

# Dutasteride May Reduce Prostate Cancer Risk

BY FRAN LOWRY  
Orlando Bureau

ORLANDO — The investigational 5- $\alpha$ -reductase inhibitor dutasteride induces genetic changes in noncancerous prostate tissue and may play a role in reducing the risk of prostate cancer, Dr. Elahe Mostaghel said at a symposium on prostate cancer sponsored by the American Society of Clinical Oncology.

Dutasteride, which is currently used to treat benign prostatic hyperplasia, reduced the activity of 98 genes—including trefoil factor 3 (TFF3), whose overexpression has been associated with the development of prostate and other cancers—by more than twofold, said Dr. Mostaghel of the Fred Hutchinson Cancer Research Center, Seattle.

The 5- $\alpha$ -reductase inhibitors curb the conversion of testosterone to dihydrotestosterone (DHT) inside the prostate,

**Dutasteride reduced the activity of genes whose overexpression has been associated with the development of prostate and other cancers.**

decreasing DHT levels and thereby inhibiting cancer development. In the Prostate Cancer Prevention Trial, inhibition with the 5- $\alpha$ -reductase inhibitor finasteride resulted in a 25% reduction in the overall incidence of prostate cancer,

but this finding was accompanied by an unexpected increase in the number of high-grade prostate cancers in the men who did get cancer.

“The results from the [Prostate Cancer Prevention] trial are what have really prevented this chemoprevention idea from becoming more widespread, because we really don’t understand yet why there was an increase in the number of higher-grade tumors. It appears to be an artifact in the way the study was performed, the way that the biopsies were done, and the way that the prostate-specific antigen thresholds were adjusted,” Dr. Mostaghel said at the symposium, cosponsored by the Society of Urologic Oncology and the American Society for Therapeutic Radiology and Oncology.

In the present study, the researchers wanted to determine what was actually going on at the molecular level to decrease the development of prostatic tumors. Accordingly, Dr. Mostaghel and her coinvestigators examined gene expression changes in benign prostate epithelium from 75 men diagnosed with localized prostate cancer.

The men were randomized to prostatectomy alone (n = 25) or neoadjuvant dutasteride at 0.5 mg (n = 26) or 3.5 mg (n = 24) orally per day for 4 months prior to prostatectomy.

Dihydrotestosterone levels fell by 93% in the men treated with 0.5 mg dutasteride, and by 98% in the 3.5-mg-per-day group. Treatment with dutasteride induced up-regulation of 32 genes and downregulat-

ed 98 genes, including several genes potentially involved in prostate cancer development. Among them were:

► **Insulinlike growth factor-binding protein 3 (IGFBP3).** This gene was up-regulated in response to dutasteride. It promotes apoptosis and inhibits cell proliferation and is decreased in patients with prostate cancer.

► **Transmembrane protease, serine 2 (TMPRSS2).** This gene was downregulated in response to dutasteride. It is an

androgen-regulated gene that is thought to promote the development of prostate tumors when it fuses with other oncogenes, such as ETS. TMPRSS2-ETS fusions have been found in up to 70% of prostate cancers.

► **TFF3.** This gene inhibits apoptosis and promotes tumor aggression. It is also overexpressed in gastrointestinal and breast cancers, in addition to prostate cancer.

Dutasteride is being evaluated in the Reduction by Dutasteride of Prostate Cancer

Events (REDUCE) trial, which will be completed in 2009, Dr. Mostaghel said.

“We need to wait for the results of the REDUCE trial,” he said. “In our exploratory study, we demonstrated a mechanism by which dutasteride may reduce the risk of prostate cancer. REDUCE will tell us whether the gene expression changes we are seeing with dutasteride will correlate with developing or not developing prostate cancer, so our findings need validation in larger studies of longer duration.” ■



Discover **Levemir**<sup>®</sup>:  
a long-acting basal insulin  
with a light touch

Levemir: for your patients who need a safe and effective way to improve A1C control

With proven reductions in A1C and FPG levels over time, Levemir can help your patients get to goal with up to 24 hours of glycemic control. Patients with diabetes can experience a consistent blood glucose response from injection to injection. Less weight gain was observed with Levemir in 12 of 12 clinical trials.\* And Levemir is available in the Levemir<sup>®</sup> FlexPen<sup>®</sup>. FlexPen<sup>®</sup> is the world's #1 selling prefilled insulin pen.† So start your patients with diabetes on Levemir, and help them experience the light side of basal insulin.

Levemir is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

**Important safety information**  
Levemir should not be diluted or mixed with any other insulin preparations.

Levemir is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.

Hypoglycemia is the most common adverse effect of all insulin therapies, including Levemir. As with other insulins, the timing of hypoglycemic events may differ among various insulin preparations. Glucose monitoring is recommended for all patients with diabetes. Any change of insulin dose should be made cautiously and only under medical supervision. Concomitant oral antidiabetes treatment may require adjustment.

Levemir is not to be used in insulin infusion pumps. Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic ketoacidosis. Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. Dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia in patients being switched to Levemir from other intermediate or long-acting insulin preparations. The dose of Levemir may need to be adjusted in patients with renal or hepatic impairment.

Other adverse events commonly associated with insulin therapy may include injection site reactions (on average, 3% to 4% of patients in clinical trials) such as lipodystrophy, redness, pain, itching, hives, swelling, and inflammation.

\*Whether these observed differences represent true differences in the effects of Levemir and NPH insulin is not known, since these trials were not blinded and the protocols (eg, diet and exercise instructions and monitoring) were not specifically directed at exploring hypotheses related to weight effects of the treatments compared. The clinical significance of the observed differences in weight has not been established.

Reference: 1. IMS Health, IMS MIDAS [12 months ending September 2005]. Please see brief summary of Prescribing Information on adjacent page. FlexPen and Levemir are registered trademarks of Novo Nordisk A/S. © 2006 Novo Nordisk Inc. 131007 September 2006

**Levemir**<sup>®</sup>  
insulin detemir (rDNA origin) injection  
Lighter years ahead