National PBM Drug Monograph
Dutasteride (Avodart™)
March 2003

Introduction

Dutasteride is a Type 1 and Type 2 alpha-reductase inhibitor originally approved by the FDA in April 2002 following the evaluation of efficacy and safety data from the first 12 months of a planned 48 month series of clinical trials. Marketing of the drug was postponed until November 2002 when the 24 month data had matured, producing additional clinical information on the risk of acute urinary retention and the need for surgical interventions when compared to placebo.

Pharmacology/Pharmacokinetics[1, 2, 3, 4]

Metabolism	Extensively metabolized; not all pathways have been identified. Metabolized by CYP3A4 to 2 minor metabolites (not metabolized by CYP 1A2, 2C9, 2C19, or 2D6)
Elimination	Primarily in feces; <1% unchanged drug found in urine
Half-life	Terminal half-life approximately 5 weeks at steady state
Protein Binding	Highly bound (99%) to albumin and alpha-1 acid glycoprotein (96.6%)
Bioavailability	About 60%; reduced by 10-15% when given with food (not clinically significant)

Testosterone is the principal circulating androgen. For maximal activity in the prostate, it must be converted to dihydrotestosterone (DHT) by the enzyme 5-alpha-reductase. DHT is about twice as potent as testosterone and has a greater affinity for the androgen receptor. Two genes have been identified that encode for the isoenzymes 5-alpha-reductase type 1 and type 2. Type 1 isoenzyme is found in the liver starting at birth, and in two waves in the skin: just before birth until 2 or 3 years old, then again from puberty through adulthood. Type 2 isoenzyme is found in all prostate tissue, seminal vesicles, epididymis, fetal genital skin, in the skin and scalp from just before birth until 2 or 3 years old, and in the adult liver. More recently, type 1 mRNA has also been found in prostate tissue.

Benign prostatic hyperplasia (BPH) is an androgen dependent process with a multifactoral etiology that includes hormones, ageing, growth factors, and stromal-epithelial interactions. DHT levels in the prostate remain at normal levels despite the decrease in testosterone that occurs with ageing. Conversion of testosterone to DHT in peripheral tissues may have implications in treating BPH. Finasteride inhibits 5-alpha-reductase type 2, with little affinity for type 1. It has been shown to be effective in lowering DHT levels by approximately 70% leading to a reduction in prostate volume and improved symptoms in men with BPH. Dutasteride inhibits both type 1 and type 2 5-alpha-reductase isoenzymes, theoretically providing a greater suppression of DHT than a selective inhibitor.

FDA Approved Indication(s) and Off-label Uses

Treatment of symptomatic benign prostatic hyperplasia in men with an enlarged prostate to: improve symptoms, reduce the risk of acute urinary retention, and to reduce the risk for the need for BPH-related surgery.
Off-label uses: investigations are on going for male pattern hair loss, prevention of prostate cancer, in combination with tamsulosin for BPH, and as neoadjuvant therapy for prostate cancer.

Dosage and Administration

The recommended dose is 0.5mg (1 capsule) every day. The capsule should be swallowed whole and may be given with or without food.

Renal Impairment: No pharmacokinetic studies have been performed in patients with renal impairment. However, since <1% is recovered in the urine, no dose adjustments are expected.

Hepatic Impairment: The effect of hepatic impairment has not been studied. Because dutasteride is metabolized extensively, there may be higher exposure is patients with hepatic impairment.

Geriatric: No dose adjustments are needed based on age. In the 3 pivotal studies, >60% of patients were age 65 or over. No differences in safety or efficacy were seen.

Adverse Effects (Safety Data)

Adverse Event Onset	Dutasteride	Placebo
Impotence		
Month 0-6	4.7%	1.7%
Month 7-12	1.4	1.5
Month 13-18	1.0	0.5
Month 19-24	0.8	0.9
Decreased libido		
Month 0-6	3.0	1.4
Month 7-12	0.7	0.6
Month 13-18	0.3	0.2
Month 19-24	0.3	0.1
Ejaculation Disorder		
Month 0-6	1.4	0.5
Month 7-12	0.5	0.3
Month 13-18	0.5	0.1
Month 19-24	0.1	0.0
Gynecomastia		
Month 0-6	0.5	0.2
Month 7-12	0.8	0.3
Month 13-18	1.1	0.3
Month 19-24	0.6	0.1

Pregnancy: **Pregnancy Category X**: Preclinical data suggest suppression of dihydrotestosterone may inhibit the development of external genitalia in a male fetus in a woman exposed to dutasteride.

Precautions/Contraindications

Contraindications: Use in women and children, patients with known hypersensitivity to dutasteride, other 5α-reductase inhibitors, or any component of the preparation.

Precautions:

- **Exposure of women/risk to male fetus**: Due to absorption thru the skin, women who are pregnant or may be pregnant should not handle dutasteride capsules because of the possibility of potential risk of a genital anomaly to a male fetus.
- **Blood Donation**: Men receiving dutasteride should not donate blood until at least 6 months following the last dose to prevent inadvertent administration to a pregnant female transfusion patient.
- **Use with potent CYP3A4 inhibitors**: The effect of potent CYP3A4 inhibitors on dutasteride pharmacokinetics has not been studied. Caution should be exercised when giving dutasteride to patients on chronic CYP3A4 inhibitors due to potential for drug-drug interactions.
- **Effects on PSA and prostate cancer detection**: Dutasteride reduces serum PSA by approximately 50% following at least 6 months of therapy. A new baseline PSA should be obtained after 3-6 months of therapy to use when assessing the potential for cancer-related changes in the PSA. To interpret an isolated PSA in a patient receiving dutasteride for 6 months or longer, the PSA value should be doubled to compare it to normal values.

Drug Interactions

Caution is advised when administering dutasteride to patients taking potent CYP3A4 inhibitors.

Dutasteride does not inhibit the substrates for the isoenzymes CYP1A2, 2C9, 2C19, 2D6, or 3A4 at concentrations 25 times greater than steady-state concentrations. In vitro studies show it does not displace warfarin, phenytoin, or diazepam from plasma proteins.

Studies in healthy volunteers:
Digoxin- dutasteride did not alter the steady-state pharmacokinetics of digoxin
Warfarin- dutasteride did not alter the steady-state pharmacokinetics of S- or R- warfarin or alter the effect on prothrombin.
Alpha-blockers: the administration of terazosin or tamsulosin in combination with dutasteride had no effect on steady-state pharmacokinetics of either drug.
Cholestyramine: A single dose of dutasteride followed one hour later by 12 g cholestyramine did not affect relative bioavailability.

In clinical trials:
Tamsulosin: When investigating the tolerability of dutasteride and tamsulosin for up to 36 weeks, results found no excess of serious side effects or discontinuation compared to monotherapy.
Calcium Channel Blockers: CYP3A4 inhibitors verapamil and diltiazem produced decreases in the clearance of dutasteride by 37% and 44%, respectively. The decrease in clearance is not considered clinically significant. No decrease in clearance was documented with amlodipine, which is not a CYP3A4 inhibitor.
Other Therapies: In the pivotal phase III trials, many patients were taking concomitant medications including anti-hyperlipidemics, ACE inhibitors, beta-blockers, corticosteroids, diuretics, NSAIDs, and quinolones. No clinically significant adverse interactions were attributed to combination therapy.

Efficacy Measures

Primary Endpoints in pivotal trials
- Changes in the American Urological Association –Symptom Index Score (AUA-SI), a questionnaire that evaluates 7 urinary symptoms on a 0-5 scale with a total possible score of 35.
- Incidence of Acute Urinary Retention (AUR)

Secondary Endpoints
- Changes in Total Prostate Volume (TPV)
- Qmax- peak urine flow rate
- Incidence of surgical intervention
- Serum PSA
- Serum testosterone
- Serum dihydrotestosterone (DHT)

Clinical Trials[5]

Citation	Roehrborn CG, Boyle P, Nicek J.C., Hoefner K, Andriole G, on behalf of the ARIA3001, ARIA3002, and ARIA3003 Study Investigators. Efficacy and Safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology 2002;60:434-441.
Study Goals	To test the safety and efficacy of dutasteride in three 2-year Phase III studies
Methods	• Study Design ➢ Following a 1-month run-in with placebo, patients were randomized to dutasteride 0.5mg/ day or a matching placebo in three double-blind trials. Patients were followed for 24 months with multiple assessments. The primary endpoints were changes in the AUA-SI and risk of AUR. Secondary endpoints: changes in TPV, Qmax, serum PSA, serum testosterone and DHT, surgical interventions, tolerability.

<table>
<tr><td></td><td>

- Data Analysis
  - Data from all three studies was pooled, and analyses used a last observation carried forward approach in addition to an “at visit” analysis. The “at visit” analysis was reported in this publication. Statistical analyses used a two-sided test of significance at the 0.05 level.

</td></tr>
<tr><td>Criteria</td><td>

- Inclusion criteria
  - Men age 50 years or older with a clinical diagnosis of BPH
  - A measured prostate volume of at least 30cm^3 or greater
  - AUA-SI of 12 points or higher
  - Qmax of 15ml/s or less
- Exclusion criteria
  - Residual volume greater than 250ml
  - History of prostate cancer
  - Prior prostate surgery, prior history of AUR within 3 months
  - Use of an alpha-blocker within 4 weeks
  - Any use of a 5-alpha-reductase inhibitor
  - Serum PSA less than 1.5ng/ml or greater than 10 ng/ml

</td></tr>
<tr><td>Results</td><td>

Table 1. Baseline Data

Parameter	Placebo	Dutasteride
Age (yrs)	66.1	66.5
Serum DHT (pg/ml)	415	428
Serum testosterone (pg/ml)	3987	4026
Total Prostate Volume (cm^3)	54	54.9
AUA-SI (0-35)	17.1	17.0
Qmax (ml/s)	10.4	10.1
Serum PSA (ng/ml)	4.0	4.0

Table 2. Change from baseline at month 24

Parameter	Placebo (n=2158)	Dutasteride (n=2167)	Between Group Comparison
Serum DHT	426	40	
Change	16	-389	<0.001
Significance from BL	<0.001	<0.001	
Testosterone	4002	4817	
Change	36	749	<0.001
Significance from BL	NS	<0.001	
Prostate Volume	54.1	41.2	
Change	0.8	-14.6	<0.001
Significance from BL	0.040	<0.001	
AUA-SI	14.7	12.2	
Change	-2.3	-4.5	<0.001
Significance from BL	<0.001	<0.001	
Qmax	11.2	12.5	
Change	0.6	2.2	<0.001
Significance from BL	<0.001	<0.001	
PSA	4.3	1.9	
Change	0.5	-2.2	<0.001
Significance from BL	<0.001	<0.001	

The AUA-SI decreased from baseline as soon as 3 months in one study, reached significance in pooled data at 6 months, and continued to improve at months 12,18, and 24.
The differences in Qmax between placebo and dutasteride reached significance at month 3.
Significant decreases in prostate volume were seen as soon as 3 months in one trial and by 6 months in pooled data.

AUR episodes: Placebo=90 Dutasteride=39 RR 0.43 (95%CI 0.29, 0.62)
BPH-related surgeries: Placebo=89 Dutasteride=47 RR 0.52 (95%CI 0.37, 0.74)

</td></tr>
</table>

<table>
<tr><td></td><td>Table 3. Drug Related Adverse Events
<table>
<tr><th></th><th>Placebo</th><th>Dutasteride</th></tr>
<tr><td>Decreased libido</td><td>2.1%</td><td>4.2%*</td></tr>
<tr><td>Impotence</td><td>4.0</td><td>7.3*</td></tr>
<tr><td>Ejaculation Disorder</td><td>0.8</td><td>2.2*</td></tr>
<tr><td>Gynecomastia</td><td>0.7</td><td>2.3*</td></tr>
<tr><td>Sexual function disorder</td><td><1</td><td><1</td></tr>
<tr><td>Prostate cancer diagnosis</td><td>1.9</td><td>1.1</td></tr>
<tr><td>*p <0.001</td><td></td><td></td></tr>
</table>
The incidence of most sexual adverse events decreased with duration of treatment except for gynecomastia, which remained constant during treatment.</td></tr>
<tr><td>Conclusions</td><td>Inhibition of Type I and Type II 5-alpha-reductase isoenzymes produces almost complete reduction in DHT levels and prevents progression of BPH. Dutasteride provides an additional therapeutic option, especially in men with LUTS (lower urinary tract symptoms such as weak urinary stream, hesitancy, frequency, urgency, nocturia, sensation of incomplete voiding) and an enlarged prostate (>30cm^3)</td></tr>
<tr><td>Critique</td><td>• Strengths
o Large number of patients
o Blinded randomization after blinded placebo run-in
o Assessment of endpoints at various time periods from study entry

• Limitations
o 32% discontinuation rate; 717 in the placebo group and 657 in the dutasteride group; the only statistically significant difference between discontinuation groups was for lack of efficacy (n=212 in placebo and n=134 in dutasteride; p<0.001)
o No comparison to standard therapy (alpha blocker) or finasteride</td></tr>
</table>

Acquisition Costs

Drug	Dose	Cost/Day/patient ($)	Cost/Year/patient ($)
Dutasteride	0.5mg	1.56	569.40
Finasteride	5mg	1.30	474.50

Data Compilation Tables

	Dutasteride AUR	Dutasteride BPH related surgery
Relative Risk	0.43 (0.29,0.62)	0.52 (0.37,0.74)
Relative Risk Reduction	57% (p <0.001)	48% (p <0.001)
Absolute Risk Reduction	2.4%	2%
NNT	42	50

Conclusions

Efficacy: Dutasteride is a 5-alpha-reductase type 1 and type 2 inhibitor that decreases AUA scores and decreases the incidence of episodes of acute urinary retention when compared to placebo in men with BPH and prostates volumes >30cm^3. In addition, dutasteride decreases prostate volumes, increases urinary flow

rates, and decreases PSA relative to placebo. Improvement in some parameters occurred as early as 3 months in some trials, but only reached significance by 6 months. The decrease in DHT by 90+% is expected because of the inhibition of the two isotypes of 5-alpha-reductase. The clinical significance of the amount of DHT suppression is unknown. The premise that a greater reduction of DHT would lead to better outcomes has not been shown by this data. Although they have not been compared, the outcomes from the dutasteride trials after 24 months of follow-up do not seem to differ significantly from finasteride although that could change with further follow-up after the next 24 months of open label therapy. A comparison to alpha-blockers has not been done. There are current trials comparing dutasteride to tamsulosin, placebo, and the combination of dutasteride and tamsulosin in addition to exploring a once a week dosage form.

Safety: The adverse event profile of dutasteride is similar to finasteride, producing events expected by the pharmacologic action of this agent. The majority of the events are sexual, occur more frequently at the beginning of therapy, and decrease with continued use except gynecomastia.

Cost: Currently the cost of therapy with dutasteride is higher than with finasteride with no real clinical benefit.

Dutasteride is an effective 5-alpha-reductase type-1 and type-2 inhibitor, which prevents progression of BPH in men with large prostates and moderate symptoms. Like finasteride, it should be considered as second line therapy after alpha-blockers. There is no data to show any clinical advantage over finasteride at this time.

Recommendations

Until there is clinical data showing an advantage in significant outcomes over finasteride, dutasteride should not be added to the national formulary. This agent may be reviewed again when data from the 24 month open label portion of the registration trials are available.

References:

1. Product Information Avodart™(dutasteride) GlaxoSmithKline, Research Triangle Park, North Carolina, 2002.
2. Center for Drug Evaluation and Research, Application Number 21-319 Medical Review, 2001.
3. Thigpen AE, Silver RI, Guileyardo JM, Casey ML, McConnell JD, Russell DW. Tissue distribution and ontogeny of steroid 5alpha-reductase isozyme expression. J Clin Invest 1993; 92:903-910.
4. Bartsch G, Rittmaster RS, Klocker H. Dihydrotestosterone and the concept of 5α-reductase inhibition in human benign prostatic hyperplasia. World J Urol 2002; 19:413-425.
5. Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G, on behalf of the ARIA3001, ARIA3002, and ARIA3003 study investigators. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology 2002;60:434-441.

Prepared by: Mark C. Geraci, Pharm.D. BCOP
Date: March 2003