate when the results are in opposite directions. In addition, the statistical reviewer makes a compelling argument against using the combined results as evidence of efficacy.

2. It is of great concern that the M1 patients who took CASODEX had a significant survival disadvantage. It is difficult to imagine a mechanism whereby M1 patients who take CASODEX have a survival disadvantage while M0 patients have an advantage. In addition, the diagnosis of M0 and M1 patients is not precise in these trials. Because of the high PSA levels in the M0 patients, one can conclude that many of them actually were M1.

3. There was insufficient QOL, adverse event or bone density data to conclude that CASODEX would provide an improved quality of life to prostate cancer patients even if survival benefit had been demonstrated to be equivalent to castration.

RECOMMENDATION TO CORRECT DEFICIENCIES

The sponsor should provide substantial evidence from new clinical trials that CASODEX 150 mg provides an equivalent survival benefit compared to castration while providing improved safety, tolerability and “quality of life” in patients with advanced prostate cancer. The Division would cooperate with the sponsor in the design of these trials

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