CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022460Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Review for Regulatory Action

Date	June 14, 2010
From	George S. Benson, MD
Subject	Division Deputy Director Summary Review
NDA/BLA #	NDA 22-460/S000
Applicant Name	GlaxoSmithKline
Date of Submission	April 14, 2010
PDUFA Goal Date	June 14, 2010
Proprietary Name / Established Name	Jalyn Dutasteride/tamsulosin (fixed-dose combination)
Dosage Forms / Strength	Oral capsule/Fixed dose combination of dutasteride 0.5 mg and tamsulosin 0.4 mg once daily
Proposed Indication(s)	Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Christine P. Nguyen, MD
Statistical Review	Kate Dwyer, PhD Mahboob Sobhan, PhD
Pharmacology/toxicology Review	Laurie McLeod-Flynn, PhD Lynnda Reid, PhD
CMC Review	Yichun Sun, PhD Moo-Jhong Rhee, PhD
Microbiology Review	Vinayak B. Pawar, PhD Stephen E. Langille, PhD
Clinical Pharmacology Review	Chongwoo Yu, PhD Myong Jin Kim, PharmD
DDMAC	Janice Maniwang, PharmD
DSI	Sripal Mada, PhD Martin Yau, PhD
CDTL Review	Suresh Kaul, MD
OSE/DMEPA	Walter Fava, PharmD Judy Park, PharmD Carlos Mena-Grillasca, RPh Carol Holquist, RPh
OSE/DRISK	Melissa Hulett, PharmD
Project Management	Olga Salis Margaret Kober

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Table of contents:

1. Introduction

NDA 22-460 consists of a fixed-dose combination oral capsule containing dutasteride 0.5 mg and tamsulosin 0.4 mg which is proposed for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate gland. Both dutasteride (Avodart) (GlaxoSmithKline) and tamsulosin (Flomax) (Boehringer Ingelheim) are currently approved for the treatment of BPH. The mechanism of action of action of dutasteride is through inhibition of the 5-alpha reductase enzyme and the mechanism of action of tamsulosin is through alpha adrenergic blockade. A summary of approved pharmacologic treatment of BPH is shown in Table 1.

Table 1: Approved pharmacologic treatments of BPH

Pharmacologic Class	Agents	Indication (s)	Proposed mechanism of action	Common adverse reactions
5α-reductase inhibitors	Finasteride Dutasteride	Treatment of symptomatic BPH; reduction in risks of AUR, BPH-related surgery	Decrease prostate volume	Sexual dysfunction (libido decreased, impotence, ejaculation disorders) Breast disorders
Alpha-adrenergic antagonists	Doxazosin Alfuzosin Terazosin Tamsulosin Silodosin	Treatment of symptomatic BPH	Relax prostatic smooth muscle	Ejaculation disorder Headaches Dizziness Postural hypotension
Co-administration of 5α-reductase inhibitors + Alpha-adrenergic antagonists	Finasteride + doxazosin Dutasteride + tamsulosin	Reduction in the risk of symptomatic progression of BPH Treatment of symptomatic BPH	Combined mechanism	Ejaculation disorder Sexual disorders Breast disorders

The co-administration of dutasteride and tamsulosin for the treatment of symptomatic BPH in men with an enlarged prostate was approved on June 19, 2008, in efficacy supplement 014 to NDA 21-319. GlaxoSmithKline (GSK) is the NDA holder of Avodart (NDA 21-319) and Boehringer Ingelheim Pharmaceuticals is the NDA holder of Flomax (NDA 20-579). The primary study which supported approval of the co-administration of

dutasteride and tamsulosin (NDA 21-319/S014) for the treatment of BPH was trial ARI40005. This study was a large (4844 patients), multicenter trial which compared the co-administration of dutasteride and tamsulosin to dutasteride alone and to tamsulosin alone. The primary endpoint was the International Prostate Symptom Score (IPSS).

The current NDA (22-460) differs from the previously approved dutasteride/tamsulosin NDA (21-319) in that the two drugs are contained in the same capsule instead of being co-administered as two separate drugs.

During the initial review of NDA 22-460, Boehringer Ingelheim responded to a pediatric Written Request and was granted an additional six months of patent exclusivity for tamsulosin. The new tamsulosin patent expiration date is April 27, 2010. Because of the tamsulosin patent date extension, a "tentative approval" action was taken on January 20, 2010. The sponsor resubmitted NDA 22-460 as a Class 1 submission on April 14, 2010.

2. Background

Avodart (dutasteride) 0.5 mg soft gelatin capsule was approved for the treatment of symptomatic BPH in men with an enlarged prostate on November 20, 2001, under NDA 21-319. Flomax (tamsulosin) 0.4 mg capsule was approved in the U.S. for the treatment of signs and symptoms of BPH on April 15, 1997, under NDA 20-579. The co-administration of dutasteride and tamsulosin for the treatment of symptomatic BPH in men with an enlarged prostate was approved on June 19, 2008, in efficacy supplement 014 to NDA 21-319. The primary study supporting approval of the co-administration of dutasteride and tamsulosin was ARI40005 (a 4 year trial comparing the co-administration of dutasteride and tamsulosin to dutasteride alone and to tamsulosin alone). The two year data from this trial (primary endpoint was IPSS) were reviewed to support the approval of the co-administration dutasteride and tamsulosin.

The Applicant for this NDA, GlaxoSmithKline, met with the Division of Reproductive and Urologic Products (DRUP) in March, 2003, to discuss protocol ARI40005 and the overall development plan for a dutasteride/tamsulosin combination product for treatment of BPH. In a regulatory letter dated October 25, 2005 (in response to IND 47,838/serial 330 submission), DRUP agreed that the following clinical pharmacokinetic (PK) studies would adequately bridge to the efficacy and safety results of the co-administration trial ARI40005 and would support an application for a fixed-dose dutasteride/tamsulosin combination product:

- A bioequivalence (BE) study conducted in the fed state bridging the fixed-dose combination product to the separately marketed products of dutasteride and tamsulosin co-administered
- A food effect study evaluating the fixed-dose formulation in the fed and fasted state

A Special Protocol Assessment was submitted to IND 47,838 (serial 0432) dated June 25, 2007, regarding CMC information for the fixed dose combination product.

On September 19, 2008, the sponsor submitted pre-NDA questions concerning the content and format for the fixed dose combination dutasteride/tamsulosin NDA submission. The Division provided responses to these questions via written communication dated October 23, 2008.

In summary, this NDA contains no new clinical efficacy data for the combined dutasteride/tamsulosin drug product. Efficacy of the fixed dose combination product relies on cross-referencing the co-administration trial ARI40005 (2 year data where the primary efficacy endpoint is IPSS). Safety data are derived from updated safety information from the ongoing 4 year trial ARI40005. Pharmacokinetic data and bioequivalence data from trial ARI109882 were used to bridge the co-administration trial ARI40005 to the fixed dose combination dutasteride/tamsulosin product.

Patent exclusivity for tamsulosin expired on April 27, 2010.

3. CMC/Device

The chemistry reviewer concluded that "this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product."

The reviewer notes that a tradename has not been agreed upon and that the manufacturing site inspection reports have not been received from Compliance. "Therefore, from a CMC perspective, this NDA is not recommended for "Approval" in its present form until the Office of Compliance issues an overall "Acceptable" recommendation and the issues on the established name and strength are resolved."

On January 4, 2009, the "Office of Compliance gave an overall "Acceptable" recommendation for all the facilities involved in the manufacture and test of the drug substance and drug product, but the issues on the container labels are still pending."

"However, since this NDA is to be "Tentatively Approval" due to patent issues and the sponsor is to resubmit the NDA when the patent issues are resolved, the labeling issues will be resolved at the second review cycle."

On January 11, 2010, the CMC reviewer concluded "therefore, this application is recommended for tentative approval from the CMC perspective with pending review on container labels."

Comment: I agree with the CMC reviewer that there are no outstanding CMC issues other than approval of a tradename and review and approval of container labels, which are both unresolved issues at the time of his review.

Addendum: The Division of Medication Error Prevention and Analysis (DMEPA) found the tradename "Jalyn" to be acceptable on June 11, 2010. The labeling (including cartons) have been found to be acceptable.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer concluded that "there is no impediment to approval from a pharmacology/toxicology perspective." In addition, "a battery of in vitro assays revealed no evidence of overlapping primary or secondary pharmacological activity which would be of concern with regard to this combination of drugs."

Comment: I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewer concluded that "the Office of Clinical Pharmacology/Division of Clinical Pharmacology III has reviewed NDA 22-460 submitted on March 20, 2009. The overall Clinical Pharmacology information submitted to support this NDA is acceptable."

The reviewer also comments that:

Tamsulosin administered as a combination capsule at steady state was bioequivalent to tamsulosin co-administered as Flomax with Avodart at steady state (Study ARI111402).

Dutasteride administered as a combination capsule was bioequivalent to dutasteride administered as Avodart under fasted conditions (Study ARI103880).

6. Clinical Microbiology

Following resolution of an issue dealing with "possible contamination by adventitious microorganisms during the manufacturing process," the microbiology reviewer concluded that "the NDA is recommended for approval from product quality microbiology standpoint."

A microbiological quality control testing site was added by the sponsor. The newly added site is (b) (4). A FDA inspection of the site was performed in July, 2009, during the review of NDA 22-417. The site received an NAI, and was deemed acceptable. No further inspection is thought to be needed at this time.

7. Clinical/Statistical-Efficacy

The efficacy of the fixed dose combination dutasteride/tamsulosin product relies on bridging to the two year efficacy data of ongoing four year trial ARI40005 which formed the primary data base for the approval of the co-administration of dutasteride and tamsulosin for the treatment of benign prostatic hyperplasia on June 17, 2008. The trial design, demographics, and subject disposition are summarized on pages 24 and 25 of the primary medical officer review.

The Year 2 primary efficacy endpoint was the change from baseline in the International Prostatic Symptom Score (IPSS) at Month 24. The IPSS questionnaire is currently used

as a primary endpoint in phase 3 clinical trials evaluating treatment of symptomatic BPH. At Month 24, the mean difference in change from baseline IPSS between the co-administration and dutasteride groups was -1.3 units and between the co-administration and tamsulosin groups was -1.8 units. The statistical analysis was appropriately adjusted for multiple comparisons between the co-administration group and each monotherapy group for the primary endpoint at Month 24. Statistically significant improvement in the primary endpoint of the co-administration group over each monotherapy was observed from Month 9 ($p < 0.001$) to Month 24 ($p < 0.001$). (Table 2).

Table 2: Change from baseline IPSS (LOCF, ITT)

Time - point	Mean change from baseline IPSS (SE)					
	N	Co-administration	N	Dutasteride	N	Tamsulosin
Month 3	1564	-4.8 (0.14)	1582	-2.8 (0.14)	1573	-4.5 (0.14)
Month 9	1575	-5.4 (0.14)	1592	-4.0 (0.14)	1582	-4.7 (0.14)
Month 12	1575	-5.6 (0.15)	1592	-4.2 (0.15)	1582	-4.5 (0.15)
Month 24	1575	-6.2 (0.15)	1592	-4.9 (0.15)	1582	-4.3 (0.15)
	Mean difference of co-administration group from each monotherapy (95% CI)					
	Dutasteride		P-value	Tamsulosin		P-value
Month 3	-2.0 (-2.33, -1.57)		<0.001	-0.26 (-0.63, 0.12)		0.18
Month 9	-1.4 (-1.79, -1.01)		<0.001	-0.74 (-1.13, -0.35)		<0.001
Month 12	-1.4 (-1.8, -1.01)		<0.001	-1.1 (-1.53, -0.73)		<0.001
Month 24	-1.3 (-1.69, -0.86)		<0.001	-1.8 (-2.23, -1.40)		<0.001

Source: Primary Clinical Review of NDA 21-319/S014, p. 6

Statistical review:

The statistical reviewer concluded that "the safety and efficacy data to support dutasteride and tamsulosin hydrochloride capsule were cross referenced from the 2-year data from Study ARI40005 in NDA 21-319/S-014 and, therefore, no statistical review was necessary."

Bioequivalence trial ARI109882:

To investigate the bioequivalence (BE) of a combination capsule formulation of dutasteride 0.5 mg/tamsulosin hydrochloride 0.4 mg relative to concomitant dosing of dutasteride 0.5 mg and tamsulosin 0.4 mg separately in the fed state, the sponsor conducted study ARI109882.

This was a 2-center, single-dose, randomized, 3-period, partial cross-over BE study in healthy male subjects. Subjects between the ages of 18-45 years with BMI 19-30 kg/m^2 were randomized to one of the following sequences of treatment sessions: ABC, BCA, CAB, CBA, ABD, ADB, BAD, BDA, DAB, or DBA. All subjects were to receive treatments A and B, and half of the subjects were randomized to receive treatment C and

the other half to receive treatment D. Each dosing session was separated by a 4-week washout period. Table 3 describes the treatment groups.

Table 3: Treatment group description

Treatment Group	Treatment Description (all single dose)
A	Co-administration: Flomax 0.4 mg + Avodart 0.5 mg in fed state* (reference)
B	Combination: dutasteride 0.5 mg/tamsulosin 0.4mg combination capsule in fed state* (test)
C	Co-administration: Flomax 0.4 mg + Avodart 0.5 mg in fasted state (reference)
D	Combination: dutasteride 0.5 mg/tamsulosin 0.4mg combination capsule in fasted state (test)

*Dosing occurred 30 minutes after the start of the meal, which is consistent with the Flomax prescribing information and the dosing regimen of tamsulosin in ARI40005

Pharmacokinetic Results: The PK population, which consisted of all subjects for whom at least one PK sample was obtained and analyzed, included 101 subjects. Statistical assessment of serum dutasteride and tamsulosin PK parameters demonstrated bioequivalence based on $AUC_{(0\text{-}t)}$ and C_{max} between combination dutasteride/tamsulosin and dutasteride and tamsulosin co-administered in the fed state. The 90% confidence interval for regimen B: A comparison was within the equivalence interval of 0.8 – 1.25. Bioequivalence was also observed when comparing PK parameters of combination dutasteride/tamsulosin to concomitantly dosed dutasteride and tamsulosin in the fasted state (D:C comparison). (Table 4).

Table 4: Bioequivalence of combination dutasteride/tamsulosin and dutasteride and tamsulosin co-administered

Dutasteride PK			
PK parameters	Group comparison*	Point estimate	90% CI
AUC (0-t)	B:A (fed)	0.97	0.92, 1.03
	D:C (fasted)	1.01	0.91, 1.12
Cmax	B:A	1.00	0.94, 1.05
	D:C	0.99	0.89, 1.09
Tmax	B-A	0.0	-0.02, 0.50
	D-C	0.0	0.00, 0.00
Tamsulosin PK			
PK parameters	Group comparison	Point estimate	90% CI
AUC (0-t)	B:A (fed)	1.03	0.97, 1.09
	D:C (fasted)	1.00	0.91, 1.10
Cmax	B:A	1.08	1.00, 1.15
	D:C	1.07	0.95, 1.21
Tmax	B - A	-0.50	-1.50, 0.00
	D - C	0.00	-0.07, 0.00

Source: NDA 22-460, Module 5.3.1.2, Study ARI109882
*Group A = co-administration of dutasteride + tamsulosin in fed state (reference)
Group B = combination dutasteride/tamsulosin in fed state (test)
Group C = co-administration of dutasteride + tamsulosin in fasted state (reference)
Group D = combination dutasteride/tamsulosin in fasted state (test)

Efficacy summary:

The co-administration of dutasteride and tamsulosin for the treatment of BPH was approved on June 19, 2008. Trial ARI40005 demonstrated that the co-administration of dutasteride and tamsulosin was more effective than either drug alone. In the current NDA submission (22-460), bioequivalence for both dutasteride and tamsulosin was demonstrated between the combined capsule and the two drugs administered separately at the same time. The two year efficacy data (primary endpoint is IPSS) from trial ARI40005 were cross-referenced. Efficacy for the combined dutasteride and tamsulosin product has, therefore, been adequately demonstrated.

8. Safety

Submitted safety data for the combination dutasteride/tamsulosin capsule submitted which led to the "tentative approval" action of January 20, 2010, consisted of:

- Safety information from Study ARI40005. The submitted cumulative safety data consisted of data from the time period from post-randomization of ARI40005 to the cut-off date for this NDA (i.e. post-randomization of ARI40005 to December 8, 2008).

- Updated post-marketing experience for the co-administration of dutasteride and tamsulosin from the sponsor's internal post-marketing safety database and 2 external safety databases.

- 120-Day Safety Update

- Published literature

Because four year study ARI40005 was still ongoing at the time of the NDA submission, the cumulative safety database is incomplete. The safety information submitted in this NDA included line listings, summary tables, case narratives, and case report forms. No datasets were submitted. This approach is acceptable, because the principal support of safety for the combination dutasteride/tamsulosin product is based on the Year 2 safety data of ARI40005 which have been previously analyzed and determined to be acceptable and formed the primary safety database for the approval of NDA 21-319 (S014).

Trial ARI40005:

Exposure:

In study ARI40005, a total of 4844 male subjects with BPH, aged 49-88 years, were randomized in a 1:1:1 ratio to receive dutasteride 0.5 mg (n=1623), tamsulosin 0.4 mg (n=1611), or the co-administration of the 2 drugs (n=1610). Approximately 78-80% of subjects in each treatment arm completed 2 years of treatment. Of the 1610 subjects randomized to co-administration therapy, 1377 (86%) completed at least 12 months of treatment and 1261 (81%) completed at least 24 months of treatment. In a subsequent supplemental labeling request, the sponsor noted that 1096 co-administration subjects (68%), 1067 dutasteride subjects (66%), and 956 tamsulosin subjects (59%) completed 4 years of treatment in ARI40005.

Deaths:

The cumulative data for deaths in ARI40005 (post-randomization to December 8, 2008) by MedDRA System Organ Class (SOC) are summarized in Table 5. A total of 110 patients (2%) died; the all-cause mortality rate was the same for the 3 treatment groups at

2%. The most common causes of death were in the SOC cardiac disorders (37 subjects) and neoplasms (29 subjects). Myocardial infarction was the most common cause of death by Preferred Term (PT) across the 3 treatment groups (co-administration: 3 subjects; dutasteride: 7; tamsulosin: 10). Compared to each monotherapy group, the co-administration group did not have a higher incidence of deaths by any specific SOC or PT.

Table 5: Cause of death by System Organ Class (cumulative, ITT)

System Organ Class	Co-administration N=1610 n (%)	Dutasteride N=1623 n (%)	Tamsulosin N=1611 n (%)	Total N=4844 n (%)
Any fatal AE	36 (2)	37 (2)	37 (2)	110 (2)
Cardiac	14	11	12	37
Neoplasms	10	9	10	29
Nervous system disorders	3	5	4	12
General disorders and administration site conditions	2	3	4	9
Infections	2	5	1	8
Respiratory, thoracic, and mediastinal disorders	1	5	2	8
Injury, poisoning and procedural complications	2	0	4	6
Vascular	1	1	2	4
Gastrointestinal disorders	1	1	1	3
Blood and lymphatic system disorders	1	0	1	2
Psychiatric disorders	1	1	0	2
Renal and urinary disorders	1	0	1	2
Hepatobiliary disorders	0	0	1	2

Source: NDA 22-460, Module 5.3.5.1.22, Table 7 and Listing 7, MO analysis

The safety profile of fatal SAEs in Year 3 and Year 4 did not appear to differ from the Year 2 data of ARI40005.

All narratives of fatal events were reviewed by the primary medical officer and none was thought to be related to study drug.

Nonfatal Serious Adverse Events (SAE's):

In the cumulative database of non-fatal SAE's, a total 827 patients, or 17%, experienced at least one non-fatal SAE. The incidence of non-fatal SAEs was slightly higher in the monotherapy groups (18% each) compared to the co-administration group (16%). The most common SAE's were in the SOC's cardiac disorders (4%) and neoplasms (3%).

Non-fatal SAE's by SOC reported by ≥ 1% of subjects in any treatment group are shown in Table 6.

Table 6: Common non-fatal SAEs (≥ 1% of subjects/group) by System Organ Class (cumulative, ITT)

System Organ Class	Co-administration N=1611 n (%)	Dutasteride N=1623 n (%)	Tamsulosin N=1611 n (%)	Total N=4844 n (%)
Any non-fatal SAE	252 (16)	286 (18)	289 (18)	827 (17)
Cardiac disorders	59 (4)	61 (4)	66 (4)	186 (4)
Neoplasms benign, malignant, and unspecified	47 (3)	50 (3)	59 (4)	156 (3)
Gastrointestinal disorders	25 (2)	41 (3)	37 (2)	103 (2)
Infections	28 (2)	29 (2)	34 (2)	91 (2)
Nervous system disorders	33 (2)	34 (2)	22 (1)	89 (2)
Musculoskeletal and connective tissue disorder	19 (1)	30 (2)	21 (1)	70 (1)
Injury, poisoning and procedural complications	26 (2)	20 (1)	21 (1)	67 (1)
Renal and urinary disorders	11 (<1)	23 (1)	32 (2)	66 (1)
Respiratory, thoracic and mediastinal disorders	20 (1)	16 (<1)	17 (1)	53 (1)
Vascular disorders	20 (1)	16 (<1)	13 (<1)	49 (1)

Source: NDA 22-460, Module 5.3.1.22, Line Listing 8 and Table 8, MO analysis

There are no significant imbalances between treatment groups.

Table 7 shows the most common SAEs (≥ 10 subjects in any treatment group) by Preferred Term (PT) in the cumulative database. The most frequently reported SAE's were prostate cancer, coronary artery disease, myocardial infarction, and angina. No specific SAE PT was reported more frequently in the co-administration compared to each monotherapy, except for pneumonia.

Table 7: Common non-fatal SAE's (≥ 10 subjects/group) by Preferred Terms (cumulative, ITT)

Preferred Term	Co-administration N=1610 n (%)	Dutasteride N=1623 n (%)	Tamsulosin N=1611 n (%)	Total N=4844 n (%)
Prostate cancer	20 (1)	16 (<1)	24 (1)	60 (1)
Coronary artery disease	12	10	16	38
Myocardial infarction	10	16	10	36
Angina pectoris	11	11	11	33
Inguinal hernia	4	16	10	30
Osteoarthritis	8	11	9	28
Urinary retention	2	5	15	22
Pneumonia	13	6	4	20

Source: NDA 22-460, Module 5.3.5.1.22, Table 8

The primary medical officer reviewed all of the narratives for patients who experienced pneumonia and concluded that none of those cases were likely to be drug related. Neither dutasteride nor tamsulosin are associated with an increased risk of infection or pulmonary infection and there is no apparent biologic plausibility for the co-administration of these two drugs and an increased risk of pneumonia. In the Year 2 submission, 9 subjects in the co-administration group, 4 in the dutasteride group, and 4 in the tamsulosin group had an SAE of pneumonia. The primary medical officer does not consider the differences of pneumonia between the treatment groups to be significant given that the incidence of community acquired pneumonia in adults in the U.S. is approximately 8 to 15 per 1000 persons per year and I agree.

Patient Discontinuation:

According to the cumulative safety data of ARI40005, a total of 590 patients (12%) permanently discontinued investigational drug due to an adverse event (258 serious and 332 non-serious). The analysis of the drug discontinuation data is separated into SAEs and non-SAE's.

Cumulative SAE's leading to drug discontinuation: A total of 258 patients (5.3%) experienced an SAE which led to permanent drug discontinuation. The incidence of SAE's leading to drug discontinuation was highest in the tamsulosin group (6% vs. 5% in the other 2 treatment groups). The most common SAE's by SOC (reported in ≥ 5 subjects in any treatment group) included neoplasms, cardiac disorders, renal and urinary disorders, nervous disorders, and infections. The incidence of SAE's leading to drug discontinuation was not higher in the co-administration group compared to each monotherapy group for any specific SOC (Table 9.)

Table 9: Common SAE's (≥ 5 subjects/group) leading to drug discontinuation by System Organ Class (cumulative, ITT)

System Organ Class	Co-administration N = 1610 n (%)	Dutasteride N = 1623 n (%)	Tamsulosin N = 1611 n (%)
Year 2: Any SAEs leading to drug discontinuation	52 (3)	47 (3)	72 (4)
Cumulative: Any SAEs leading to drug discontinuation	78 (5)	79 (5)	101 (6)
Neoplasms	30 (2)	27 (2)	42 (3)
Cardiac disorders	19 (1)	18 (1)	13 (<1)
Renal and urinary disorders	3	11	16 (1)
Nervous system disorders	9	5	8
Infections	7	5	1

Source: NDA 22-460, Module 5.3.5.1.22, Table 5
Primary Clinical Review of NDA 21-319/S014, p. 40

Cumulative non-SAE's leading to drug discontinuation: A total of 332 subjects (7%) permanently discontinued study drug due to a non-SAE. A higher incidence of drug discontinuation was seen in the co-administration group compared to each monotherapy group (8% vs. 6%). This difference was primarily attributable to more drug discontinuation from reproductive and breast disorders in the co-administration group. The most common non-SAE's leading to drug discontinuation by SOC was reproductive and breast disorders and by PT was erectile dysfunction. (Table 10).

Table 10: Non-SAEs leading to drug discontinuation by System Organ Class and Preferred Term (cumulative, ITT)

System Organ Class * Preferred Term	Co-administration N = 1610 n (%)	Dutasteride N = 1623 n (%)	Tamsulosin N = 1611 n (%)
Year 2: Any non-SAE leading to drug discontinuation	112 (7)	80 (5)	76 (5)
Cumulative: Any non-SAE leading to drug discontinuation	129 (8)	101 (6)	102 (6)
Reproductive system and breast disorders	57 (4)	26 (2)	31 (2)
* Erectile dysfunction	* 23 (1)	* 17 (1)	* 18 (1)
* Ejaculation failure	* 8	* 0	* 2
* Nipple pain	* 8	* 2	* 1
* Breast tenderness	* 7	* 3	* 0
* Gynecomastia	* 6	* 2	* 2
* Retrograde ejaculation	* 6	* 2	* 3
Psychiatric disorders	17	16	7
* Libido decreased	* 11	* 9	* 4
Renal and urinary disorders	15	8	17
Gastrointestinal disorders	12	14	14
Neoplasm benign, malignant and unspecified	11	10	19
* Prostate cancer	*8	*10	* 19

Source: NDA 22-460, Module 5.3.1.22, Listing 6 and Table 6, MO analysis

In the Year 2 data of ARI40005, the most common non-SAEs leading to drug discontinuation where the incidence in the co-administration group significantly exceeded that of each monotherapy group were erectile dysfunction, libido decreased, ejaculation failure, and breast disorders. Most drug discontinuations due to reproductive and breast disorders occurred during the first 2 years of the study for all 3 treatment groups.

Common adverse events (AE's):

No additional safety information on common adverse events seen in ARI40005 was submitted in the current NDA. A summary of the Year 2 data for common adverse events for ARI40005 is presented below.

Approximately 64% of patients reported at least 1 adverse event. The most commonly reported AEs (≥ 5% in any treatment group) were in the SOCs infections, reproductive

and breast disorders, and gastrointestinal disorders. The 3 most common AEs by PTs were erectile dysfunction, nasopharyngitis, and hypertension. The incidence of erectile dysfunction, retrograde ejaculation, decreased libido, upper respiratory tract infection, and ejaculation failure was higher in the co-administration group compared to each monotherapy group. The higher incidence of ejaculatory disorders in the co-administration group (3- to 5-fold higher than dutasteride and tamsulosin monotherapy, respectively) reached statistical significance ($p < 0.05$). (Table 11).

Table 11: Common Adverse Events by Treatment Group (Year 2)

Preferred Term	Co-administration N = 1610 n (%)	Dutasteride N = 1623 n (%)	Tamsulosin N = 1611 n (%)
Any AE (Year 2)	1048 (65)	1039 (64)	1011 (63)
Erectile dysfunction	132 (8)	118 (7)	72 (4)
Hypertension	81 (5)	98 (6)	90 (6)
Nasopharyngitis	80 (5)	91 (6)	90 (6)
Common AEs of co-administration group > dutasteride and tamsulosin groups			
Preferred Term	Co-administration	Dutasteride	Tamsulosin
Erectile dysfunction	See above		
Retrograde ejaculation	70 (4)	10 (<1)	18 (1)
Libido decreased	60 (4)	52 (3)	28 (2)
Upper respiratory tract infection	45 (3)	36 (2)	35 (2)
Ejaculation failure	41 (3)	10 (<1)	14 (<1)

Source: Primary Clinical Review of NDA 21-319/S014, p. 43

Adverse Events of Interest:

There have been no reported cases of priapism, Intraoperative Floppy Iris Syndrome, or breast cancer in controlled clinical trials of the co-administration of dutasteride and tamsulosin.

Laboratory findings:

In NDA 21-319/S014, no safety concerns were identified for the co-administration group, compared to the monotherapy groups, in the analyses of central tendency, shifts from normal to abnormal, or outliers of laboratory measurements.

In the current NDA, the sponsor submitted cumulative data on laboratory outliers for the 4 years of ARI40005. A review of cumulative data did not reveal any higher incidence of outlier values for hematology or chemistry laboratory tests for the co-administration group compared to each monotherapy group.

Additional submissions related to safety issues:

The 120-Day Safety Update was received on July 16, 2009. This Safety Update included new SAE's which occurred between December 9, 2008, and May 1, 2009, and updates on previously submitted SAE's. The safety update also contains post-marketing safety information received between December 2, 2008, and May 1, 2009.

During the Safety Update period, 31 subjects experienced at least one SAE. Three (3) subjects died and 28 subjects experienced a non-fatal SAE. Significant safety updates on previously reported SAE's were provided for 15 patients. No new safety findings were identified in the review of the 120-Day Safety Update.

No significant findings were noted in the review of the updates of previously reported SAE's for 15 subjects.

In this NDA submission, the sponsor analyzed the following sources for post-marketing safety information for the co-administration of dutasteride and tamsulosin.

- Published literature
- GSK's worldwide safety reporting database (Operating Companies Event Accession & Notification System [OCEANS])
- FDA Adverse Event Reporting System (AERS) database
- World Health Organization (WHO) Vigibase

According the sponsor, there were no new safety findings in the published literature or from spontaneously reported adverse events databases during the update period.
No new safety signals were detected during the review of the postmarketing data of the co-administration of dutasteride and tamsulosin. (see pages 53 to 55 of the primary medical officer review).

Additional safety consideration – "heart failure"

During the review of NDA 22-460, the sponsor submitted a supplemental labeling request (SLR) to NDA 21-319/Sequence 022 submission dated July 27, 2009. This SLR requested the addition of cardiac failure in patients taking both dutasteride and an alpha blocker to the Warnings and Precautions section of the Avodart (dutasteride) label. This proposed labeling was based on data from Trial ARI40005 and Trial ARI40006 (REDUCE). The SLR submission contained summary cardiac safety data from ARI40006 (a large prostate cancer prevention trial) and ARI40005 as of January 9, 2009, which was the completion date of the treatment phase for ARI40005. The final study reports for ARI40005 (Year 4) and ARI40006 were submitted to NDA 21-319 on November 4, 2009, and September 29, 2009, respectively. However, the submissions containing the Year 4 analyses of ARI40005 (NDA 21-319/S021) and the prostate cancer prevention trial ARI40006 (NDA 21-319/S016) were withdrawn due to discrepancies in the investigator identification information. The datasets containing the safety information for these two trials were resubmitted to NDA 21-319/Sequence 022 on February 11, 2010.

According to the sponsor, "cardiovascular events were evaluated prospectively as events of special interest in Study ARI40005…..due to previous questions from the European Regulatory Authorities about the hypothetical potential for long-term dutasteride therapy to induce a hypogonadal state leading to an increased risk of cardiovascular events." The specific cardiovascular (CV) events of interest, which were composite AE terms comprising multiple MedDRA PTs, included acute coronary syndrome, ischemic coronary artery disorders/atherosclerosis, cardiac arrhythmias/ventricular, peripheral vascular disease, ischemic cerebrovascular events, and cardiac failure. The proportions of subjects with any CV AE of interest and with individual composite CV AE were similar among the 3 treatment groups, with the exception of cardiac failure. (Table 12).

Table 12. Number of subjects with CV events of interest in ARI40005 (ITT, Year 4)

Cardiovascular Event of Interest (Composite Term)	Dut + Tam (N=1610) n (%)	Dutasteride (N=1623) n (%)	Tamsulosin (N=1611) n (%)
Any Cardiovascular Event of Interest	95 (5.9)	93 (5.7)	92 (5.7)
Ischaemic Coronary Artery Disorders/Atherosclerosis	34 (2.1)	36 (2.2)	32 (2.0)
Acute Coronary Syndrome	30 (1.9)	31 (1.9)	28 (1.7)
Cardiac Failure	14 (0.9)	4 (0.2)	10 (0.6)
Cardiac Arrhythmias	3 (0.2)	5 (0.3)	6 (0.4)
Peripheral Vascular Disease	2 (0.1)	2 (0.1)	1 (<0.1)
Ischemic Cerebrovascular Events	24 (1.5)	26 (1.6)	24 (1.5)

Source: NDA 21-319/S0022, Module 5.3.6, Table 5, p.18

A summary of cardiac failure events is shown in Table 13. The composite term "cardiac failure" included the Preferred Terms cardiac failure congestive, cardiac failure, left ventricular failure, cardiac failure acute, cardiogenic shock, left ventricular failure acute, right ventricular failure and right ventricular failure acute. Cardiac failure was not pre-defined in the study protocol but was prospectively defined in the Reporting and Statistical Analysis Plan. According to the SLR and NDA 22-460 submissions, after approximately 4 years of treatment, more subjects in the co-administration group (14) than either dutasteride (4) or tamsulosin (10) experienced a composite cardiac failure AE. The time of onset of cardiac failure ranged from 12 days to 48 months post-randomization; the median time of onset of first cardiac failure was approximately 22, 17, and 27 months for the co-administration, dutasteride, and tamsulosin groups, respectively.

Table 13: Summary of cardiac failure events (cumulative, ITT)

	Co-administration N=1610 n	Dutasteride N=1623 n	Tamsulosin N=1611 n
Year 2 cardiac failure	9	2	4
Cumulative cardiac failure	14	4	10
SAE's -Deaths* -Nonfatal SAEs	10 3 7	3 3 0	7 2 5
Leading to drug discontinuation	5	3	2
Resolved (on therapy)	9 (8)	0	3 (2)
Time of first cardiac failure • Year 0-2 • Year 3-4	 • 9 • 5	 • 2 • 2	 • 4 • 6

Source: NDA 22-460, Module 5.3.5.1.22, Listings 3 & 4, cardiac failure case narratives, MO analysis
*Deaths = deaths directly associated with "cardiac failure"

During the review of NDA 21-319/S014 (approved on June 18, 2008), it was noted that the number of patients who experienced "cardiac failure" was numerically higher than in either of the monotherapy (dutasteride or tamsulosin) groups in the two year data. (Table 14).

Table 14: Cardiovascular AE's of interest occurring in ≥ 5 subjects in any treatment group

	Number (%) Subjects		
Composite AE category	Combination N=1610	Dutasteride N=1623	Tamsulosin N=1611
Any CV AE	53 (3.3)	52 (3.2)	58 (3.6)
Ischemic coronary artery disorders/atherosclerosis[a]	18 (1.1)	18 (1.1)	22 (1.4)
Acute coronary syndrome[b]	17 (1.1)	15 (0.9)	18 (1.1)
Ischemic cerebrovascular events	10 (0.6)	15 (0.9)	9 (0.6)
Cardiac failure	9 (0.6)	2 (0.1)	4 (0.2)
Cardiac arrhythmias	1 (<0.1)	5 (0.3)	5 (0.3)

Source: Study ARI40005 Table S50
a. Category includes coronary artery disease
b. Category includes myocardial infarction

Source: Summary of Clinical Safety, Table 57, p. 72

In my review of the two year data from ARI40005 on June 18, 2009, I concluded that "the number of patients who experienced cardiac failure in the co-administration group was numerically higher than in either of the monotherapy groups. I agree with the medical officer's conclusion (pages 49-52 of the primary medical officer review) that

cardiac failure is not a significant safety concern in patients taking both dutasteride and tamsulosin. An individual review of the cases of cardiac failure showed that the majority were unlikely to be drug related, the incidence of cardiac failure in the co-administration group did not exceed the background incidence, and clinical evidence of causal association between cardiac failure and either dutasteride or tamsulosin is lacking."

In the SLR submission, the sponsor also submitted cardiac failure safety data from a large dutasteride prostate cancer prevention trial. Trial ARI40006 was a randomized, double-blind, placebo-controlled 4-year study evaluating the effect of dutasteride monotherapy compared to placebo on the risk of biopsy detectable prostate cancer in approximately 8,000 men. The study population of ARI40006 appeared to be similar to that of ARI40005 with respect to baseline demographics and cardiovascular risk profile. The cumulative incidence of composite cardiac failure was 0.7% (30 subjects) in the dutasteride group compared to 0.4% (15 subjects) in the placebo group (Table 15).

Table 15: Subjects with Cardiac Failure AE's in ARI40006 (ITT, Year 4)

Composite Term MedDRA Preferred Term	Placebo n (%) N=4126	Dutasteride n (%) N=4105
Any Cardiac Failure AE	15 (0.4)	30 (0.7)
Cardiac Failure	7 (0.2)	16 (0.4)
Congestive cardiac failure	5 (0.1)	8 (0.2)
Acute cardiac failure	1 (<0.1)	3 (<0.1)
Congestive cardiomyopathy	2 (<0.1)	1 (<0.1)
Cardiogenic shock	0	1 (<0.1)
Left ventricular failure	1 (<0.1)	0
Cardiopulmonary failure	0	1 (<0.1)

Source: Source Table 4

Source: NDA 21-319, Sequence 0022, Module 5.3.6, p. 15

In addition to trials ARI40005 and ARI40006, the sponsor also reanalyzed results from three placebo-controlled phase 3 trials for BPH with respect to heart failure.

The sponsor concluded that an integrated analysis did not demonstrate a difference between dutasteride monotherapy and placebo in the incidence of cardiac failure (composite term). However, the sponsor did conclude that their analysis demonstrated an imbalance of composite cardiac failure events in ARI40006 and ARI40005 when dutasteride was concomitantly dosed with an alpha-adrenergic antagonist, such as tamsulosin. The sponsor believes that no clear drug-causality or pathophysiologic explanation is apparent at this time.

In the SLR submission, the sponsor requested that the finding of a higher incidence of composite cardiac failure seen with the co-administration of dutasteride and an alpha-adrenergic antagonist be added to the Warnings and Precautions section of the Avodart prescribing information. The wording proposed by the sponsor for the Highlights, Warnings and Precautions section of the label is "The incidence of cardiac failure (a

composite term) was higher among subjects taking the combination of AVODART and an alpha-blocker, primarily tamsulosin, than among subjects not taking the combination."

The congestive heart failure issue is discussed on pages 36 to 47 of the primary medical officer's review. Although the sponsor has not yet requested that the congestive heart failure information relating to dutasteride and alpha blockers (including tamsulosin) be included in the labeling proposed for NDA 22-460, approval of the SLR for NDA 21-319 would require that the information also be included in the label for NDA 22-460.

An analysis of the "cardiac failure" issue is complicated by the fact that there is no placebo control group in ARI40005 and no alpha blocker comparator arm in ARI40006. In addition, the finding of a potential risk of developing heart failure with dutasteride is not consistent with the results of pooled placebo-controlled data from BPH studies with dutasteride, published literature, or biologic plausibility. The primary medical officer, cross-discipline team leader, and a consultant from the Division of Cardiorenal Products reviewed in depth the submitted data related to "heart failure."

The primary medical officer review of case narratives for the composite definition of heart failure in trials ARI40005 and ARI40006 revealed some coding errors. In trial ARI40005, after exclusion of miscoded cases (e.g., circulatory collapse secondary to aortic aneurysm rupture or fatal myocardial infarction coded as cardiac failure), the total numbers of subjects with composite cardiac failure were 12 for the co-administration group (0.7%), 2 for dutasteride (0.1%), and 8 for tamsulosin (0.5%). In trial ARI40006, after 4 cases of cardiac failure in the dutasteride group and 1 case in the placebo group were excluded because of miscoding, 26 dutasteride subjects (0.6%) and 14 placebo subjects (0.3%) had a composite cardiac failure AE.

The primary medical officer concluded:

1. "Compared to placebo, does dutasteride increase the risk of composite cardiac failure? Study ARI40006 provides the first and only evidence known to this reviewer which suggests a potential increase in risk of developing CHF with dutasteride. This finding is not consistent with those from pooled placebo-controlled data from BPH studies with dutasteride, published literature, or biologic plausibility. A review of the case narratives indicated that, for a majority of CHF cases, the patients' co-morbidities were more likely the cause of CHF than dutasteride. The strength of the evidence does not support a direct causal link between dutasteride and CHF. However, because ARI40006 is a large, well-designed and adequately controlled trial and because the target population compromises of older men with CV risks, it may be prudent to include the CHF data in the Adverse Reactions section of the Avodart label for dutasteride monotherapy.

2. Compared to placebo, does tamsulosin increase the risk of composite cardiac failure? To date, there have been no long-term placebo-controlled studies evaluating CHF outcome with tamsulosin or other alpha-blockers. FDA has previously concluded that there was insufficient evidence to warrant labeling doxazosin or other alpha blockers

for CHF. The physiological effects of alpha adrenergic blockade could plausibly contribute to cardiac failure, especially in a compromised heart. However, this reviewer does not believe the data from ARI40005 or ARI40006 are convincing enough to justify labeling tamsulosin (or other alpha-blockers) for a contributory role in CHF.

3. Does the co-administration of dutasteride and tamsulosin increase the risk of CHF over dutasteride or tamsulosin alone? A drug-drug interaction study did not demonstrate a PK/PD interaction for tamsulosin and dutasteride, respectively. A review of the case narratives indicated all but one case of CHF (one in tamsulosin) were more likely to be attributable to the subject's co-morbidities than to drug exposure. The clinical significance of small differences between the treatment groups for a clinical syndrome that is not rare in the population of older men is questionable. The incidence of the composite cardiac failure for the co-administration group was similar to that of the pooled placebo data from the dutasteride development program. At this time, this reviewer does not believe that substantial evidence exists to indicate a cardiac failure safety signal for the co-administration of dutasteride and tamsulosin to warrant special risk management."

DRUP consulted the Division of Cardiovascular and Renal Products to evaluate the cardiac failure data from trials ARI40005 and ARI40006 and the consultant concluded the following:

DRUP consulted the Division of Cardiovascular and Renal Products (DCRP) to assess whether the available evidence indicated a safety concern of cardiac failure for the co-administration of dutasteride and tamsulosin, dutasteride alone, or tamsulosin alone. The consultant reviewed the clinical trial data of ARI40005 and ARI40006, the Sponsor's integrated analyses, and conducted an MGPS datamining analysis of postmarketing data for dutasteride + tamsulosin and for the alpha blockers alfuzosin, tamsulosin, terazosin, and doxazosin for signals for congestive heart failure. The consultant concluded the following:

- The results of Study ARI40006 were contradictory with those from pooled placebo controlled data from BPH studies with dutasteride, published literature and postmarketing surveillance. A review of the case narratives for dutasteride monotherapy indicated that with the exception of one case each in ARI40005 and ARI40006 with no known risk factors, for a majority of CHF cases, the patient's co-morbidities were more likely the cause of CHF although an association to dutasteride cannot be excluded. The CHF data may be included in the Adverse Reactions section of the Avodart label for dutasteride monotherapy at the discretion of the review division.
- FDA has previously concluded that there was insufficient evidence to warrant labeling doxazosin or other alpha blockers for CHF.
    - There have been no long-term placebo-controlled studies evaluating CHF outcome with tamsulosin or other alpha-blockers. DCRP's view has been that the increased incidence of CHF seen with the doxazosin arm in the

ALLHAT trial may be due to the beneficial effects of chlorthalidone and lisinopril on CHF. The six-year rate of heart failure was also higher in the amlodipine arm compared to chlorthalidone (10.2% vs. 7.7%; RR, 1.38; 95% CI, 1.25-1.52) as well as to lisinopril (8.7% vs. 7.7%; RR, 1.19; 95% CI, 1.07-1.31)3 which again illustrated the fact that chlorthalidone and lisinopril are beneficial in heart failure while amlodipine has no effect.

- Again on review of the ARI40005 and ARI40006 narratives, there were only two cases in the tamsulosin arm of ARI40005 and one case in ARI40006 on α-blocker therapy with no known risk factors other than advanced age. Data from these trials do not justify labeling tamsulosin (or other alpha-blockers) for a contributory role in CHF. This is re-enforced on review of the post-marketing data.

- A drug-drug interaction study did not demonstrate a PK/PD interaction for tamsulosin and dutasteride, respectively. A review of the case narratives indicated all the cases of CHF in the combination group were more likely to be attributable to the subject's comorbidities than to drug exposure. We agree that the clinical significance of small differences between the treatment groups for a common clinical condition in the older population is questionable. The incidence of the composite cardiac failure for the coadministration group was similar to that of the pooled placebo data from the dutasteride development program. At this time, this reviewer does not believe that substantial evidence exists to indicate a cardiac failure safety signal for the co-administration of dutasteride and tamsulosin to warrant special risk management. The results of ARI40005 can be included in the adverse reactions section of the label. We recommend that the language related to post-hoc analyses of α-blocker therapy in ARI40006 be deleted.

Therefore, both the DRUP and DCRP reviewers concluded that the strength of the 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. However, the DRUP primary medical officer recommends including the clinical trial data from ARI40005 and ARI40006 in the ADVERSE REACTIONS section of the Full Prescribing Information (FPI) of the Avodart label. I agree and believe that this information should also be included in the labeling for the combination dutasteride/tamsulosin capsule which is the subject of this NDA review. The heart failure issue was discussed at length at a meeting attended by members of the Division of Reproductive and Urologic Products, the Office of Surveillance and Epidemiology (OSE), the Division of Drug Oncology Products (DDOP) on April 27, 2010. There was agreement that a statement in the Warnings and Precautions section of the label was currently not warranted and that the trial data would be placed in the Adverse Events section of the label.

Safety summary:

In summary, from a safety perspective, no new significant concerns were identified following review of the updated safety information for the co-administration of dutasteride and tamsulosin. The congestive heart failure safety results from Trials ARI40005 and ARI40006 will be included in the Adverse Events section of labeling. The increase in erectile and ejaculatory adverse events can be adequately managed in labeling.

9. Advisory Committee Meeting

No Advisory Committee meeting was convened for this combination drug product. Both dutasteride and tamsulosin are approved products and the co-administration of the two drugs for the treatment of BPH was approved on June 19, 2008, under NDA 21-319 (S014).

10. Pediatrics

The sponsor requested and the Pediatric Review Committee (PeRC) agreed to grant a full pediatric waiver for this product on September 23, 2009. Benign prostatic hyperplasia does not exist in children and dutasteride, because of its mechanism of action of blocking the conversion of testosterone to dihydrotestosterone, is contraindicated in children.

11. Other Relevant Regulatory Issues

Financial disclosure:

All of the principal investigators and sub-investigators from the two sites of study 109882 had no disclosures to report. Adequate information was submitted to demonstrate compliance with financial disclosure requirements.

Division of Scientific Investigation (DSI):

The DSI inspected the GSK Bioequivalence Laboratory where the samples were analyzed for trial ARI109882 and two Covance clinical sites where the study was conducted. A Form 483 was issued to GSK following inspection of the analytical site from December 7-10, 2009. One of the two Covance clinical sites also received a Form 483 following inspection on July 13-21, 2009.

GSK responded to the issues raised in the 483 for the analytical site on January 8, 2010. Both DSI and clinical pharmacology reviewed the sponsor's responses to the 483 deficiencies. DSI concluded that "following evaluation of all Form FDA-483 items and written responses from GSK and Covance-Austin, DSI concludes that the inspectional findings should not have significant impacts on the outcomes of study ARI109882." After review of the responses to the Form 483 deficiencies, the clinical pharmacology

reviewer amended the original clinical pharmacology review and concluded: "The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds NDA 22-460 acceptable from a Clinical Pharmacology perspective provided that a satisfactory agreement is reached regarding the labeling language." The clinical pharmacology and clinical reviewers agree that the 483 findings for the Covance clinical site do not preclude a tentative approval action for NDA 22-460.

Division of Medication Errors and Prevention (DMEPA):

DMEPA has objected to several proprietary names proposed by the sponsor to date. At the time of the writing of this review, DMEPA is reviewing the sponsor's most recent tradename submission.

Addendum: On June 11, 2010, DMEPA approved the tradename "Jalyn."

Division of Drug Marketing, Advertising, and Communication (DDMAC):

DDMAC reviewed the sponsor's proposed physician's label. Their comments and recommendations were considered in label negotiations conducted with the sponsor.

Division of Risk Management (DRISK):

DRISK's comments and recommendations were considered for incorporation into the Patient Package Insert (PPI).

12. Labeling

Labeling in Physicians Labeling Rule format was submitted and reviewed. Labeling negotiations with the sponsor have been completed. The Warnings and Precautions section of labeling is consistent with the previously approved combination dutasteride/tamsulosin labeling. Two significant additions to the labeling have been made:

1. The Warning and Precaution for the reduction in total serum prostate-specific antigen now reads:

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

2. The cardiac failure data from Trials ARI40005 and ARI40006 have been placed in the Adverse Events section (6.1)

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 monotherapy 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.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action:

I agree with the cross discipline team leader and primary medical officer, as well as the clinical pharmacology, chemistry, statistical, and DSI reviewers that NDA 22-460 (dutasteride/tamsulosin combination tablet) should be approved for the indication treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate. Labeling negotiations with the sponsor have been successfully completed. Multiple tradenames have been, to date, rejected by DMEPA and this combination drug product will be approved without a tradename.

Addendum (June 14, 2010): On June 11, 2010, DMEPA approved the tradename "Jalyn."

Risk Benefit Assessment:

The co-administration of dutasteride and tamsulosin for the treatment of BPH was approved on June 19, 2008. Trial ARI40005 (using the IPSS as the primary endpoint) demonstrated that the co-administration of dutasteride and tamsulosin was more effective than either drug alone. In the current NDA submission (22-460), bioequivalence for both dutasteride and tamsulosin was demonstrated between the combined capsule and the two drugs administered separately at the same time. The two year efficacy data (primary endpoint is IPSS) from trial ARI40005 were cross-referenced. Efficacy for the combined dutasteride and tamsulosin product has, therefore, been adequately demonstrated.

The safety of both individual components of the combination drug is well described. Tamsulosin (Flomax) was approved in 1997 and dutasteride (Avodart) was approved in 2001. These two drugs act by different mechanisms. The co-administration of dutasteride and tamsulosin for the treatment of symptomatic BPH in men with an enlarged prostate was approved on June 19, 2008, in efficacy supplement 014 to NDA 21-319. No new significant safety concerns were identified following review of either the 2 year or

updated safety information from trial ARI40005. In summary, from a safety perspective, no new significant concerns were identified following the co-administration of dutasteride and tamsulosin in NDA 22-406. The increase in erectile and ejaculatory adverse events seen with the combination or co-administration of dutasteride and tamsulosin can be adequately managed in labeling. New wording was added to the Warnings and Precautions section of labeling concerning the effect of the drug on serum PSA values and the cardiac failure data from trials ARI40005 and ARI40006 were added to the Adverse Events section of labeling.

Recommendations for Risk Evaluation and Mitigation Strategies (REMS)/Post Marketing Requirement:

None.

With the approval of the tradename "Jalyn" and the finding that the carton labeling is acceptable, there are no outstanding issues pertaining to this NDA and an approval letter will be sent to the sponsor.

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEORGE S BENSON
06/14/2010