Drugs

FDA Drug Safety Communication: 5-alpha reductase inhibitors (5-ARIs) may increase the risk of a more serious form of prostate cancer

Safety Announcement

[6-9-2011] The U.S. Food and Drug Administration (FDA) is informing healthcare professionals that the *Warnings and Precautions* section of the labels for the 5-alpha reductase inhibitor (5-ARI) class of drugs has been revised to include new safety information about the increased risk of being diagnosed with a more serious form of prostate cancer (high-grade prostate cancer). This risk appears to be low, but healthcare professionals should be aware of this safety information, and weigh the known benefits against the potential risks when deciding to start or continue treatment with 5-ARIs in men.

The new safety information is based on FDA's review of two large, randomized controlled trials--the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial--which evaluated daily use of finasteride 5 mg versus placebo for 7 years and daily use of dutasteride 0.5 mg versus placebo for 4 years, respectively, for the reduction in the risk of prostate cancer in men at least 50 years of age. The trials demonstrated an overall reduction in prostate cancer diagnoses with finasteride 5 mg and dutasteride treatment (see Data Summary below). This overall reduction was due to a decreased incidence of lower risk forms of prostate cancer. However, both trials showed an increased incidence of high-grade prostate cancer with finasteride and dutasteride treatment.

For more information about this safety issue, also refer to the Questions and Answers[1].

Facts about 5-ARIs

- Drugs in this class are finasteride (marketed as Proscar [finasteride 5 mg] and Propecia [finasteride 1 mg]) and dutasteride (marketed as Avodart). Dutasteride is also available in combination with tamsulosin, under the brand-name Jalyn.
- Proscar, Avodart, and Jalyn are approved to improve symptoms of an enlarged prostate gland (benign prostatic hyperplasia or BPH). Proscar and Avodart are also approved to reduce the risk of urinary retention or surgery related to an enlarged prostate.
- Propecia is approved to treat male pattern hair loss.
- Approximately 5 million male patients received a prescription for a 5-ARI between years 2002 to 2009. Of these, nearly 3 million patients were between the ages of 50 to 79 years.[1]

Additional Information for Patients

- Drugs in the 5-ARI class are finasteride and dutasteride. These drugs are marketed under the brand-names Proscar, Propecia, Avodart, and Jalyn.
- Finasteride is available in two different strengths: Proscar 5 mg tablets and Propecia 1 mg tablets.
- Discuss any questions or concerns about 5-ARIs with your healthcare professional.
- Report any side effects you experience to the FDA MedWatch program, using the information at th bottom of the page in the "Contact Us" box.

Additional Information for Healthcare Professionals

- Be aware that 5-ARIs may increase the risk of high-grade prostate cancer.
- Prior to initiating therapy with 5-ARIs, consideration should be given to other urological conditions that might mimic benign prostatic hyperplasia (BPH).
- 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 while on a 5-ARI may signal the presence of prostate cancer and should be evaluated, even if that PSA 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, using the information at the bottom of the page in the "Contact Us" box.

Data Summary

The PCPT was a randomized, double-blind, placebo-controlled, multicenter trial in 18,882 men age 55 or older with a normal digital rectal examination and PSA levels ≤ 3 ng/mL. Men at higher risk for developing prostate cancer, such as those men with prior prostate biopsies demonstrating high-grade prostatic intraepithelial neoplasia, were excluded from the study. The trial compared the use of finasteride 5 mg (n=9423) to placebo (n=9459) for the reduction in the risk of prostate cancer. Treatment was continued for seven years following randomization or until diagnosis of prostate cancer, initiation of treatment for BPH with a 5-ARI, or unacceptable side effects. The study protocol specified that transrectal ultrasound and sextant prostate biopsy were to be performed for an elevation in PSA level or an abnormal digital rectal examination during the study. All participants who were not previously diagnosed with prostate cancer were to undergo transrectal ultrasound and sextant core prostate biopsy after completing 7 years on study.

The results of the PCPT showed that men on the finasteride arm had a 26% overall lower risk of being diagnosed with prostate cancer when compared to the placebo arm ($p<0.0001$). The reduction in risk of prostate cancer was limited to Gleason score (GS) 6 or lower prostate cancers. However, there was an increased incidence of GS 8-10 prostate cancers with finasteride versus placebo (1.8% versus 1.1%, respectively).

The REDUCE trial was a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of once daily dosing of dutasteride in reducing the risk of biopsy-detectable prostate cancer in men 50-75 years of age considered to be at increased risk for prostate cancer. The trial allocated 8231 men to receive either placebo (n=4126) or dutasteride 0.5 mg (n=4105) once daily for a total of four years. Prostate biopsies were performed at 2 years and 4 years. Unscheduled biopsies in addition to the protocol-mandated Year 2 or 4 biopsies were allowed if clinically indicated at the discretion of the investigator, but were discouraged.

The results of the REDUCE trial showed that men on dutasteride had a 23% overall lower risk of being diagnosed with biopsy detectable prostate cancer when compared to men on placebo ($p<0.0001$). This overall risk reduction was limited to a decrease in GS 6 or lower prostate cancers. In contrast, there wa an increased incidence of GS 8-10 cancers with dutasteride versus placebo (1% versus 0.5%, respectively).

Data from the PCPT and REDUCE trials were discussed at the FDA's Oncologic Drugs Advisory Committee held on December 1, 2010 (for complete safety reviews and background information discussed at this meeting see: December 1, 2010 AC meeting[2]).

References

1. SDI, Vector One®: Total Patient Tracker (TPT). Years 2002-2009. Data extracted 5-24-11.

Related Information

- Questions and Answers: 5-alpha reductase inhibitors (5-ARIs) may increase the risk of a more serious form of prostate cancer[3]
  6/9/2011
- December 1, 2010: Oncologic Drugs Advisory Committee Meeting Announcement[4]
- 5-Alpha Reductase Inhibitor Information[5]

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