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FDA Warns of Prostate Cancer Risk With Reductase Inhibitors

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June 9, 2011 — The US Food and Drug Administration (FDA) has alerted healthcare professionals about changes in the labeling for 5-alpha reductase inhibitors (5-ARI), which include dutasteride and finasteride.

The drug labels now warn that there is an increased risk of being diagnosed with a high-grade prostate cancer while taking these drugs.

Both drugs are marketed for use in benign prostate hypertrophy and have also been investigated for — but not approved for — prostate cancer prevention in men at high risk.

However, it was in these studies looking at prostate cancer prevention that there was a finding of an increased incidence of high-grade prostate cancer.

The FDA acknowledges that the risk appears to be low but says that practitioners need to be aware of this safety information. The known benefits can then be more accurately weighed against the potential risks when clinicians make a decision about starting or continuing treatment with 5-ARIs.

The decision to issue this new safety data is based on the FDA's review of the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. Both trials evaluated the use of these drugs as chemopreventive agents. While the trials

demonstrated an overall reduction in prostate cancer diagnoses, there was an increase in the incidence of high-grade prostate cancer in both trials, and some experts have questioned use of these agents in these settings.

Data from the PCPT and REDUCE trials were discussed at the FDA's Oncologic Drugs Advisory Committee, held on December 1, 2010, which recommended against approval of a prevention indication for these drugs.

Reduced Cancer Risk But…

The PCPT evaluated the daily use of finasteride, 5 mg, vs placebo for 7 years, and showed a reduction in the cumulative incidence of prostate cancer, from 24.4% in the placebo group to 18.4% in the finasteride group, during the study period.

The rates of prostate cancer during the 7-year period were 4.9% in the control group and 3.5% in the finasteride group, for an absolute risk reduction of 1.4 percentage points. The reduction in risk for prostate cancer was limited to prostate cancers with a Gleason score (GS) of 6 or lower. However, there was an increased incidence of prostate cancers with a GS of 8-10 with finasteride vs placebo (1.8% vs 1.1%, respectively).

In similar fashion, the REDUCE trial assessed the daily use of dutasteride, 0.5 mg, vs placebo for 4 years, for the reduction in the risk for prostate cancer in men at least 50 years of age. The results showed significantly fewer prostate cancers detected in men taking dutasteride than in those taking placebo, representing a relative risk reduction of 22.8% ($P < .001$).

This overall risk reduction was limited to a decrease in prostate cancers with a GS of 6 or lower. In contrast, there was an increased incidence of cancers with a GS of 8 to 10 with dutasteride vs placebo (1% vs 0.5%, respectively).

However, a review of these findings published in 2009 in *Clinical Cancer Research* suggested that finasteride did not cause high-grade prostate cancers but simply made them easier to diagnose (*Clin Cancer Res*. 2009;15:4694-4699).

"Our results suggest that the PCPT findings, in which finasteride use was associated with an increase in diagnoses of high-grade cancers, was likely the result of a detection bias rather than an increase in de novo high-grade prostate cancer," study author Christopher Elliott, MD, PhD, a urology resident at Stanford University in California, told *Medscape Medical News* at that time. "These results would suggest that the fear of promoting high-grade prostate cancer with finasteride is likely unfounded."

Information for Clinicians

The American Society of Clinical Oncology and the American Urological Association have also jointly recommended consideration of using both dutasteride and finasteride in asymptomatic men to reduce the risk for prostate cancer in new guidelines issued in February 2009. The

guidelines note that some men might benefit from a discussion with their physicians about the benefits and risks of 5-ARIs for the prevention of prostate cancer.

The FDA has now also issued additional information for healthcare professionals:

- Be aware that 5-ARIs may increase the risk for high-grade prostate cancer.
- Before initiating therapy with 5-ARIs, perform appropriate evaluation to rule out other urologic conditions, including prostate cancer, that may mimic benign prostatic hyperplasia.
- Be aware that treatment with 5-ARIs causes an approximate 50% reduction in prostate-specific antigen (PSA) values by 6 months; however, individual patients receiving 5-ARIs may experience varying decreases in PSA values. Therefore, any confirmed increase in PSA during 5-ARI treatment may signal the presence of prostate cancer and should be evaluated, even if that PSA level is in the normal range of men not taking a 5-ARI.
- Know that 5-ARIs are not approved for the prevention of prostate cancer.
- Report any adverse events involving 5-ARIs to the FDA MedWatch program.

More information is available at the FDA Web site.

Adverse events related to 5-ARIs should be reported to MedWatch by telephone at 1-800-332-1088, by fax at 1-800-332-1078, online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm, or by mail to MedWatch, 5600 Fishers Lane, Rockville, Maryland 20857.

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