U.S. Food and Drug Administration

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Summary Minutes of the
Oncologic Drugs Advisory Committee Meeting
December 1, 2010
Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, MD 20993

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the December 1, 2010 Meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on _1/3/2011_____.

I certify that I attended the December 1, 2010 meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

___/s/_____
Nicole Vesely, Pharm.D.
Designated Federal Official, ODAC

_____/s/_____
Wyndham Wilson, M.D., Ph.D.
Committee Chair

The Oncologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 1, 2010 at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the sponsors. The meeting was called to order by Wyndham Wilson, M.D., Ph.D. (Committee Chair); the conflict of interest statement was read into the record by Nicole Vesely, Pharm.D. (Designated Federal Official). There were approximately 150 persons in attendance. There were two (2) speakers for the Open Public Hearing session.

Issue: On December 1, 2010, the committee met to discuss supplemental New Drug Applications (sNDAs) 021319/024, trade name AVODART (dutasteride) Soft Gelatin Capsules, manufactured by SmithKline Beecham Corporation d/b/a (doing business as) GlaxoSmithKline and 020180/034, trade name PROSCAR (finasteride) tablets, manufactured by Merck & Co., Inc. The proposed indication (use) for AVODART (dutasteride) is for reduction in the risk of prostate cancer in men at increased risk of developing the disease. The population at increased risk of prostate cancer includes men with an elevated serum prostate-specific antigen (PSA) or men otherwise determined to be at increased risk based on other associated risk factors such as age, race, and family history. There is no proposed expansion of the indication for PROSCAR (finasteride); however, in light of the Prostate Cancer Prevention Trial (PCPT) which demonstrated a statistically significant reduction in the 7-year period prevalence of prostate cancer with finasteride (PROSCAR) treatment, and which reported an imbalance in high Gleason grade prostate cancers (indicating more aggressive cancers) in the finasteride treatment arm vs. placebo, the efficacy and safety of both products for use in prostate cancer risk reduction will be examined.

Attendance:

Oncologic Drug Advisory Committee Members Present (Voting):
Ralph Freedman, M.D., Ph.D., William Kelly, D.O., Patrick Loehrer, Sr., M.D., Brent Logan, Ph.D., Mikkael Sekeres, M.D., M.S., Margaret Tempero, M.D., Wyndham Wilson, M.D., Ph.D. (Committee Chair)

Special Government Employee Consultants (Temporary Voting Members):
Ralph D'Agostino, Ph.D., Mario Eisenberger, M.D., Curt Furberg, M.D., Ph.D., Marc Garnick, M.D., Ernest Hawk, M.D., M.P.H., James Kiefert, Ed.D. (Patient Representative), Mary Majumder, Ph.D. (Acting Consumer Representative), David Penson, M.D., M.P.H., William Steers, M.D.

Regular Government Employee Consultants (Temporary Voting Members):
Inger Rosner, M.D., Isabell Sesterhenn, M.D.

Oncology Drugs Advisory Committee Member (Non-Voting):
Gregory Curt, M.D. (Industry Representative)

Guest Speaker (Non-Voting, Presenting Only):
Patrick Walsh, M.D.

Speaker (Non-Voting, Presenting Only):
Peter Scardino, M.D. (Speaker)

Oncologic Drugs Advisory Committee Members Not Present:
Jean Grem, M.D., F.A.C.P.
Virginia Mason, R.N. (Consumer Representative)

FDA Participants (Non-Voting):
Richard Pazdur, M.D., Patricia Keegan, M.D., Marc Theoret, M.D., John Johnson, M.D., Yang-Min (Max) Ning, M.D., Ph.D.

Designated Federal Official:
Nicole Vesely, Pharm.D.

Open Public Hearing Speakers:
Theresa Morrow
Ana Fadich, MPH, CHES, Director, Programs and Health Promotion, Men's Health Network

The agenda was as follows:

Call to Order Introduction of Committee	**Wyndham Wilson, M.D., Ph.D.** Chair, ODAC
Conflict of Interest Statement	**Nicole Vesely, Pharm.D.** Designated Federal Official, ODAC
Opening Remarks	**Richard Pazdur, M.D.** Director, Office of Oncology Drug Products (OODP), Office of New Drugs (OND), CDER, FDA
Sponsor Presentation Introduction, Regulatory History	**Merck & Co., Inc.** **Vivian L. Fuh, M.D.** Merck
Prostate Cancer Prevention Trial	**Ian M. Thompson Jr., M.D.** Southwest Oncology Group (SWOG)
Labeling Proposal	**Vivian L. Fuh, M.D.**
FDA Presentation NDA 020180/s034: Proscar	**Marc Theoret, M.D.** Medical Officer Division of Biologic Oncology Products (DBOP), OODP, OND, CDER, FDA
Sponsor Presentation Introduction	**GlaxoSmithKline** **Paolo Paoletti, M.D.** Senior Vice President Oncology R&D, GlaxoSmithKline
Efficacy and Safety	**Gerald L. Andriole, M.D.** Chief, Division of Urologic Surgery Washington University School of Medicine St. Louis, MO
High Grade Cancers	**Christopher Logothetis, M.D.**

	Chair, Department of GU Medical Oncology MD Anderson Cancer Center Houston, TX
Clinical Perspective	**Claus Roehrborn, M.D.** Professor and Chairman of Urology University of Texas Southwestern Medical Center Dallas, TX
Risk Management and Concluding Remarks	**Anne M. Phillips, M.D.** Vice President Medicine Development Leader Oncology R&D, GlaxoSmithKline
FDA Presentation NDA 21319/s024: Avodart	**Yang-Min (Max) Ning, M.D., Ph.D.** Medical Officer Division of Drug Oncology Products (DDOP), OODP, OND, CDER, FDA
FDA Presentation Comparison of PCPT and REDUCE	**Marc Theoret, M.D.**
Speaker Presentation Comments on Chemo Prevention for Prostate Cancer	**Peter T. Scardino, M.D., FACS (Speaker)** Chairman, Department of Surgery The David H. Koch Chair Memorial Sloan-Kettering Cancer Center
Speaker Presentation The Use of 5α-reductase Inhibitors (5 ARIs) for the Chemoprevention of Prostate Cancer	**Patrick C. Walsh, M.D. (Guest Speaker)** University Distinguished Service Professor of Urology The Brady Urological Institute Johns Hopkins Medical Institutions

Questions to Presenters

Open Public Hearing

Questions to the ODAC and ODAC Discussion

Adjourn

Questions to the Committee

NDA 020180/S034
Proscar (finasteride) Tablets

APPLICANT: Merck & Co., Inc.

PROPOSED INDICATION: none requested

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NDA 021319/S024
Avodart (dutasteride) Soft Gelatin Capsules

APPLICANT: SmithKline Beecham Corp.
doing business as **GlaxoSmithKline**

PROPOSED INDICATION: for reduction in the risk of prostate cancer in men at increased risk of developing the disease, defined as those who have had a prior negative biopsy due to clinical concern and have an elevated serum prostate-specific antigen (PSA).

Today's ODAC meeting concerns the prevention of prostate cancer. Clinical trials have been conducted with two drugs. Both drugs are 5 alpha reductase inhibitors. Finasteride inhibits isoform 2 and dutasteride inhibits both isoforms 1 and 2. Finasteride was evaluated in men believed to be at low to moderate risk for prostate cancer in the Prostate Cancer Prevention Trial (PCPT). However, the Applicant for dutasteride believes the risk for prostate cancer in men enrolled in the REDUCE trial was higher than in men enrolled in the PCPT based on higher study entry PSA levels and a negative for-cause biopsy in the 6 months prior to study entry.

Major Issues:

The generalizability of the results from the two studies to the population of men in the US is of concern. The relevance of the results of these trials to clinical practice where only "for-cause" biopsies are performed is unknown. This concern is particularly applicable to the dutasteride trial where only about 10% of biopsies were done for cause. In addition, the African-American population, in whom there is a high incidence of prostate cancer in the US, is under-represented in both trials.

Prespecified and exploratory analyses demonstrated internal consistency within each trial. Consistency was also demonstrated across the two prostate cancer risk reduction trials. A modest reduction in Gleason score ≤6 prostate cancers and an increase in Gleason score 8-10 prostate cancers were observed.

In addition to the safety concern of a higher incidence of higher grade prostate cancer from finasteride and dutasteride, unrecognized toxicities may need to be considered in an evaluation of these agents. These drugs, if approved, will be used widely for the risk reduction of prostate cancer in healthy men who may never have or may never require treatment for prostate cancer. Currently
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unrecognized safety signals may become evident when these drugs are used in larger populations and for longer time periods.

The COMBAT and REDEEM trials were submitted, but are of limited value in assessing the use of alpha reductase inhibitors in the risk reduction of prostate cancer. These trials were conducted with objectives other than the evaluation of prostate cancer risk reduction.

Finasteride Proposed Indication and Trial Design of PCPT:

No new indication is proposed for finasteride for the reduction in risk of prostate cancer. However, there is a proposal to revise the information in the Clinical Studies section and in the Adverse Event section of the finasteride label from the PCPT. The proposed changes could be interpreted to suggest that finasteride is safe and effective for the risk reduction of prostate cancer in otherwise healthy men age 55 or older.

The PCPT comparing treatment with finasteride to placebo daily for 7 years randomized over 18,000 men age 55 or older without prostate cancer and with normal digital rectal examinations and baseline PSA levels 3 ng/mL or less. Men on the finasteride arm of the trial had a 26% lower risk of being diagnosed with prostate cancer when compared to the placebo arm. The reduction in risk of prostate cancer was limited to Gleason score 6 or lower prostate cancers. Paradoxically, men on the finasteride arm had a 1.3% absolute increase and a 26% relative increase in high-grade prostate cancer Gleason score 7-10, of which 75% of the increase were in Gleason 8-10 cancers.

Dutasteride Proposed Indication and Trial Design of REDUCE:

The proposed new indication for dutasteride is "for reduction in the risk of prostate cancer in men at increased risk of developing disease, defined as those who have had a prior negative biopsy due to clinical concern and have an elevated serum prostate-specific antigen (PSA)." The results of the REDUCE trial are submitted in support of this new indication.

The REDUCE trial is a randomized, double-blind, placebo-controlled trial in men believed to be at increased risk of prostate cancer based on age 50-75, a negative biopsy due to clinical concern in the last 6 months and a current PSA ≥2.5-10 ng/mL. Prostate cancer incidence was assessed by mandated scheduled needle biopsies at 2 and 4 years. "For cause" biopsies at other times were permitted, but discouraged. Only about 10% of biopsies were "for cause". The duration of the trial was 4 years.

Men on dutasteride had a 23% lower risk of being diagnosed with prostate cancer than men on placebo. This risk reduction appears limited to a decrease in Gleason score 6 or 5 prostate cancers, but with no decrease in Gleason score 7-10 cancers. In contrast, there was a notable increase in Gleason score 8-10 prostate cancers with dutasteride (16 versus 32 using the current Gleason scoring criteria).

1. **VOTE:** Is the finasteride risk/benefit profile favorable for reduction in the risk of prostate cancer in men ≥55 years of age with a normal digital rectal examination and a PSA of ≤3.0 ng/mL?

   Vote : ***Yes=0*** ***No =17*** ***Abstain =1***

Concern with finasteride being used in a large population of men outside that of the proposed indication was mentioned by numerous members as having a potentially large impact on public health. Concern was also

expressed that the PCPT study was not of sufficient duration and that it was lacking in adequate long term follow-up since it might be expected that the product could be used over an extended period of time. Members commented that they would like to see surgical pathology data presented for finasteride. It was commented that the approval bar for a chemoprevention product to be used in an otherwise healthy population should be high and that the risks of adverse effects occurring in this population may not be negligible.

Committee members voiced concern over the increase in high grade prostate cancer seen during treatment. The committee also noted that the PSA (prostate specific antigen) test is an imperfect measure and that efforts need to be made to continue to improve the test. Diagnostic imaging was suggested as a tool for measuring disease reduction. The members stressed that there is an unmet need in this population

2. **VOTE:** Is the dutasteride risk/benefit profile favorable for reduction in the risk of prostate cancer in men at increased risk of developing the disease, defined as those who have had a prior negative biopsy due to clinical concern and have an elevated serum prostate-specific antigen (PSA)?

   Vote : ***Yes=2*** ***No =14*** ***Abstain =2***

Concern was raised by the committee members regarding the lack of availability of long term trial data and the presumption that, if available, dutasteride might be used in a large population resulting with a potentially large impact on public health.. Concern was also expressed regarding the increased incidence of high grade prostate cancer occurrence seen with the product. Some members were not convinced that the group of men studied was made up of higher risk patients. A limited number of members felt that the REDUCE study did actually include high-risk patients, that clinical benefit was demonstrated and that because of this unnecessary procedures would be minimized.