HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

31 May 2006

CASODEX 150 mg, film-coated tablet
B/30 (CIP code: 368 138-3)

CASODEX 50 mg, coated tablet
B/30 (CIP code: 339 163-3)

Applicant: ASTRAZENECA

bicalutamide

List I

Date of Marketing Authorisation (AMM):
- 150 mg dose: 22 February 2005
- 50 mg dose: 5 May 1995 (new indication obtained on 17 February 2005)

Reason for request:

- Inclusion on the list of medicines reimbursed by National Health Insurance and approved for use by hospitals and various public services (dosage at 150 mg)

- Inclusion on the list of medicines reimbursed by National Health Insurance and approved for use by hospitals and various public services with the extension of indication “Treatment of locally advanced, nonmetastatic prostate cancer, as adjuvant therapy to radical prostatectomy or radiotherapy” (50 mg dosage)

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Bicalutamide

1.2. Indications

Treatment of locally advanced, nonmetastatic prostate cancer, as adjuvant therapy to radical prostatectomy or radiotherapy.

Benefit/Risk Ratio with Casodex (bicalutamide) is not good for patients with localised tumours (T1T2).

1.3. Dosage

150 mg dose
In adult males, including elderly patients, one 150 mg tablet daily.

50 mg dose
In adult males, including elderly patients, three 50 mg tablets daily.

Treatment is currently recommended for 5 years.

- Renal impairment: no dosage adjustment is necessary.
- Mild hepatic impairment: no dosage adjustment is necessary. Increased accumulation may occur in patients with moderate to severe hepatic impairment.

2 SIMILAR MEDICINAL PRODUCTS

2.1. 2004 ATC Classification

L	Antineoplastic and immunomodulating agents
02	Endocrine therapy
B	Hormone antagonists and related agents
B	Anti-androgens
03	Bicalutamide

2.2. Medicinal products in the same therapeutic category

Comparator drugs:
None

2.3. Medicinal products with the same therapeutic aim

As adjuvant to radiotherapy:
- Goserelin (Zoladex) 3.6 mg and 10.8 mg implant for subcutaneous injection
As adjuvant to radical prostatectomy:
- None

3 ANALYSIS OF AVAILABLE DATA

The data described in the dossier relate to the 150 mg dose. The company submitted a study confirming the equivalence of a single 150 mg dose with 3 x 50 mg tablets.
Three analyses were performed on the studies submitted:

- separate analysis of each study
- pooled analysis of all 3 studies with a median follow up of 5.4 years
- pooled analysis of all 3 studies with a median follow up of 7.4 years.

3.1. Efficacy

A/ Efficacy data with a median follow up of 5.4 years

The dossier included three clinical studies: studies 023, 024 and 025 consisting of a total of 8 113 patients.

All three trials (023, 024 and 025) had a similar design, i.e. randomised double-blind, placebo-controlled phase III trials.

In each trial, patients were randomised (1:1) and received either Casodex 150 mg/day, or placebo.

The analysis was Intent-toTreat (ITT)

Primary outcomes: progression-free survival[1], overall survival.

Secondary outcomes: time to treatment failure, PSA doubling time, safety.

Trial 023 (conducted in North America)

This 2-year trial included 3 292 patients with prostate cancer treated either by radical prostatectomy or by radiotherapy.

Results

72% of patients had localised disease (T1, T2) and 28% locally advanced disease (T3 only). 80% of patients were treated with radical prostatectomy and 20% with radiotherapy.

Mean age of patients was 64.5 years.

The results provided on progression-free survival (primary outcome) are those from an analysis of time to progression and are expressed as event occurrence rate during follow up.

There was no difference in event occurrence rate between the two groups: 10.7% with Casodex compared with 10.3 % in the placebo arm.

Nor was there any difference in overall survival expressed as all-cause mortality rate, i.e. 8.8% compared with 8.1%.

The number of patients with a doubling in PSA value was 12.8% with Casodex and 20.2% with placebo. However, no information was provided on PSA doubling time.
9% of patients in the placebo group discontinued treatment after an undesirable effect compared with 31% in the Casodex group (including 17.5% for breast pain and 11.7% for gynaecomastia).

Information was not provided on impact of treatment on quality of life.

[1] Progression was defined as incidence of clinical signs of progression (confirmed radiologically) or d death from all causes. An isolated increase in PSA was not considered to be evidence of progression.

Trial 024 (mainly conducted in Europe)

3603 patients with prostate cancer were included to receive radical prostatectomy, radiotherapy or watchful waiting. Patients were treated until progression, for a maximum of 5 years.

Results

64% of patients presented with localized (T1, T2) and 36% with locally advanced prostate cancer (including 33% T3).

45% of patients had been treated by radical prostatectomy, 20% by radiotherapy and 35% by watchful waiting.

Mean age of patients was 68.5 years.

The results provided on progression-free survival (primary outcome) are those from analysis of time to progression, and are expressed as event occurrence rate during follow-up.

The event occurrencerate differed between the twogroups, i.e. 22.5% with Casodex compared with 28.1% in the placebo group ($p<0.001$), corresponding to a relative risk of 0.728 (95% confidence interval 0.639–0.830).

There was no significant difference in overall survival expressed as all-cause mortality rate: 17.8% compared with 17.5%.

Seven percent (7.0%) of patients on Casodex and 24.4% of patients on placebo doubled their PSA value. However, there was no information on PSA doubling time.

10.9% of patients in the placebo group discontinued treatment after occurrence of an undesirable effect compared with 29.4% in the Casodex group (including 11.3% because of breast pain and 12.9% because of gynaecomastia).

There was no data on the impact of treatment on quality of life.

Trial 025 (conducted in Scandinavia)

1 218 patients with prostate cancer were included to receive treatment by radical prostatectomy, radiotherapy or watchful waiting. Patients were treated until progression.

Results

60% of patients had localized (T1, T2) and 40% had locally advanced prostate cancer (including 39% T3).

13% of patients had been treated by radical prostatectomy, 7% by radiotherapy and 80% by watchful waiting.

Mean age of patients was 68.5 years.

The results provided on progression-free survival (primary outcome) are from the analysis of time to progression and are expressed as event occurrence rate during follow-up.

The event occurrence rate differed between the two groups: 35.4% in the Casodex group compared with 46.2% in the placebo group ($p<0.001$), corresponding to a relative risk of 0.571 (95% CI 0.477–0.683).

There was no difference in overall survival expressed as all-cause mortality rate between the two groups26.9% for Casodex compared with 25.9% for placebo.

The number of patients whose PSA value doubled was 24.4% in the Casodex group and 39.8% In the placebo group. However, there was no information on PSA doubling time.

8.5% of the placebo group discontinued treatment after an undesirable effect compared with 19.7% in the Casodex group (including 3.1% with breast pain and 2.6% with gynaecomastia).

Reduced libido and increased impotence (assessed by the GRISS[2] questionnaire) was recorded in the Casodex group compared with the placebo group.

Pooled analysis (excluding watchful waiting) of all three studies:

A retrospective analysis was carried out on all patients (principally at the locally advanced stage, in three studies) who had had a radical prostatectomy or radiotherapy. Median follow up of patients was 5.4 years.

- *In the patients receiving Casodex as adjuvant to radical prostatectomy* (n=1719), 90.6% had no lymph node involvement. Tumours were poorly differentiated (Gleason score 7–10) in 57.6% of cases and moderately differentiated (Gleason score 5–6) in 35.7% of cases.
- *In the patients receiving Casodex as adjuvant to radiotherapy* (n=305), 50.9% had no lymph node involvement and lymph node involvement was not specified in 44.7% of cases. Tumours were poorly differentiated (Gleason score 7–10) in 30.4% of cases, moderately differentiated (Gleason score 5–6) in 44.1% of cases and well-differentiated (Gleason score 2–4) in 24.2% of cases.

Analysis of progression-free survival (primary outcome) showed:

- *in the "adjuvant to radiotherapy" subgroup*, a 42% reduction in risk of clinical progression under Casodex compared with placebo (RR=0.58; CI 95% 0.41–0.84)
- *in the "adjuvant to radical prostatectomy" subgroup*, a 29% reduction in risk of clinical progression under Casodex compared with placebo (RR=0.71; CI 95% 0.27–0.89).

No statistically significant benefit in terms of overall survival was demonstrated in either subgroup.

B/ Follow-up data after a median of 7.4 years

Of the 2681 patients with locally advanced prostate cancer, 2024 had an indication for adjuvant therapy including 1719 who had been treated by radical prostatectomy and 305 by radiotherapy.

For adjuvant therapy after radiotherapy in patients with locally advanced prostate cancer, the results of the 3rd analysis of the three pooled studies showed a significant (44%) reduction in risk of clinical progression (95% CI 0.40–0.78).

There was a 12% improvement in overall survival (30.4% of patients had died in the Casodex group compared with 42.4% in the placebo group, RR (risk ratio) = 0.65; 95% CI 0.44–0.95).

For adjuvant therapy after radical prostatectomy, the results of the 3rd analysis confirmed those of the 2nd analysis, i.e. no difference in terms of overall survival compared to placebo (RR = 1.09; 95% CI 0.85–1.39).

There was no change as regards safety of use of the product in comparison with follow up data at 5 years.

[2] Golombok Rust Inventory of Sexual Satisfaction

3.2. Undesirable effects

The most common undesirable effects (from all three studies) in the Casodex group 150 mg compared with the placebo group were gynaecomastia (73.6% versus 7.6%) and breast pain (68.3% versus 8.3%). Incidence of other undesirable effects was similar in both groups.

3.3. Conclusion

Data submitted in this dossier were derived from three studies comparing the efficacy and safety of Casodex at a dose of 150 mg/day with that of placebo, in patients with various stages (localised and locally advanced) of nonmetastatic prostate cancer, for different treatment periods (2 years, 5 years or until progression) and using different treatment strategies (watchful waiting, radiotherapy and prostatectomy).

Data collected in the "adjuvant to radiotherapy" and " adjuvant to radical prostatectomy" subgroups showed that prognostic factors were similar in all the study populations, in terms of disease stage (mainly advanced), number of nodes involved and Gleason score.

Results for subgroups derived from the pooled analysis, with a median follow up of 5.4 years, showed that Casodex affected progression-free survival, with a reduction in relative risk of 29% (95% CI 0.27–0.89) in the prostatectomy subgroup and 42% (95% CI 0.41–0.84) in the radiotherapy subgroup, with no effect on overall survival compared with placebo in either subgroup.

After 7.4 years of follow-up, results for the pooled subgroup of patients with a locally advanced tumour were:

- *As adjuvant therapy to radiotherapy,* Casodex 150 mg reduced the risk of clinical progression by 44% and improved overall survival by12%.
- *As adjuvant therapy to prostatectomy* Casodex 150 mg reduced the risk of clinical progression by 25%, with no improvement in overall survival.

The Committee emphasised that the results of follow up at 7.4 years show:

- no change in the results of each of the 3 trials: there was a reduced risk of progression in the subgroups of patients with a locally advanced tumour in 2 out of the three trials, with no improvement in overall survival.
- there was no benefit in terms of overall survival for the whole population included (all stages combined).
- no benefit in terms of overall survival in the subgroup of patients treated by radiotherapy. Benefit was observed only in the subgroup of patients with a locally advanced tumour.

Undesirable effects are those already described for the 50 mg/day dose, i.e. breast pain and gynaecomastia.

The Committee noted that an alternative medicinal product exists as adjuvant to radiotherapy, goserelin (Zoladex), which in a phase III trial[3], comparing radiotherapy alone to radiotherapy + goserelin (Zoladex), showed a significant improvement in overall survival at 5 years (78% against 62%; p= 0.0002).

[3] Bolla M. et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet 2002;360:103-108.

4 CONCLUSIONS OF THE TRANSPARENCY COMMITTEE

4.1. Actual Benefit

- Prostate cancer is a life-threatening disease.
- These medicinal products are intended for use as curative therapy.
- The efficacy/undesirable effects ratio for these medicinal products in this indication is moderate.
- These medicinal products are first-line therapies.
- There is an alternative drug as adjuvant to radiotherapy (Zoladex [goserelin]).
- Expected Public Health Impact
  - Prostate cancer is a serious and common clinical condition, which constitutes a significant public health burden.
  - The burden induced by nonmetastatic locally advanced stages is moderate because the number of patients involved is small.
  - Improving prostate cancer treatment is a public health need. However, the medicinal product Casodex does not, overall, provide a different response to this need from that provided by existing treatments.
  - In view of the data from clinical trials and taking into account other existing treatments, no impact from Casodex is expected in terms of morbidity and mortality.
  - Consequently, there is no expected public health benefit from the medicinal product Casodex.

The Actual Benefit of Casodex is substantial.

4.2. Improvement in actual Benefit

Casodex (50 mg, 150 mg) does not provide any improvement in Actual Benefit (level V) in the current management of patients with nonmetastatic prostate cancer at a locally advanced stage, as adjuvant therapy to radical prostatectomy or radiotherapy.

4.3. Therapeutic use

The locally advanced stage corresponds to grades T3-T4, N0-N1, and M0 of the 2002 TNM classification.

From the *Association Française d'Urologie* 2002 guidelines, updated in 2004:

''At the locally advanced stage

The different treatment options in locally advanced prostate cancers are mainly:
- combination of radiotherapy and hormone therapy
- surveillance ,with postponement of hormone therapy
- radical prostatectomy, on its own or combined with adjuvant therapy (radiotherapy, hormone therapy)
- hormone therapy.

Stage T3

- The combination of hormone therapy and radiotherapy is currently the standard treatment in locally advanced tumours (T3) for patients with a life expectancy of more than 10 years.
- Neo-adjuvant hormone therapy reduces tumour volume and may decrease the secondary effects of irradiation. Hormone therapy may maximize the effect of radiotherapy and improve results in terms of local control and survival without clinical and biological recurrence.
- Watchful waiting may be offered to elderly patients with a life expectancy of 5 or 10 years or less, who are asymptomatic or who do not want the side effects of treatment, when the tumour is developing slowly. Hormone therapy should be offered when the disease progresses. Regular monitoring is needed.
- - Radical prostatectomy may be offered with a confined low-grade T3 tumour, with PSA<20ng/ml, or when there is a single microscopic tumour spread to a lymph node, found during immediate examination of removed nodes, when life expectancy is more than 10 years. Neo-adjuvant hormone therapy before total prostatectomy is not recommended.
- The use of immediate hormone therapy alone in locally advanced forms, originally reserved for metastatic prostate cancer, is now the subject of consensus among professionals for rapidly developing tumours. Some articles have shown that in these locally advanced tumours immediate hormone therapy is associated with better survival than delayed treatment.

Stage T4

Patients with T4 disease vary as some patients initially have the same prognosis as patients with local and regional spread. Hormone therapy is the treatment of choice in T4 Nx (nodal status not evaluated). There is no evidence that combined hormone therapy and external radiotherapy would achieve better results than hormone therapy alone. The aim of treatment should focus on quality of life.

The available data suggest that Casodex appears to be another option for active hormonal deprivation therapy, when the gold standard hormone supression therapy is active.

4.4. Target population

The target population for Casodex that ofpatients with nonmetastatic locally advanced prostate cancer, for use as adjuvant therapy to radical prostatectomy or radiotherapy.

In France, the estimated incidence of prostate cancer was about 40 000 cases in 2000[4].

The only published data for estimating the proportion of patients diagnosed at the locally advanced stage come from a sample of 5 of the 8 French cancer registries. Of the 1 000 patients who were diagnosed with prostate cancer in 1995, 18% presented with stage T3–T4 or N+[5].

According to an unpublished survey by the company in a representative sample of 98 urologists, 20% of 1 156 patients presented with locally advanced disease at diagnosis. After re-assessment of clinical stage, a further 11% of patients were found to havelocally advanced disease, whereas they had originally been classified as having localized disease.

[4] Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000 (INVS 2003) (Changes in cancer incidence and mortality in France 1978-2000)

[5] Bauvin E. et al. Medical and non-medical determinants of prostate cancer management: a population-based study. Eur J Cancer 2003

The estimated number of patients presenting with locally advanced disease is thus 31%, i.e. 12 400 patients.

One third [6] of patients were managed by watchful waiting or hormone therapy

Based on these data, the estimated target population for Casodex is 8 300 patients a year.

4.5. Transparency Committee recommendations

Casodex 150 mg: The Committee recommended inclusion on the list of medicinal products approved for use by hospitals and various public services

Casodex 50 mg: The Committee recommended inclusion on the list of medicinal products approved for use by hospitals and various public services in the extension of indication.

4.5.1. Packaging: The packaging is suitable for the prescription conditions.

4.5.2. Reimbursement rate: 100%

[6] Louis Harris study 2004