IMPORTANT DRUG SAFETY INFORMATION

Accelerated deaths using Casodex® (bicalutamide) 150 mg in patients with localized prostate cancer otherwise undergoing watchful waiting

Health Canada has withdrawn its approval (Notice of Compliance with conditions) for CASODEX 150 mg.

AstraZeneca

August 18, 2003

Dear Health Care Professional,

RECOMMENDATIONS: It is recommended that clinicians **discontinue CASODEX 150 mg in patients with localized prostate cancer**

BASIS FOR CONCERN: Data from **a planned second analysis** of the Early Prostate Cancer (EPC) trial program shows that at a median 5.4 years follow-up, in patients with **localized prostate cancer otherwise managed by watchful waiting and CASODEX 150 therapy**, there was a trend towards **accelerated deaths** compared to that of placebo.

RESULTS AND EXPOSURE: Patients otherwise undergoing watchful waiting were present in Trials 024 (European trial) and 025 (Scandinavian trial) only. There were no watchful waiting patients in Trial 023 (North American trial). In Trial 025, patients in the **CASODEX arm received 4.6 yrs of therapy** compared with **3.4 years for placebo-treated patients**. In Trial 024, patients received 3.8 years of CASODEX 150 compared with 3.7 years for placebo patients. The overall results in patients with localized prostate cancer otherwise managed by watchful waiting were [196 (25.2%) deaths vs 174 (20.5%) deaths, hazard ratio (HR) = 1.23, 95% CI 1.00, 1.50].

In November 2002, Health Canada granted a Notice of Compliance with Conditions (NOC/c) to CASODEX 150 mg, as immediate therapy in some patients with localized prostate cancer who are inappropriate for surgery or radiation therapy. In this population, CASODEX 150 mg once daily oral therapy was recommended for those who have a PSA doubling time less than (<) 5 years, Gleason grade greater than (>) 6, or PSA values greater than (>) 10. This conditional approval was based on the promising nature of the clinical evidence in patients with this serious disease, and the need for further follow up to verify the clinical benefit. Approval was based on time to objective progression (surrogate endpoint).

AstraZeneca, following discussions with Health Canada, is alerting you to important emerging safety information arising from a planned second analysis (5.4 yr median follow-up) of the Early Prostate Cancer (EPC) trial programme. This international programme of 3 prospective, double blind, placebo-controlled clinical trials (n=8113) compares CASODEX 150 mg vs. placebo, when given in addition to standard care in men with localized or locally advanced non-metastatic prostate cancer. Thus patients received either CASODEX or placebo as adjuvant therapy following primary therapy (radical prostatectomy or radiotherapy), or as immediate therapy in men who would otherwise have been managed by watchful waiting (initiation of therapy only if symptoms or signs of progression occurred). Primary endpoints are progression free survival and overall survival.

For the progression free survival endpoint across the whole programme, there continues to be a significant reduction in the risk of experiencing disease progression (HR 0.73, P<0.0001) after 5.4 years of follow-up. However in view of the estimated median time to disease progression and median survival of 7 and 10 years respectively for this class of patients, assessments have been made after a relatively short follow-up period. Conclusion can only be made regarding early benefits or risks.

As seen in the first analysis (3.3 yr follow-up), in both adjuvant and watchful waiting settings, benefits in terms of reduced risk of disease progression are largest in those with high risk of disease progression (e.g., locally advanced disease, high PSA or high Gleason grade). Health Canada previously assessed CASODEX 150 mg versus castration in the locally advanced patient population and found level 1 scientific evidence (one of the 2 randomized clinical trials) of accelerated deaths in CASODEX 150 mg treated patients.

For overall survival, as with the first analysis, the second analysis showed no difference between any treatment groups for the combined analysis or individual trials.

In exploratory sub-group analysis, some trends were seen in the watchful waiting patient subgroup. A trend was observed towards a survival deficit in the subgroup of patients with localized disease [196 (25.2%) deaths vs 174 (20.5%) deaths, HR = 1.23, 95% CI 1.00, 1.50]. This trend was mostly associated with localized patients at low risk of disease progression. Conversely, in the higher risk subgroup of patients with locally advanced disease, a trend towards a survival benefit was seen, [113(33.7%) deaths vs. 133 (41.3%) deaths, HR = 0.80, 95% CI 0.62,1.04]. As indicated above, Health Canada has not approved CASODEX 150 mg for locally advanced prostate cancer.

Patients treated in the adjuvant setting show no differences in survival, though survival data in this setting are still relatively immature at this time (approximately 10% deaths in adjuvant setting).

In view of these data, and in the absence of factors to suggest high risk of disease progression, it is recommended that clinicians discontinue CASODEX 150 mg in patients with localized prostate cancer otherwise undergoing watchful waiting. It should be noted that metastatic prostate cancer patients taking CASODEX 50 mg per day are not affected by the new information.

The identification, characterization and management of marketed health product- related adverse reactions are dependent on the active participation of health care professionals in adverse reactions reporting programmes. Any occurrences of accelerated deaths or other serious and/or unexpected adverse reactions in patients receiving CASODEX 150 mg should be reported to AstraZeneca at the following address:

AstraZeneca Canada Inc.
1004 Middlegate Road
Mississauga, Ontario
L4Y IM4
Drug Safety Tel: 1-800 433-0733 and Fax: 1-800 267-5743

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed drug use.

Sincerely,

original signed by

Kazimierz R. Borkowski, Ph.D.
Vice President, Medical Affairs
AstraZeneca Canada Inc.

Any suspected adverse reactions can also be reported to:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0201C2
OTTAWA, Ontario, K1A 1B9
Tel: (613) 957-0337 or Fax: (613) 957-0335
Toll free for consumers and health professionals:
Tel: 866 234-2345, Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

The AR Reporting Form and the AR Guidelines can be found on the TPD web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.