

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022460Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review of Class I Re-Submission

<b>Date</b>	<b>June 10, 2010</b>
<b>From</b>	<b>Suresh Kaul, MD, MPH</b>
<b>Subject</b>	<b>Cross-Discipline Team Leader Review</b>
<b>NDA #</b>	<b>22-460/S0022</b>
<b>Applicant</b>	<b>GlaxoSmithKline</b>
<b>Date of Submission</b>	<b>April 14, 2010</b>
<b>PDUFA Goal Date</b>	<b>June 14, 2010</b>
<b>Proprietary Name / Established (USAN) names</b>	<b>Jalyn Dutasteride/tamsulosin fixed-dose oral combination capsule</b>
<b>Proposed Indication(s)</b>	<b>Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate</b>
<b>Recommended:</b>	<b><i>Approval</i></b>

### **Executive Summary:**

The Applicant submitted a Class I Resubmission in response to a Tentative Approval for NDA 22-460 on April 14, 2010. The Tentative Approval was granted because one of the components (tamsulosin) of this combination capsule was still under exclusivity as of January 20<sup>th</sup>, 2010. The resubmission contained proposed labeling for the prescriber and patient. Labeling negotiations have been completed and agreed upon. DMEPA has approved the new proposed name, **Jalyn**. Therefore, from a clinical perspective, NDA 22-460 should now be **approved** for the indication of “treatment of symptomatic BPH in men with an enlarged prostate.” This clinical recommendation is based on the demonstration of bioequivalence between DTC and the co-administration of dutasteride 0.5 mg + tamsulosin 0.4 mg as a clinical bridge to the Year 2 data of Trial ARI40005 and acceptable updated safety findings of study ARI40005. The safety and efficacy findings of Year 2 of ARI40005 supported the approval of the co-administration regimen for the treatment of symptomatic BPH in men with an enlarged prostate in an efficacy supplement to the dutasteride NDA (21-319/S014).

## **Background:**

### **Drug Product:**

DTC is a fixed-dose combination oral dosage containing two active ingredients, dutasteride and tamsulosin, which have 2 distinct mechanisms of action.

Dutasteride is an inhibitor of Type I and Type II isoforms of 5-alpha-reductase enzyme. Inhibition of this enzyme interferes with the enzymatic conversion of testosterone to dihydrotestosterone (DHT), a principal hormone in age-related prostatic growth. Long-term treatment with dutasteride reduces prostate volume, which is believed to contribute to the symptomatic relief of BPH and reduction of the risks of acute urinary retention and BPH-related surgery.

Tamsulosin is an alpha-1-adrenergic antagonist. Alpha-adrenergic receptors are abundant in the prostate and base of the bladder. The density of these receptors is increased in hyperplastic prostatic tissue. Alpha-1- antagonists target alpha-1A receptors (largely in prostatic smooth muscle) and alpha-1D receptors (largely in bladder detrusor smooth muscle). Alpha- adrenergic antagonists such as tamsulosin are thought to improve symptoms of bladder outlet obstruction by relaxing the adrenergic receptors in the stroma and smooth muscle of the prostate and bladder neck, but their precise mechanism of action is unknown.

### **Regulatory**

A tentative approval letter was issued for NDA 22-460 (dutasteride/tamsulosin combination capsule for the treatment of symptomatic BPH in men with an enlarged prostate) on January 20, 2010. The tentative approval decision was rendered because of an existing exclusivity for tamsulosin (Flomax, NDA 20-197), which expired on April 27, 2010. In the tentative approval letter dated January 20, 2010, the Division of Reproductive and Urologic Products (DRUP) requested that the Applicant submit an amendment (resubmission) to NDA 22-460 on or after March 27, 2010, identifying any applicable changes in the conditions under which the product was approved (e.g., updated labeling, chemistry, safety information). From a review standpoint (and not regulatory), all scientific matters were resolved with the exception of labeling negotiations, including cardiac failure language, carton container review, and an acceptable trade name. From regulatory standpoint, no safety information was submitted because it is class I re-submission.

In the re-submission to NDA 22-460 submitted on April 14, 2010, the Applicant submitted updated labeling.

**CDTL Comment:**

*Labeling negotiations for this re-submission were successfully completed. Additionally, the agreed upon labeling changes regarding cardiac failure submitted to NDA 21-319/S018 (July 27, 2009) were also incorporated into the Adverse Reactions section of the label for NDA 22-460. The sponsor had proposed to add the cardiac failure findings to the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the Avodart product label (NDA 21-319) based on two recently completed trials in the dutasteride clinical program (ARI40005- for BPH indication and ARI40006- for risk reduction of prostate cancer). Both the studies demonstrated a numerical imbalance in the incidence of cardiac failure in the co-administration of dutasteride and tamsulosin compared to each monotherapy (ARI40005) and in the dutasteride group compared to placebo (ARI40006).*

*After reviewing all available data, DRUP in consultation with the Division of Cardiovascular and Renal Products (DCRP), members of Division of Drug Oncology Products (DDOP), and the Office of Surveillance and Epidemiology (OSE) concluded that the strength of evidence does not indicate a “reasonable evidence of causal association” between cardiac failure and the co-administration of dutasteride and tamsulosin (or other alpha blockers), tamsulosin alone, or dutasteride alone to warrant inclusion of cardiac failure in the WARNINGS AND PRECAUTIONS section of the Avodart label at this time. Both Divisions (DRUP and DCRP) recommended including the cardiac failure data from ARI40005 and ARI40006 to the ADVERSE REACTIONS section of the fixed dose combination pill label (NDA 22-460) and the SLR (NDA 22-319). DRUP’s proposed labeling verbiage for cardiac failure was accepted in full by the Applicant in labeling submissions to NDA 21-319/S018 and NDA 22-460 dated May 28, 2010. A final agreed upon label was received from the sponsor on June 10<sup>th</sup>, 2010.*

**Key labeling changes:**

**Safety:**

**Highlights of PI:**

**Warnings and Precautions:**

Jalyn reduces total serum prostate-specific antigen concentration by approximately 50%. Evaluate any confirmed increases in PSA levels from nadir while on Jalyn, even if those values are within normal range, for the presence of prostate cancer.

**Use in Specific Populations:**

Renal Impairment: Has not been studied in patients with end-stage renal disease.

Hepatic Impairment: Has not been studied in patients with severe hepatic impairment.

## **Section 6 (PI) ADVERSE REACTIONS**

**Cardiac Failure:** In Combat, after 4 years of treatment, the incidence of the composite term cardiac failure in the co-administration group (12/1,610; 0.7%) was higher than in either immunotherapy group: AVODART, 2/1,623 (0.1%) and tamsulosin, 9/1,611 (0.6%). Composite cardiac failure was also examined in a separate 4-year placebo-controlled trial evaluating AVODART in men at risk for development of prostate cancer. The incidence of cardiac failure in subjects taking AVODART was 0.6% (26/4,105) compared to 0.4% (15/4,126) in subjects on placebo. A majority of subjects with cardiac failure in both studies had co-morbidities associated with an increased risk of cardiac failure. Therefore, the clinical significance of the numerical imbalances in cardiac failure is unknown. No causal relationship between AVODART, alone or co-administered with tamsulosin, and cardiac failure has been established. No imbalance was observed in the incidence of overall cardiovascular adverse events in either study.

### ***Recommendation:***

*The clinical reviewer for this application wrote the following recommendation: From a clinical perspective, NDA 22-460 should now be **approved**.*

***I concur with the clinical reviewer Dr. Christine Nguyen's recommendation for approval of this drug product (Jalyn).***

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22460	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	DUTASTERIDE/ TAMSULOSIN HYDROCHLORIDE

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/s/

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SURESH KAUL  
06/14/2010

GEORGE S BENSON  
06/14/2010