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Dutasteride: A Review of its Use in the Management of Prostate Disorders

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Abstract: Dutasteride, a synthetic 4-azasteroid, is a selective and competitive inhibitor of both type 1 and type 2 5- α -reductase isoenzymes approved for the treatment of men with symptomatic benign prostatic hyperplasia (BPH) who have an enlarged prostate. It has been demonstrated to be effective as monotherapy, or in combination with the alpha-adrenergic antagonist (α -blocker), tamsulosin, in several randomized, double-blind, placebo controlled trials and their open-label extensions. Treatment with dutasteride is generally safe and well tolerated. Dutasteride has become established in the management of men with lower urinary tract symptoms (LUTS) and reduces the risk of acute urinary retention and surgery related to BPH. Dutasteride may also have a role as a chemopreventive agent in the future as emerging evidence demonstrates a reduced risk of prostate cancer with this agent.

Keywords: benign prostatic hyperplasia, dutasteride, prostate cancer, drug therapy

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Introduction

The potent androgen dihydrotestosterone (DHT) is a metabolite of testosterone produced by the intracellular enzyme 5 α -reductase. DHT is critical for the development of the male external genitalia, urethra, and prostate as well as male sexual maturation at puberty.¹ Later in life, DHT has been found to be the primary androgen responsible for male pattern hair loss.² In addition, DHT has a pathologic role with prostatic disorders, such as benign prostatic hyperplasia (BPH).³

There are two steroid 5 α -reductase enzymes which have been discovered, type 1 and type 2.⁴ Type 1 has been reported to be located throughout the body including the liver, prostate, and skin. Type 2 is also found in extra-prostatic tissues but is predominantly located in the male genitalia and prostate.⁵ Investigators have demonstrated presence of 5 α -reductase types 1 and 2 mRNA in each zone of the prostate. When compared with normal prostate tissue BPH tissue was found to have a significant increase in expression of 5 α -reductase types 1 and 2 mRNA. They also found in prostate cancer specimens higher expression of 5 α -reductase type 1 but not type 2 mRNA than in normal prostate tissue.^{6,7}

Males born with a deficiency of the type 2 5 α -reductase enzyme have been found to have impaired masculinization of the external genitalia and a rudimentary prostate. These individuals do not develop BPH or prostate cancer and these findings ultimately led to the development and use of 5 α -reductase inhibitors for the treatment of BPH.⁸ The two 5 α -reductase inhibitors currently approved for clinical use are finasteride and dutasteride.

Mechanism of Action and Pharmacokinetic Profile

Dutasteride, a synthetic 4-azasteroid, is a selective and competitive inhibitor of both type 1 and type 2 5 α -reductase isoenzymes. 5 α -reductase is responsible for the intracellular conversion of testosterone to DHT, the primary androgen critical in the initial development and subsequent growth of prostate tissue.⁹ In comparison to finasteride, a specific inhibitor of type 2 5 α -reductase, dutasteride is more potent with a higher reduction in DHT concentrations at equally potent doses.¹⁰ After treatment with

dutasteride 0.5 mg daily for two weeks, DHT serum levels were decreased by 90%.⁹

Dutasteride is administered orally. Following a single dose of 0.5 mg, peak serum concentrations (T_{max}) are reached within two to three hours. In healthy subjects, the absolute bioavailability is 60% (range 40%–94%). Maximum serum concentrations are reduced by food, but the reduction was not determined to be clinically significant. Upon reaching systemic circulation, dutasteride is highly bound to albumin (99%) and alpha-1 acid glycoprotein (96.6%) and widely distributed throughout the central and peripheral compartments.⁹

Dutasteride is extensively metabolized in the liver by the cytochrome P450 (CYP) isoenzymes CYP3A4 and CYP3A5. Two minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasteride) and three major metabolites (4'-hydroxydutasteride, 1,2-dihydroxydutasteride, and 6-hydroxydutasteride) are identified in the human serum. Of these metabolites, only 6-beta-hydroxydutasteride maintains activity comparable to dutasteride. Dutasteride and its metabolites are mainly excreted in the feces (5% unchanged and 40% as metabolites). Less than 1% of dutasteride was found unchanged in the urine and 55% of a dose is unaccounted for. At steady state, the terminal elimination half life of dutasteride is approximately five weeks. Serum concentrations achieve 65% of steady state after daily dosing for one month and 90% after three months and remain detectable for up to four to six months after discontinuation of treatment.⁹

In a single-dose study of dutasteride 0.5 mg in 36 healthy male subjects aged 24–87 years, the half life increased considerably with age. The half life lasted 170 hours in men aged 20–49 years, 260 hours in men aged 50–69 years, and 300 hours in men greater than 70 years old. No differences in safety were seen between the different age groups and no dose adjustment is currently recommended.⁹

The effect of renal and hepatic impairment on dutasteride pharmacokinetics has not been studied. Since dutasteride is extensively metabolized in the liver, patients with hepatic impairment are more likely to have higher systemic exposure to the drug. However, no dose adjustment recommendations have been made for this patient population. No dose



adjustments are necessary in patients with renal impairment since a minimal amount of drug is eliminated through the kidneys.⁹

Dutasteride is contraindicated for the use in women of childbearing potential and during pregnancy. This population should also avoid handling the dutasteride capsule due to the potential of absorption through contact with skin. Dutasteride use is also contraindicated in pediatric patients younger than 18 years old.⁹

Dutasteride for the Treatment of BPH

Lower urinary tract symptoms (LUTS) become increasingly common in aging men and have been associated with a reduction in quality of life.¹¹ These symptoms may be secondary to BPH and bladder outlet obstruction.¹² Autopsy studies revealed the prevalence of histologically diagnosed BPH to reach 50% by 60 years of age, then progressively rise to over 80% in men older than 80 years old.¹³ The two classes of drugs available for non-surgical management of BPH are alpha-adrenergic antagonists (α -blockers) and 5 α -reductase inhibitors. While α -blockers help in relaxing the bladder neck and prostate, 5 α -reductase inhibitors act by reducing the size of the prostate gland.¹⁴

The clinical efficacy and safety of dutasteride was evaluated in a trial of 4325 men with BPH. This was a three parallel, randomized, double-blind, placebo-controlled phase III trial of 24 months duration. Serum DHT levels were reduced from baseline by more than 90% at two years. This resulted in a risk reduction of acute urinary retention by 57 percent and surgical intervention by 48 percent when compared with placebo. Treatment with dutasteride also resulted in improved urinary flow rate, improved symptom score, and a reduction in total prostate volume by 25.7%. Side effects including decreased libido, impotence, ejaculation disorders, and gynecomastia were more frequent in patients treated with dutasteride.¹²

Pooled data is also available from an open-label extension period of an additional 2 years, where all patients received dutasteride 0.5 mg daily, giving 4 years of efficacy and safety data on dutasteride.¹⁵⁻¹⁸ Those patients maintained on dutasteride after 24 months were found to have continuing improvements in maximal flow rate (Q_{\max}), symptom scores, and reductions in

total prostate volume (TPV). These improvements were evident in patients with either slightly enlarged (30 to less than 40 cc) or severely enlarged (40 cc or greater) prostate volumes at baseline.¹⁸ Patients continued on dutasteride experienced long-term suppression of DHT with a 93% reduction from baseline at 48 months.¹⁵ Additionally, a reduction in TPV as well as improvements in Q_{\max} and symptoms scores were noted from 24 to 48 months in those who switched from placebo to dutasteride at 2 years.¹⁶

The combination of a 5 α -reductase inhibitor and an α -blocker is also utilized for the treatment of LUTS in men with BPH. The Combination of Avodart and Tamsulosin (CombAT) study looked at combination therapy with dutasteride and tamsulosin compared to monotherapy alone. This is an ongoing multicenter, double-blind, parallel group study, in which 4,844 men were randomized to receive dutasteride (n = 1,623), tamsulosin (n = 1,611), or combination therapy (n = 1,610). Included in the study were men 50 years or older who had an International Prostate Symptoms Score (IPSS) of 12 points or more, prostate volume ≥ 30 cc, and total serum PSA ≥ 1.5 ng/mL.¹⁹

An interim two-year analysis was recently reported from the CombAT study with the primary end point being the change in IPSS from baseline. Combination therapy produced a significant reduction in IPSS compared with dutasteride starting from month three (mean decrease in IPSS from baseline starting at month three: 4.8 vs. 2.8, $P < 0.001$) and compared with tamsulosin starting from month nine (mean decrease in IPSS from baseline at month nine: 5.4 vs. 4.7, $P < 0.001$). The proportion of men considered IPSS responders (25% or greater, 2-point or greater and 3-point or greater improvement) in the combination group was significantly greater than the proportion in the tamsulosin or dutasteride groups ($P < 0.001$). There was a significant reduction in Q_{\max} for combination therapy compared to either monotherapy starting at month 6 to the end of the interim period of two years. Overall, patients receiving combination therapy experienced significantly ($P < 0.001$) greater improvements in symptoms compared to monotherapy with dutasteride or tamsulosin at 24 months. There was a significantly greater number of drug related adverse events in the combination group compared to either monotherapy group, although only five percent or less from each



treatment group actually withdrew from the study due to these events.¹⁹ In June 2010, the US Food and Drug Administration (FDA) approved the use of Jalyn, a single-capsule combination of dutasteride and tamsulosin for the treatment of symptomatic BPH.²⁰

Dutasteride as a Chemopreventive Agent

While 5 α -reductase inhibitors are routinely used for treatment of symptomatic BPH, there has been increasing interest for their role as potential chemopreventive agents. Given current understanding that both benign and prostate cancer cells are androgen responsive coupled with the knowledge that DHT has the most potent androgenic effect in the prostate, gives logic to exploring the use of 5 α -reductase inhibitors to reduce DHT levels in an effort to prevent prostate cancer.²¹ Finasteride was evaluated as a chemopreventive agent in the Prostate Cancer Prevention Trial (PCPT). This trial showed that there was a 24.8% (95% CI, 18.6 to 30.6%, $P < 0.001$) decrease in the prevalence of prostate cancer over a 7-year period when compared to placebo. Unfortunately, the PCPT also revealed that there was an increased prevalence of high-grade tumors in the finasteride group.²² This finding has been a source of great debate, with some suggesting that finasteride potentially induces high-grade prostate cancer. After further analysis, one explanation for this is potential detection bias for high grade prostate cancer due to prostate volume reduction as well as improved prostate-specific antigen sensitivity and specificity for detecting prostate cancer.²³

The effect of dutasteride on the incidence of prostate cancer was investigated in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. This 4-year multicenter, double-blind, placebo-controlled, chemoprevention study evaluated 6729 men with 3305 men who received a dose of dutasteride at 0.5 mg daily and 3424 men in the placebo group. Those eligible were considered to be at increased risk of prostate cancer who had an elevated PSA (>2.5 ng/mL in men aged 50–60 and >3.0 ng/mL in men aged 60–75),²⁴ unlike the men in the PCPT considered to be at low risk of prostate cancer with a PSA ≤ 3 ng/mL.²² Additional inclusion criteria included men with one prior negative prostate biopsy within 6 months of enrollment and men who

were 50 to 75 years of age. Men enrolled in the study underwent subsequent 10-core transrectal ultrasound-guided biopsies at 2 and 4 years. To preserve the blinded nature of the study the PSA of participants in the dutasteride group was doubled, correcting for an average PSA reduction of 50% by dutasteride, and then randomly adjusted by 0.1 ng/mL assuring that final reported values were equally even and odd.^{21,24} The primary endpoint was biopsy detectable prostate cancer at 2 and 4 years of treatment. Other end points included gleason score, tumor volume, percent of positive biopsy cores, presence of high-grade intraepithelial neoplasia (HGPIN) or atypical acinar proliferation (ASAP), BPH-related outcomes, as well as safety and tolerability.²⁴

During the 4 year REDUCE study period dutasteride resulted in an overall relative risk reduction of 22.8% (CI 95%, 15.2 to 29.8%, $P < 0.001$) and an absolute risk reduction of 5.1%. The reduced risk of prostate cancer was present across all major prespecified risk groups.²⁴ In comparison to PCPT which observed an increase in Gleason score 7 to 10 tumors with finasteride,²² there was no significant difference in those with Gleason score 7 to 10 tumors in the dutasteride group when compared with placebo.²⁴ While the number of Gleason 8 to 10 tumors was similar between the groups at two years (17 in the dutasteride group and 18 in the placebo group), there was a significant difference detected at four years with 12 Gleason 8 to 10 tumors detected in the dutasteride group compared with only 1 in the placebo group. Among patients with prostate cancer on biopsy there was no difference between the two groups in the average number of positive cores, tumor volume, and percentage of cores with cancer.²⁴

In the REDUCE trial, dutasteride also resulted in a reduction in lesions associated with prostate cancer with a relative risk reduction of 39.2% for HGPIN ($P < 0.001$) and 21.2% for ASAP ($P = 0.04$). Investigators noted a significant reduction in the risk of acute urinary retention and surgery related to BPH. Dutasteride was mostly well tolerated in this study with the frequency of side effects in line with previous reports on dutasteride for the treatment of BPH.²⁴

The Combat study, which was initially utilized to explore the use of combination therapy with dutasteride and tamsulosin compared with either monotherapy alone for men with LUTS,¹⁹ was also



used to study the effect of dutasteride on the risk of prostate cancer diagnosis. Participants were older men (≥ 50 years old) with a clinical diagnosis of BPH who were considered by the authors to be at above-average risk for prostate cancer with PSA level 1.5–10 ng/mL. The study was thought to reflect more of a typical clinical setting in which men were screened annually with PSA and digital rectal examination (DRE). Prostate biopsies were performed only for-cause based on the investigator's judgment such as a change in DRE, increase in PSA, or nodular areas detected on transrectal ultrasound of the prostate. There was a reduction in prostate cancer with dutasteride administration (either as monotherapy or in combination with tamsulosin) with a relative risk reduction of 40% (CI 95%, $P = 0.002$) pooling both dutasteride arms and absolute risk reduction of 1.5% when compared to treatment with tamsulosin alone. The reduction of prostate cancer risk was demonstrated across all Gleason scores. Men treated with dutasteride also underwent fewer prostate biopsies (40% reduction in the likelihood of biopsy) and the biopsies which were performed in the dutasteride arms resulted in a higher diagnostic yield when compared to tamsulosin monotherapy.²⁵

Despite the reduced risk of prostate cancer demonstrated, the Oncologic Drugs Advisory Committee (ODAC) of the FDA voted against the use of dutasteride for chemoprevention in a recent supplemental New Drug Application (sNDA) for dutasteride. These men were defined as high-risk for prostate cancer with a previous negative prostate biopsy and elevated PSA. The panel members did not feel that there was a sufficient benefit-to-risk ratio to support the use of dutasteride in this patient population.²⁶ The FDA followed this with a complete response letter indicating that the sNDA could not be approved in its present form.²⁷

Safety and Tolerability

Clinical trials^{12,28–30} have shown treatment with dutasteride to be safe and well tolerated. Most adverse events experienced were not serious and decreased as therapy continued. Sexual side effects including impotence, decreased libido, gynecomastia and ejaculation disorder were most commonly seen in patients treated with dutasteride compared to placebo.^{12,28} In three large, randomized, double-blind placebo controlled

clinical trials, sexual side effects occurred in at least one percent of patients who received dutasteride 0.5 mg daily over a two year period.^{12,28} Patients experienced the majority of these sexual side effects during the initial six months of dutasteride therapy. With the exception of gynecomastia, there were no significant sexual side effects seen beyond six months of treatment. At the end of four years in an open-label extension study, tolerability was maintained with less than one percent of patients withdrawing from the study due to drug-related adverse effects.^{29,30}

The CombAT trial evaluated the safety and efficacy of the combination of dutasteride and tamsulosin. Safety and tolerability of combination therapy was consistent in comparison to the separate monotherapy treatments. The drug-related adverse events were significantly higher in the combination therapy versus the monotherapy groups ($P < 0.001$) which was mainly attributed to the incidence of ejaculatory disorders. The rates of withdrawal due to drug-related adverse effects, however, were no different between the groups.³¹

Place in Therapy

Dutasteride was initially FDA approved as monotherapy for the treatment of symptomatic BPH with an enlarged prostate and is now also approved to use in combination with tamsulosin for the same indication.⁹ Both the European Association of Urology and the American Urological Association (AUA) agree that a trial of conservative management without medication for men with mild to moderate uncomplicated LUTS is reasonable to consider initially according to their most recent guidelines.^{32,33} Medical therapies for moderate to severe LUTS or for those who fail watchful waiting include α -blockers (alfuzosin, doxazosin, tamsulosin, and terazosin), 5 α -reductase inhibitors (Finasteride and dutasteride) for those with LUTS and an enlarged prostate, or a combination of an α -blocker and a 5 α -reductase inhibitor.^{32,33} While patients may choose surgical therapy as their first option, these treatments such as transurethral microwave heat treatment, transurethral needle ablation, transurethral resection of the prostate, and transurethral laser vaporization are typically reserved for patients with complications of BPH or patients with persistent bothersome symptoms despite maximal medical therapy.³²



One advantage of monotherapy with a 5 α -reductase inhibitor is the reduced risk of acute urinary retention or need for surgery for individuals with an enlarged prostate.³⁴ 5 α -reductase inhibitors act by reducing the size of the prostate gland while α -blockers help in relaxing the bladder neck and prostate.¹⁴ Minimum treatment duration of 6 to 12 months is generally needed to give time for adequate reduction in prostate size allowing for a notable improvement in symptoms. Then again, treatment with an α -blocker has a rapid onset of action and is not dependent on prostate size.³³ Treatment with 5 α -reductase inhibitors will also reduce an individual's PSA level. For example, a reduction in PSA by 59.5% has been demonstrated in those who received Dutasteride for 2 years. This knowledge has prompted suggested use of a PSA doubling factor for those men on dutasteride to help maintain the usefulness of PSA for prostate cancer detection.³⁵ However, some argue that doubling the PSA could potentially either overestimate or underestimate actual PSA in some patients. Given this concern a PSA increase of 0.3 ng/mL or greater from nadir was proposed as an alternative to the doubling rule as a threshold for triggering prostate biopsy.³⁶

The potential role of dutasteride as a chemopreventive agent is still evolving. The American Society of Clinical Oncology (ASCO)/AUA guideline on the use of 5 α -reductase inhibitors for prostate cancer chemoprevention urges physicians to inform men considering use of these agents that 5 α -reductase inhibitors reduce, but not completely eliminate, the risk of prostate cancer.³⁷ Patients should be made aware that there was an increased risk of high-grade prostate cancers (Gleason score 7 to 10) found in the PCPT study with finasteride.²² There was not an increase in Gleason 7 to 10 tumors with dutasteride in the REDUCE trial, however there was an increase in Gleason 8 to 10 tumors at four years with dutasteride when compared with placebo.²⁴ Other key points from the ASCO/AUA guideline are that physicians should inform men of the possible but reversible side effects but also the likely improvement in LUTs with 5 α -reductase inhibitors.³⁷ What may be more difficult, however, is deciding if the advantages outweigh the disadvantages in addition to accounting for cost effectiveness when determining whether to utilize 5 α -reductase inhibitors or not for chemoprevention.

Despite the reported risk reduction in prostate cancer, to date both finasteride and dutasteride are not yet approved for use as prostate cancer chemopreventive agents.

Conclusion

Dutasteride is a dual inhibitor of both isoforms of 5 α -reductase and is currently established as an effective and tolerable option in the management of LUTS for men with an enlarged prostate. Treatment with dutasteride will decrease the TPV as well as lower the risk of acute urinary retention and surgery related to BPH. In addition, dutasteride has been shown to reduce the risk of prostate cancer in older men considered to be at increased risk for prostate cancer with an elevated PSA. Further investigation is needed, though, to help further define the potential role of dutasteride as a chemopreventive agent.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. E. David Crawford has the following disclosures: Consultant/Employee: Ferring. Lecturer: GlaxoSmithKline, Sanofi Aventis, Johnson and Johnson, Amgen. Consultant: Gtx. The authors confirm that they have permission to reproduce any copyrighted material.

References

1. Sakhri S, Gooren LJ. Safety aspects of androgen treatment with 5 α -dihydrotestosterone. *Andrologia*. 2007;39:216–22.
2. Eun HC, Kwon OS, Yeon JH, et al. Efficacy, safety, and tolerability of dutasteride 0.5 mg once daily in male patients with male pattern hair loss: A randomized, double-blind, placebo-controlled, phase III study. *J Am Acad Dermatol*. 2010;63:252–8.
3. Andriole G, Bruchovsky N, Chung L. Dihydrotestosterone and the prostate: The scientific rationale for 5 α -reductase inhibitors in the treatment of benign prostatic hyperplasia. *J Urol*. 2004;172:1399–403.
4. Russell DW, Wilson JD. Steroid 5 α -reductase: Two genes/two enzymes. *Annu Rev Biochem*. 1994;63:25–61.
5. Carson C, Rittmaster R. The role of dihydrotestosterone in benign prostatic hyperplasia. *Urology*. 2003;61(4 Suppl 1):2–7.
6. Lehle C, Radvanyi F, Medina S, et al. Differences in steroid 5 α -reductase isoenzymes expression between normal and pathological human prostate tissue. *J Steroid Biochem Mol Biol*. 1999;68:189–95.
7. Thomas LN, Lazier CB, Gupta R, et al. Differential alterations in 5-alpha reductase type 1 and type 2 levels during development of prostate cancer. *Prostate*. 2005;63:231–9.
8. Imperato-McGinley J, Gautier T, Zirinsky K, et al. Prostate visualization studies in male homozygotes and heterozygotes for 5 alpha-reductase deficiency. *J Clin Endocrin Metab*. 1992;75:1022–6.



9. GlaxoSmithKline. Prescribing information: Avodart® (dutasteride) soft gelatin capsules. Triangle Park (NC): GlaxoSmithKline, September 2004.
10. Clark RV, Hermann DJ, Cunningham GR, et al. Marked suppression of dihydrotestosterone in men with benign prostatic hyperplasia by dutasteride, a dual 5 α -reductase inhibitor. *J Clin Endocrinol Metab.* 2004 May;89:2179–84.
11. Girman CJ, Jacobsen SJ, Tsukamoto T, et al. Health-related quality of life associated with lower urinary tract symptoms in four countries. *Urology.* 1998;51:428–36.
12. Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G. Efficacy and safety of a dual inhibitor of 5 alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology.* 2002;60:434–41.
13. Berry SJ, Coffey DS, Walsh PC, et al. The development of human benign prostatic hyperplasia with age. *J Urol.* 1984;132:474–9.
14. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med.* 2003;349:2387–98.
15. Roehrborn CG, Marks LS, Fenter T, et al. Efficacy and safety of dutasteride in the four-year treatment of men with benign prostatic hyperplasia. *Urology.* 2004;63:709–15.
16. Debruyne F, Barkin J, Van Erps P, Reis M, Tammela TL, Roehrborn CG. Efficacy and safety of long-term treatment with the dual 5 alpha-reductase inhibitor dutasteride in men with symptomatic benign prostatic hyperplasia. *Eur Urol.* 2004;46:488–95.
17. Roehrborn CG, Lukkarinen O, Mark S, et al. Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5 alpha-reductase inhibitor dutasteride: results of 4-year studies. *BJU Int.* 2005;96:572–7.
18. Gittelman M, Ramsdell J, Young J, et al. Dutasteride improves objective and subjective disease measures in men with benign prostatic hyperplasia and modest or severe prostate enlargement. *J Urol.* 2006;176:1045–50.
19. Roehrborn CG, Siami P, Barkin J, et al. The effects of dutasteride, tamsulosin, and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. *J Urol.* 2008;179:616–21.
20. Benson G. *FDA approval letter for Jalyn.* 6/14/2010. Available at <http://www.fda.gov>. Accessed January 3, 2011.
21. Andriole G, Bostwick D, Brawley O, et al. Chemoprevention of prostate cancer in men at high risk: rationale and design of the reduction by dutasteride of prostate cancer events (REDUCE) trial. *J Urol.* 2004;172:1314–7.
22. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med.* 2003;349:215–24.
23. Akduman B, Crawford ED. The PCPT: new findings, new insights, and clinical implications for the prevention of prostate cancer. *Eur Urol Suppl.* 2006;5:634–9.
24. Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med.* 2010;362:1192–202.
25. Roehrborn CG, Andriole GL, Wilson TH, et al. Effect of dutasteride on prostate biopsy rates and the diagnosis of prostate cancer in men with lower urinary tract symptoms and enlarged prostates in the combination of avodart and tamsulosin trial. *Eur Urol.* 2011;59:244–9.
26. Avodart reviewed by FDA advisory committee for prostate cancer risk reduction [news release]. GlaxoSmithKline, December 1, 2010. Accessed January 28, 2011.
27. GSK receives FDA Complete Response letter for Avodart for prostate cancer risk reduction supplemental indication [news release]. GlaxoSmithKline, January 26, 2011. Accessed January 28, 2011.
28. Andriole GL, Kirby R. Safety and tolerability of the dual 5 α -reductase inhibitor dutasteride in the treatment of benign prostatic hyperplasia. *Eur Urol.* 2003;44(1):82–8.
29. Schulman C, Pommerville P, Hofner K, et al. Long-term therapy with the dual 5 α -reductase inhibitor dutasteride is well tolerated in men with symptomatic benign prostatic hyperplasia. *BJU Int.* 2006 Jan;97(1):73–9.
30. Debruyne F, Barkin J, van Erps P, et al. Efficacy and safety of long-term treatment with the dual 5 α -reductase inhibitor dutasteride in men with symptomatic benign prostatic hyperplasia. *Eur Urol.* 2004 Oct;46(4):499–5.
31. Roehrborn CG, Siami P, Barkin J, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. *Eur Urol.* 2010;57:123–31.
32. AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: diagnosis and treatment recommendations. *J Urol.* 2003;170:530–47.
33. Oelke M, Bachmann A, Descoteaux A, et al. Guidelines on conservative treatment of non-neurogenic male LUTS. *European Association of Urology* (online). Update April 2010. Available at <http://www.uroweb.org/gls/pdf/BPH%202010.pdf>. Accessed December 29, 2010.
34. Roehrborn CG. BPH progression: concept and key learning from MTOPS, ALTESS, COMBAT, and ALF-ONE. *BJU Int.* 2008;101 Suppl 3:17–21.
35. Andriole GL, Marberger M, Roehrborn CG. Clinical usefulness of serum prostate specific antigen for the detection of prostate cancer is preserved in men receiving the dual 5 alpha-reductase inhibitor dutasteride. *J Urol.* 2006;175:1657–62.
36. Marks LS, Andriole GL, Fitzpatrick JM, et al. The interpretation of serum prostate specific antigen in men receiving 5-alpha reductase inhibitors: a review and clinical recommendations. *J Urol.* 2006;176:868–74.
37. Kramer BS, Hagerty KL, Justman S, et al. The use of 5 alpha-reductase inhibitors for prostate cancer chemoprevention: American society of clinical oncology/American urological association 2008 clinical practice guideline. *J Urol.* 2009;181:1642–57.

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