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APPLICATION NUMBER:

022460Orig1s000

MEDICAL REVIEW(S)

Medical Officer Review of NDA Resubmission

Application Number:	22-460/S0022
Date of submission:	April 14, 2010
PDUFA date:	June 14, 2010
Date review completed:	June 10, 2010
Product:	Dutasteride/tamsulosin fixed-dose oral combination capsule
Indication:	Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate
Applicant:	GlaxoSmithKline

Executive Summary:

The Applicant submitted a Class I Resubmission in response to a Tentative Approval for NDA 22-460 on April 14, 2010. The resubmission contained proposed labeling for the prescriber and patient. Labeling negotiations have been completed. Although the trade name for the product has yet to be approved, this is not an approvability issue. From a clinical perspective, NDA 22-460 should now be **approved**.

Regulatory Background:

A tentative approval letter was issued for NDA 22-460 (fixed-dose 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.

In the resubmission to NDA 22-460 submitted on April 14, 2010, the Applicant submitted updated labeling and is the subject of this review.

Reviewer's comment*: In the resubmission cover letter dated April 14, 2010, the Applicant indicated that there was no new chemistry or safety update information since the tentative approval date of January 20, 2010.*

The Office of Surveillance and Epidemiology (OSE) has yet to determine an acceptable trade name as of June 10, 2010. An action for NDA 22-460 will be taken on the PDUFA date of June 14, 2010, with or without an approved trade name.

Medical Officer's Review:
Labeling negotiations have been successfully completed. The agreed upon labeling changes regarding cardiac failure submitted to NDA 21-319/S018 (July 27, 2009) were also incorporated into the labeling for NDA 22-460. The reader is referred to the clinical review of the Supplemental Labeling Request (SLR) submitted to NDA 21-319/S018 for detailed discussion of the analyses of the cardiac failure data. A brief summary of the SLR review is presented below:

- Two recently completed trials in the dutasteride clinical program (ARI40005-BPH indication, ARI40006-risk reduction of prostate cancer) demonstrated a numerical imbalance in the incidence of cardiac failure for the co-administration of dutasteride and tamsulosin compared to each monotherapy (ARI40005) and for the dutasteride group compared to placebo (ARI40006). The Applicant proposed to add the cardiac failure findings to the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the Avodart label (NDA 21-319).
- After reviewing all available data (proprietary and published literature), DRUP and the Division of Cardiovascular and Renal Products (consultant) 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. Both Divisions recommended including the cardiac failure data from ARI40005 and ARI40006 in the ADVERSE REACTIONS section of the Avodart label.
- An internal meeting was held with members of the Division of Drug Oncology Products (DDOP), which is reviewing study ARI40006 for the prostate cancer prevention indication, and the Office of Surveillance and Epidemiology (OSE) to discuss the cardiac failure findings. Both DDOP and OSE believed that these findings did not indicate a safety signal of cardiac failure for dutasteride, alone or in combination with an alpha-adrenergic antagonist. DDOP and OSE concurred with DRUP's position to include the clinical trial data for cardiac failure in the ADVERSE REACTIONS section of the Avodart label.
- Cardiac failure labeling recommendations also applied to the product label of the fixed-dose combination capsule containing dutasteride and tamsulosin (NDA 22-460), which relied primarily on the safety and efficacy findings of ARI40005.
- 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.

***Reviewer's comment**: No postmarketing risk management strategies or requirements are recommended for NDA 22-460 other than routine surveillance.*

The complete clinical review of NDA 22-460 (dated January 19, 2010) is appended to this memo for ease of review.

Recommended Regulatory Action: From a clinical perspective, NDA 22-460 should now be **approved**.

CLINICAL REVIEW

Application Type	N
Application Number(s)	22-460
Priority or Standard	S
Submit Date(s)	March 20, 2009
Received Date(s)	March 20, 2009
PDUFA Goal Date	January 20, 2010
Division / Office	Reproductive and Urologic Products
Reviewer Name(s)	Christine P. Nguyen
Review Completion Date	January 15, 2010
Established Name	Dutasteride/tamsulosin
(Proposed) Trade Name	Flodart
Therapeutic Class	5-alpha reductase inhibitor/alpha adrenergic antagonist
Applicant	GlaxoSmithKline
Formulation(s)	Oral capsule
Dosing Regimen	Fixed-dose combination dutasteride 0.5 mg/tamsulosin 0.4 mg once daily
Indication(s)	Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate

Intended Population(s)	Men with symptomatic BPH and an enlarged prostate

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the **clinical perspective**, fixed-dose combination dutasteride 0.5 mg/tamsulosin 0.4 mg capsule (DTC) taken once daily should 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 the ongoing 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).

From a **regulatory perspective**, this NDA could only be **tentatively approved** at this time because the patent/exclusivity for tamsulosin does not expire until April 27, 2010. The final approval determination is contingent upon labeling negotiations, which will be addressed during the next review cycle.

1.2 Risk Benefit Assessment

The data to support the co-administration of dutasteride and tamsulosin came from one large, international, multicenter, randomized, double-blind, parallel group study of 4-year duration in men with moderate to severe BPH symptoms and an enlarged prostate (study ARI40005). The first 2 years of the trial were designed to evaluate the safety and efficacy of dutasteride and tamsulosin administered concomitantly ("co-administration" group) compared to each monotherapy in improving BPH symptoms. The last 2 years of the study were designed to determine the effects of the co-administration regimen on the time to event of acute urinary retention (AUR) or BPH-related prostate surgery. The Year 4 analyses of ARI40005 will be submitted in a separate submission.

Benefit: The co-administration of dutasteride and tamsulosin resulted in statistically significant improvement in the primary endpoint (International Prostate Symptom Score or IPSS) and the main secondary endpoint (maximum urinary flow rate or Qmax) compared to each monotherapy at 24 months. At Month 24, the mean difference between the co-administration and dutasteride groups was -1.3 units and between the co-administration therapy and tamsulosin was -1.8 units (see Table 1). Although Trial ARI40005 did not have a placebo-control group, there was sufficient evidence to reasonably conclude that dutasteride and tamsulosin monotherapy performed as expected. In summary, the benefit of the co-administration regimen over each monotherapy was established based on substantial evidence of effectiveness for the

products' intended use, as demonstrated by one large adequate and well-controlled clinical study, and satisfactory fulfillment of the Combination Drug Rule.
No clinical efficacy studies were conducted with DTC. The efficacy of DTC is expected to be comparable to that of the co-administration regimen because the 2 products were shown to be bioequivalent in study ARI109882.

Table 1: Change from baseline IPSS at Month 24 in ARI40005 (LOCF, ITT)

Time point	**Mean change from baseline IPSS (SE)**					
	N	Combination	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 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

Risk: The safety database of DTC includes: a) the clinical bridge to the safety database of ARI40005, which consisted of 4844 patients, 1610 of whom received at least one dose of the co-administration regimen and b) 110 healthy male subjects who received at least one dose of DTC. The study population in ARI40005 is representative of the target population of DTC.

The safety and tolerability of the co-administration regimen compared to each monotherapy was overall acceptable based on the Year 2 data of ARI40005. Compared to each monotherapy, the co-administration regimen was not associated with an excess of overall treatment-emergent adverse events, deaths, or non-fatal serious adverse events. No significant excesses in hepatic, hematologic, or renal toxicity were identified in the co-administration group compared to each monotherapy. Significantly more subjects in the co-administration group withdrew due to an adverse event (AE) or reported a drug-related adverse event, which was primarily sexual or breast-related. Among the common adverse events, the incidence of reproductive and breast disorders was higher in the co-administration group (20%) than dutasteride (16%) or tamsulosin (12%). Compared to each monotherapy, the incidence of ejaculation disorders was 3- to 5-fold higher for the co-administration group and this difference was statistically significant. Updated safety information on significant adverse events (from cut-off date of the 120-Day Safety Update of Year 2 of ARI40005 [September 1, 2007] to the December 8, 2008 cut off date of the DTC NDA) and preliminary ~ 4-year cumulative safety information from ARI40005 did not reveal any new trend or unexpected safety findings compared to the Year 2 data of ARI40005, with the exception of composite cardiac failure event.

Composite cardiac failure included all events coded to the MedDRA 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. The incidence of cardiac failure over 4 years was higher in the co-administration group (12 subjects, 0.7%) than tamsulosin (9 subjects, 0.6 %) or dutasteride (2 subjects, 0.1%). A review of the case narratives indicated that all but one (1 tamsulosin subject) had more plausible alternative explanations for the adverse outcome or had clinical experience inconsistent with cardiac failure. The concomitant administration of dutasteride and tamsulosin does not alter tamsulosin pharmacokinetic or dutasteride pharmacodynamic parameters. The incidence of cardiac failure in the co-administration group (0.7%) was similar to that observed in the integrated analysis of placebo data from the major dutasteride trials whose study populations were similar to that of ARI40005. Cardiac failure is not a labeled adverse reaction of 5-alpha reductase inhibitors or alpha-adrenergic antagonists. At this time, this reviewer does not believe the totality of evidence indicates a significant cardiac failure signal for the co-administration regimen.

The cardiac failure data from Trial ARI40005 reviewed by DRUP (co-administration of dutasteride and tamsulosin for BPH treatment) and Trial ARI40006 reviewed by the Division of Drug Oncology Products (dutasteride vs. placebo for reduction of the risk of prostate cancer) are currently being consulted to the Division of Cardiovascular and Renal Products. Because the comprehensive evaluation of the cardiac failure issue will require interdivisional discussions, it is premature at this time to conclude whether or not cardiac failure is a safety concern and to propose any potential risk management strategy for NDA 22-460. The approvability of this NDA depends primarily on the Year 2 data of ARI40005 and will be handled separately from the cardiac failure issue.

***Reviewer's comment**: Cardiac failure is the subject of review in* (b) (4) *:*

1. *Supplement Labeling Request (SLR) to NDA 21-319 dated July 27, 2009, to include cardiac failure in the Warnings and Precautions section of the AVODART label*

(b) (4)

No unexpected safety findings were identified in healthy subjects receiving DTC.

Risk:benefit conclusion: The overall risk/benefit profile for the combination of dutasteride and tamsulosin was assessed in the efficacy supplement 014 to NDA 21-319 and was determined to be favorable. Since the approval of this efficacy supplement, no significant safety issues, other than the aforementioned cardiac failure, have been identified for the co-administration of dutasteride and tamsulosin. Cardiac failure will be addressed separately from this NDA. At this time, this reviewer does not believe the strength of the evidence of cardiac failure precludes the approval of this NDA. It is anticipated that the overall risk benefit profile for DTC will be comparable to the currently approved co-administration of dutasteride and tamsulosin because the 2 products are bioequivalent.

1.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No post-marketing risk evaluation and mitigation strategies are warranted for DTC at this time.

1.4 Recommendation for Postmarketing Requirements and Commitments

No new safety concerns have been identified to require actions other than routine post-marketing surveillance.

2 Introduction and Regulatory Background

2.1 Product Information

The dutasteride/tamsulosin combination capsule (DTC) is a hard shell capsule containing dutasteride intermediate (soft gelatin capsule containing 0.5 mg dutasteride) and tamsulosin hydrochloride product intermediate (pellet containing 0.4 mg tamsulosin hydrochloride). The manufacture of DTC involves the over-encapsulation of the intermediates of the 2 active ingredients. The drug substance and dose of each active ingredient are the same as those commercially available for dutasteride 0.5 mg and tamsulosin 0.4 mg that were used in study ARI40005.

The product information of dutasteride and tamsulosin monotherapies as well as for the co-administration of these 2 drugs is summarized Table 2 below.

Table 2: Summary of Product Information

Product	Dutasteride	Tamsulosin	Co-administration of dutasteride and tamsulosin
Trade name (U.S.)	Avodart	Flomax	Avodart + tamsulosin
Indication (s) (year of approval)	Treatment of BPH in men with an enlarged prostate to: • Improve symptoms (2001) • Reduce the risks of acute urinary retention and need for BPH-related surgery (2002)	The treatment of symptomatic BPH (1997)	Treatment of symptomatic BPH in men with an enlarged prostate (2008)
Dose and regimen	0.5 mg once daily	0.4 mg (up to 0.8 mg) once daily	0.5 mg dutasteride + 0.4 mg tamsulosin once daily
Intended population	Men with symptomatic BPH and an enlarged prostate	Men with BPH	Men with symptomatic BPH and an enlarged prostate
Sponsor	GSK	Boehringer Ingelheim	GSK

Source: Approved product labels of Avodart (6/2008) and Flomax (10/2009)

2.2 Currently Available Treatments for Proposed Indication

Benign prostatic hyperplasia (BPH) is a common medical condition among older men and affects approximately 50% of men after the age of 60 years. BPH can cause considerable disability, leading to obstructive and/or irritative voiding symptoms requiring medical or surgical treatment. The decision to treat is usually based on the type and severity of symptoms and the patient's tolerance for these symptoms. In general, men who develop significant upper tract changes (e.g., hydronephrosis, renal dysfunction) or significant lower tract changes (e.g., urinary retention, recurrent infection, bladder decompensation) require invasive therapy. Otherwise, symptomatic BPH may be treated medically with an alpha-adrenergic antagonist (doxazosin, alfuzosin, terazosin, tamsulosin, and silodosin), a 5α-reductase inhibitor (dutasteride, finasteride) or the combination of both (dutasteride + tamsulosin, finasteride + doxazosin). Treatment with a 5α-reductase inhibitor (5ARIs), alone or in combination, is typically reserved for men with symptomatic BPH associated with demonstrable prostatic enlargement. Table 3 summarizes the currently approved drug treatments for symptomatic BPH.

Table 3: FDA-approved pharmacologic treatments of BPH

Pharmacologic Class	Agents	Indication (s)	Typical onset of symptom relief	Proposed mechanism of action	Common adverse reactions
5α-reductase inhibitors	Finasteride Dutasteride	Treatment of symptomatic BPH; reduction in risks of AUR, BPH-related surgery	6-12 months	Decrease prostate volume	Sexual dysfunction (libido decreased, impotence, ejaculation disorders) Breast disorders
Alpha-adrenergic antagonists	Doxazosin Alfuzosin Terazosin Tamsulosin Silodosin	Treatment of symptomatic BPH	2-4 weeks	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	4 weeks	Combined mechanisms	Ejaculation disorder Sexual disorders Breast disorders

2.3 Availability of Proposed Active Ingredient in the United States

Both dutasteride 0.5 mg soft gelatin capsules and tamsulosin 0.4 mg capsules are approved and marketed in the U.S for the treatment of BPH.

2.4 Important Safety Issues With Consideration to Related Drugs

5 α-reductase inhibitors (5ARIs):

- 5ARIs may cause abnormalities of the external genitalia of a male fetus and are contraindicated in women who are or who may potentially become pregnant. These women are cautioned not to handle crushed or broken drug capsules because of the possibility of systemic drug absorption and the subsequent potential risk to a male fetus.
- 5ARIs decrease serum PSA levels by approximately 50% after 3 to 6 months of treatment and this suppression is maintained throughout the treatment period. This pharmacodynamic effect should be taken into consideration when interpreting PSA results for prostate cancer screening and monitoring. Any rise in PSA levels after nadir may signal the presence of prostate cancer and should be evaluated accordingly.

- Common adverse reactions include impotence, decreased libido, decreased volume of ejaculate, ejaculation disorder, and breast disorders. The association between male breast cancer and long-term 5ARI use is currently unknown.

Alpha-adrenergic antagonists:

- Alpha-adrenergic antagonists cause peripheral adrenergic blockade, leading to peripheral vasodilatation and subsequent fall in blood pressure. Clinically significant outcomes are orthostatic hypotension and syncope. The hypotensive effects can be potentiated by the concomitant use of other alpha-adrenergic antagonists or phosphodiesterase-5 inhibitors (PDE5-Is). Alpha-adrenergic antagonists should not be used concomitantly with one another; alpha-adrenergic antagonist should be used with caution in combination with a PDE5-I.
- Rare but potentially serious adverse effects of alpha-adrenergic antagonist treatment include Intraoperative Floppy Iris Syndrome (IFIS) and priapism.
- Hypersensitivity reactions to tamsulosin have been observed in patients with sulfa allergy.
- Common adverse reactions include dizziness, somnolence, asthenia, nasal congestion, rhinitis, and abnormal ejaculation.

Co-administration of 5ARI and alpha-adrenergic antagonist:
In controlled studies, no unexpected clinical adverse experience was observed other than those already labeled for 5ARIs and alpha-adrenergic antagonists. The co-administration of these 2 products resulted at least an additive effect on ejaculatory disorders compared to each monotherapy.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

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. Tamsulosin (Flomax) 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 Avodart 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 Applicant of 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 support a marketing 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 DTC.

On September 19, 2008, the Applicant submitted pre-NDA questions concerning the content and format for the DTC NDA submission. The Division provided responses to these questions via written communication dated October 23, 2008.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Division of Scientific Investigation (DSI) was conducted a routine audit for study ARI109882, because this was the key BE study providing the clinical bridge to the pivotal safety and efficacy study ARI40005. DSI issued a "VAI – Voluntary Action Indicated" to the bioanalytical site and one of the 2 clinical sites. After evaluating the Applicant's responses, DSI concluded that "the inspectional findings should not have significant impact on the outcomes of study ARI109882." The clinical pharmacology team concurred that the deficiencies cited in the DSI audit would not likely alter the overall results of study ARI109882. From DSI's perspective, there are no outstanding issues for this application.

The Applicant has in place standard operating procedures that are consistent with the ICH Good Clinical Practice, including archiving of source data, data validation of CRF data, internal audits, and the use of a validated central laboratory.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all clinical studies submitted were conducted in compliance with Good Clinical Practices. In support of this, the Applicant submitted samples of informed consent, documents of IRB approval, and required case report forms.

3.3 Financial Disclosures

Form FDA 3454 (4/06), dated February 19, 2009, and signed by Craig A. Metz, Ph.D., Vice President, Regulatory Affairs, GlaxoSmithKline, was submitted. Financial disclosure documents were submitted for clinical investigators (principal and sub-investigators) of study 109882, the key BE study. Financial disclosures for study ARI40005, the primary study supporting the safety and efficacy of the co-administration of dutasteride and tamsulosin, was submitted previously in efficacy supplement 014 to NDA 21-319. This approach is acceptable, because the approval of this NDA is based on study 109882 with cross-referencing to study ARI40005.

All of the principal investigators (2) and sub-investigators (6) from 2 sites of study 109882 had no disclosures in the categories of compensation potentially affected by the outcome of the covered study [21 CFR 54.4(a)(3)(i), 54.2 (a)], significant payments of other sorts from the Applicant of the covered study [21 CFR 54.4 (a)(3)(ii), 54.2(f)], proprietary interest in the tested product [21 CFR 54.4(a)(3)(iii), 54.2(c)], or significant equity interest in the Applicant of the covered study product [21 CFR 54.4(a)(3)(iv), 54.2(b)].

In summary, adequate information was submitted to demonstrate compliance with financial disclosure requirements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

From the chemistry perspective, the chemistry team recommends approval of this NDA. The Office of Compliance issued an “Acceptable” recommendation for all the facilities involved in the manufacture and test of the drug substance and drug product. Because this application is tentative approved, labeling recommendations will be addressed in the next review cycle.

4.2 Clinical Microbiology

The clinical microbiology reviewer recommends approval of this NDA from a microbiology perspective.

4.3 Preclinical Pharmacology/Toxicology

No preclinical studies were conducted with DTC. No impurities were identified in the DTC product that warranted further preclinical evaluation. The Applicant relies on the

approved Avodart and Flomax package inserts to label preclinical findings for DTC. The preclinical pharmacology/toxicology team recommends approval of this NDA from a preclinical pharmacology/toxicology perspective. Because this application is tentatively approved, labeling recommendations will be addressed in the next review cycle.

4.4 Clinical Pharmacology

The clinical pharmacology team recommends the approval of this NDA from a clinical pharmacology perspective. Because this application is tentatively approved, labeling recommendations will be addressed in the next review cycle. This NDA for DTC relies on one key bioequivalence (BE) study (ARI109882) and 4 supporting biopharmaceutics studies to establish the BE of dutasteride and tamsulosin monotherapies co-administered (as in Trial ARI40005) to DTC. The BE assessment from Study ARI109882 is used to bridge the safety and efficacy data of Trial ARI40005 to DTC. The reader is referred to the clinical pharmacology review for a detailed review of the clinical pharmacology of DTC

4.4.1 Mechanism of Action

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

Dutasteride is an inhibitor of the 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. The Type 2 isoform is present in prostatic and other androgen-sensitive tissues and is believed to be important to prostatic enlargement. The Type 1 isoform is present in liver and skin and, to some extent, in the prostate. The clinical relevance of the Type 1 isoform in the prostate is unknown. 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.

4.4.2 Pharmacodynamics

No pharmacodynamic assessments were conducted with DTC. The following pharmacodynamic effects have been well-characterized for dutasteride and tamsulosin:

Dutasteride:
- Dutasteride decreases DHT levels in a dose-dependent manner. After daily dosing with dutasteride 0.5 mg, the maximum reduction in DHT is achieved within 2 weeks of therapy (median reduction of 90%) and is maintained throughout the treatment duration. The median increase in serum testosterone levels, ranging 18-22%, is seen after 8 weeks and is maintained throughout the treatment duration. Mean and median levels of serum testosterone remains within the physiologic range.
- Dutasteride 0.5 mg once daily decreases prostate-specific antigen (PSA) levels ~ 50% by 3 to 6 months of treatment.

Tamsulosin:
- Alpha-blockade results in peripheral vasodilation, which results in a fall in blood pressure.

4.4.3 Pharmacokinetics

The absorption and food effect data for DTC were obtained from Study ARI109882, the pivotal BE study. The Applicant relies on the approved Avodart and Flomax prescribing information to label the remainder of the pharmacokinetics of DTC.

The pharmacokinetics of dutasteride and tamsulosin from DTC are equivalent to the pharmacokinetics of dutasteride and tamsulosin when administered separately.

The PK parameters of dutasteride and tamsulosin observed after administration of DTC in a single dose, randomized, three-period partial cross-over study are summarized in the table below.

Geometric Means (%CV) of Serum Dutasteride and Tamsulosin Single-dose PK Parameters

Component	Condition	N	AUC (0-t) (ng·hr/mL)	C_{max} (ng/mL)	Tmax (hr)[a]	$t_{½}$ (hr)
Dutasteride	Fed	91	33.3 (78.6)	2.01 (35.5)	4.00 (1.00-6.03)	
	Fasted	46	29.2 (91.7)	2.02 (49.4)	2.00 (1.00-10.0)	
Tamsulosin	Fed	91	164 (52.6)	9.75 (44.7)	7.00 (2.00-24.0)	12.9 (28.7)
	Fasted	46	184 (46.1)	14.6 (35.3)	5.00 (2.00-8.00)	12.3 (29.6)

[a] Median (range)
Source: Primary Clinical Pharmacology review, NDA 22-460

Dutasteride:
Dutasteride has an absolute bioavailability of 60% and a Tmax ranging from 2-4 hours. Drug absorption is not significantly affected by food intake. Dutasteride has a large

volume of distribution (300-500 L) and is highly bound to plasma albumin (99.0%) and alpha-1-acid glycoprotein (96.6%). Dutasteride is extensively metabolized, primarily by the CPY3A4 and CYP3A5 isoenzymes; only a trace amount of dutasteride (<1%) is excreted unchanged in urine. Dutasteride and its metabolites are primarily excreted in feces. Approximately 55% of administered dutasteride dose is unaccounted for. The terminal half-life of dutasteride is approximately 5 weeks at steady state. No dose adjustment is anticipated in patients with renal impairment; caution should be used in hepatically impaired patients.

Tamsulosin:
Tamsulosin is almost completely absorbed (>90%) following oral intake under fasting conditions. Compared to fed conditions, administering tamsulosin under fasted conditions results in increased exposure (a 30% increase in AUC and 40-70% increase in Cmax) and a shorter time to Tmax. Tamsulosin has a volume of distribution of 16L and is extensively bound to plasma proteins (>90%), primarily to alpha-1 acid glycoprotein. Tamsulosin is extensively metabolized primarily by the CYP3A4 and CYP2D6 isoenzymes; less than 10% of the dose is excreted in the urine unchanged. The primary route of excretion for tamsulosin and its metabolites is via the kidney (76% of the administered dose). The apparent half-life is approximately 14 hours. Patients with renal impairment or mild/moderate hepatic dysfunction do not require an adjustment in tamsulosin dosing.

Reviewer's comment*: Because of the increased exposure in the fasted state, tamsulosin is to be administered 30 minutes after the same meal each day. The same dosing schedule was used in ARI40005, and the Applicant proposes that DTC be administered 30 minutes after the same meal each day.*

Drug-drug interaction between dutasteride and tamsulosin: Dutasteride administered with tamsulosin has no effect on the steady state PK of tamsulosin (Study ARIA1101 submitted in efficacy supplement 014 to NDA 21-319). The effect of tamsulosin on dutasteride PK parameters has not been evaluated. In efficacy supplement 014 to NDA 21-319, the Applicant submitted information which supported the probable lack of effect of tamsulosin on dutasteride pharmacokinetics

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4 summarizes the clinical studies conducted to support the safety and efficacy of DTC and which were analyzed in this clinical review.

Table 4: Clinical studies supporting DTC

Study/Design	Investigational products	Treatment duration	# subjects	Study outcomes
Pivotal clinical safety and efficacy: ARI40005/ Multicenter, randomized, double-blind, parallel group	1. Co-administration of dutasteride 0.5 mg + tamsulosin 0.4 mg once daily 2. Dutasteride 0.5 mg once daily + placebo 3. Tamsulosin 0.4 mg once daily + placebo	4 years	Total: 4844 Co-admi: 1610 Dut: 1623 Tam: 1611	IPSS Qmax
Pivotal Bioequivalence: ARI109882/ Two-center, randomized, open-label, 3-way partial crossover	DTC, fasted or fed Co-administration of dutasteride 0.5 mg + tamsulosin 0.4 mg, fasted or fed	Single dose	101 healthy male subjects	PK parameters

Source: NDA 22-460, Module 5.2

5.2 Review Strategy

The following approach was used to conduct the clinical review of this NDA:

1. The main focus of the clinical review was cumulative and updated safety information from the ongoing study ARI400005. This safety review is located in Section 7 (Review of Safety).
2. A detailed review of safety findings and a high-level review of PK findings of study ARI109882 were conducted. This review is found in Section 5.3 (Discussion of Individual Studies/Clinical Trials)
3. No clinical efficacy information for DTC was submitted. Clinical efficacy of DTC relies on the Year 2 findings of ARI40005, which is summarized in Section 6 (Review of Efficacy).
4. The safety data from the BE study (ARI109892) are not pooled with ARI40005 because of significant differences in study design, dosing, study population, and study outcomes.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study ARI40005: "A randomized, double-blind, parallel group study to investigate the efficacy and safety of treatment with Dutasteride (0.5mg) and Tamsulosin (0.4 mg), administered once daily for 4 years, alone and in combination, on the improvement of symptoms and clinical outcome in men with moderate to severe symptomatic benign prostatic hyperplasia"

Study ARI40005 was a 4-year, multicenter, randomized, double-blind, parallel group study to investigate the efficacy and safety of dutasteride and tamsulosin, alone and co-administered, on BPH outcomes in approximately 4,800 men with moderate to severe symptomatic BPH and an enlarged prostate. The first 2 years of the study was designed to evaluate the effect of dutasteride and tamsulosin co-administered compared to each monotherapy on BPH symptoms ("Year 2" study) as the primary outcome. The remaining 2 years were designed to evaluate clinical progression of BPH (i.e. time to acute urinary retention or BPH-related surgery) among the 3 treatment groups ("Year 4" study). The Year 2 data of ARI40005 provide the primary support for the clinical efficacy and safety of DTC. The review of ARI40005 is located in Section 6 and Section 7 of this clinical review.

5.3.2 Study ARI109882: "An Open-Label, Randomized, Single Dose Three-Period Partial Crossover Study to Determine the Bioequivalence and Food Effect of a Combination Capsule Formulation of Dutasteride and Tamsulosin Hydrochloride (0.5mg/0.4mg) Compared to Concomitant Dosing of AVODART® 0.5mg and Flomax 0.4mg Commercial Capsules in Healthy Male Subjects"

Primary Objective: 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 in fed state

Study design and conduct: 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 sequence 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 receiving treatment D. Each dosing session was separated by 4-week washout period. Table 5 describes the treatment groups.

Table 5: 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 (DTC) 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

Blood samples were collected for PK parameters of dutasteride and tamsulosin over a 72-hour period following dosing. The primary comparison for equivalence between DTC and the co-administration of dutasteride and tamsulosin was levels of drug exposure (AUC and Cmax) between treatment A and treatment B.

Changes in planned analysis: For dutasteride, $AUC_{(0-72)}$ could not be consistently determined because over 25% of the PK concentration from the last sample was not quantifiable or the actual sampling time of 72 hour sample was earlier than 72 hour. Therefore, $AUC_{(0-t)}$ was used as the primary PK parameter for dutasteride instead of $AUC_{(0-72)}$.

Study findings:

Subject Disposition and Demographics: One hundred one (101) subjects were enrolled and randomized. All subjects were male with a median age of 29.5 years. The most common ethnicity was Caucasian (77%), followed by Black (22%). Of 101 subjects, 81 (80%) completed the study. Twenty subjects (20%) withdrew prematurely and the most common reasons for withdrawal were consent withdrawal and protocol violation (7% each). See Table 6.

Table 6: Subject disposition

Disposition variables	N (%)
Number of subjects randomized	101
• Number of subjects completed	81 (80)
• Number of subjects withdrawn	20 (20)
* Adverse event	4 (4)
* Consent withdrawal	7 (7)
* Protocol violation	7 (7)
* Lost to follow up	1 (1)
* Investigator's discretion	1 (1)

Source: NDA 22-460, Study ARI109882, MO's analysis of ds.xpt

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 $AUC_{(0-t)}$ and Cmax between DTC 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 DTC to concomitantly dosed dutasteride and tamsulosin in the fasted state (D:C comparison). See table 7.

Table 7: Bioequivalence of DTC 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 = DTC in fed state (test)
Group C = co-administration of dutasteride + tamsulosin in fasted state (reference)
Group D = DTC in fasted state (test)

Food effect:
Dutasteride: There was no food effect on dutasteride PK with the exception of the mean Tmax occurring 1 hour later in the fed state compared to the fasted state (regimen B – D, A – C). This finding is not likely to be clinically significant.

Tamsulosin: Cmax and AUC values for treatment groups A and B (co-administration and DTC, respectively, in fed state) were 30% less than those for groups C and D (co-administration and DTC, respectively, in fasted state). Compared to fasted state, the Tmax of tamsulosin in fed state occurred approximately 1 to 1.5 hours later.

***Reviewer's comment**: The food effect on tamsulosin has been adequately addressed in the proposed DTC product label, which recommends that DTC be taken 30 minutes after a meal.*

Safety Results

Exposure: The safety population, which consisted of all subjects who received at least one dose of study drug, included 101 subjects. All subjects were randomized to receive treatments A and B; half of the subjects were randomized to receive treatments C or D. Overall, 91 subjects received treatment A, 93 received treatment B, 46 received treatment C, and 46 received treatment D. A summary of the overall safety findings is provided in Table 8.

Table 8: Summary of exposure and safety findings by treatment

Treatment group*	A N = 91 n (%)	B N = 93 n (%)	C N = 46 n (%)	D N = 46 n (%)	Total N = 101 n (%)
# subjects with any AEs	21 (23)	24 (26)	14 (30)	15 (33)	50 (50)
Deaths/SAEs	0	0	0	0	0
AE's leading to withdrawal	1	1	0	2	4 (4)

Source: NDA 22-460, Module 5, Study ARI109882, MO analysis of ae.xpt
* A = co-administration of dutasteride + tamsulosin in fed state
B = DTC in fed state
C = co-administration of dutasteride + tamsulosin in fasted state
D = DTC in fasted state

Serious Adverse Events (SAEs): No deaths or non-fatal SAEs occurred.

AE's leading to study withdrawal: Four subjects (4%) withdrew prematurely due to adverse events, which are described below:

Subject 106 (randomized to DAB): received treatment D (DTC, fasted) prior to being withdrawn for liver function test (LFT) and creatine kinase (CK) elevations. These laboratory abnormalities were detected 27 days after receiving treatment D during the protocol-specified laboratory evaluation prior to session 2. Subject 106's laboratory abnormalities are summarized below:

Subject 106: Laboratory abnormalities

Laboratory Test	AST (IU/L)	ALT (IU/L)	Creatine kinase (IU/L)
Baseline (prior to any drug)	28	25	Not measured
Pre-dose session 2 (multiples of ULN) December 14, 2007	419 (10X)*	162 (3X)+	38,300 (165X)#
Follow up: • December 15, 2007 • December 17, 2007 • December 28, 2007	 • 475 • 301 • 36	 • 199 • 209 • 56	 • 40,360 • 12,010 • 215

Source: NDA 22-460, Module 5, study ARI109882, MO review of lab.xpt file
*Normal range: 10-42 IU/L
+Normal range: 0-55 IU/L
#Normal range: 21-232 IU/L

Reviewer's comment: *Because a review of subject 106's case narrative and CRF did not reveal a possible cause of laboratory abnormality, this reviewer requested the Applicant to clarify why creatine kinase (CK), which was not a protocol-specified laboratory test, was measured and to provide a possible explanation for the patient's laboratory abnormality. The Applicant stated that creatine kinase was measured because of the finding of LFT elevation. According to the Applicant, subject 106 "had begun intense training for boot camp just prior to checking in for the study, which the site investigator felt was responsible for his extreme laboratory elevations."*

Extent of acute CK elevation and its rapid reversal in an otherwise healthy young adult is indicative of rhabdomyolysis. Elevations of AST and ALT levels can occur concurrently with CK elevation. Immediately after muscle injury, the AST:ALT ratio is often > 3 but approaches 1 within a few days because of a faster decline in AST. This is consistent with subject 106's clinical experience. One of the possible etiologies includes significant physical exercise resulting in muscle trauma. Therefore, this reviewer considers the Applicant's response to be an acceptable explanation for subject 106's abnormal laboratory findings.

Subject 203 (randomized to CAB): received treatment C (co-administration, fasted) and treatment A (co-administration, fed) prior to being withdrawn for LFT elevation.

Subject 203: LFT abnormalities

Laboratory Test	AST (IU/L)	ALT (IU/L)	GGT (IU/L)
Baseline (prior to any drug)	24	37	39
Pre-dose session 3 (January 4, 2008)	168*	237+	116#
10 days of follow up (January 14, 2008)	43	64	Not done
After end of study (February 27, 2008)	Not done	Not done	34

*Normal range: 0-40 IU/L
+Normal range: 0-55 IU/L
#Normal range: 0-65 IU/L

Reviewer's comment: *This patient was withdrawn due to the prespecified withdrawal criteria of ALT or AST elevations ≥ 3X ULN.*

The case narrative and CRF of subject 203 were reviewed. The subject's other laboratory values, including total bilirubin, were normal. The subject had no history of liver disease or evidence of concomitant medications/herbs/supplements/alternative medicine or alcohol use. Although, the subject did not report any AEs prior to study withdrawal,an isolated elevation in ALT/AST < 5X ULN without any abnormality in total bilirubin can not rule out drug causality of the LFT elevation. However, a mild increase in transaminases would not likely represent a significant hepatic impairment.

Subject 150 (randomized to DBA): received treatment D (DTC, fasted) and treatment B (DTC, fed) prior to being withdrawn for dizziness. The subject was dosed with treatment B on December 15, 2007. He reported moderate dizziness with nausea on

January 12, 2008, and again reported mild dizziness on February 8, 2008, prior to being withdrawn from the study.

Reviewer's comment: *The long interval between dosing with treatment B and the onset of symptoms render it unlikely that the subject's dizziness/nausea were drug-related*.

Subject 218 (randomized to BDA): received treatment B (DTC, fed) and treatment D (DTC, fasted) prior to being withdrawn for orthostatic hypotension 4 hours after dosing with treatment D. The AE resolved after 2 hours. This was considered drug-related (most likely due to tamsulosin) and this reviewer concurs. Hypotension is a labeled adverse reaction in the Flomax prescribing information.

Common AE's: In all, 50 subjects (50%) reported at least one AE. Adverse events reported by ≥ 5 subjects included dizziness (22 subjects, 22%), headache (21 subjects, 21%), vertigo (9 subjects, 9%), and nausea (8 subjects, 8%). See Table 9. Orthostatic hypotension occurred in 2 subjects after being dosed in the fasted state (one after treatment D, second one after treatment C). These AEs are labeled adverse reactions in the Flomax prescribing information. Adverse events commonly associated with dutasteride, such as breast and sexual disorders, are not expected to occur frequently with single doses of drug separated by a 4- week washout interval.
The incidence of common AE's was higher in fasted than fed state. This is not unexpected as most common AEs were likely due to the tamsulosin component and tamsulosin exposure is higher in the fasted state. For a given food state (fed or fasting), slightly more subjects receiving DTC reported a common AEs than when receiving the co-administration of dutasteride and tamsulosin. Because this was a small, uncontrolled study, it is unclear if these small differences are clinically meaningful.

Table 9: Common AEs (≥ 5 subjects) by treatment group (Safety Population)

	Treatment A N = 91 n (%)	Treatment B N = 93 n (%)	Treatment C N = 46 n (%)	Treatment D N = 46 n (%)
Any AE	21 (23)	24 (26)	14 (30)	15 (33)
Dizziness	8 (9)	11 (12)	6 (13)	8 (17)
Headache	6 (7)	10 (11)	3 (7)	4 (9)
Nausea	2 (2)	4 (4)	2 (4)	2 (4)
Vertigo	0	2 (2)	3 (7)	4 (9)

Source: NDA 22-460, Module 5.3.1.2, Study ARI109882, MO's analysis of ae.xpt

Partner pregnancy: None.

Laboratory:
The listing of laboratory values of "potential clinical importance" was reviewed. In all, 24 subjects (24%) had at least laboratory value that was considered of "potential clinical importance," or PCI. Whether a laboratory value was considered to be of potential

clinical significance was left to an investigator's judgment. A majority of these PCI values (15 of 24, 63%) were borderline high bicarbonate levels at the Screening visit. No subjects other than subject 106 and subject 203 experienced LFT elevations. Subject 138 (randomized to BAD) experienced increased CK levels in conjunction with LFT elevations < 2X ULN as summarized in the table below:

Subject 138: Laboratory abnormalities

Laboratory Test	CK (IU/L)*	ALT (IU/L)+	AST (IU/L)#
Baseline	Not done	Normal	Normal
Pre-dose session 2 (12/14/07)		69	115
Follow-up			
• 12/15/07	4450	65	89
• 12/17/07	831	51	38

Source: NDA 22-460, Module 5.3.1.2, Study ARI109882, MO review of lab.xpt
* Normal range: 21-232 U/L
+Normal range: 10-60 U/L
#Normal range: 10-42 U/L

Reviewer's comment*: No adverse events were recorded for this subject, who completed the study. The Applicant stated that unscheduled CK levels were obtained due to ALT/AST elevations. The Applicant reported that subject had been lifting weights prior to the laboratory measurements. This reviewer does not consider subject 138's laboratory abnormalities to be drug-related.*

REVIEWER'S ASSESSMENT OF ARI109882: In the opinion of this reviewer, study ARI109882 demonstrated that DTC is bioequivalent to concomitantly dosed dutasteride and tamsulosin. No new or unexpected safety findings were observed in this small and uncontrolled study to alter the known risk/benefit of the combination therapy.

6 Review of Efficacy

Efficacy Summary

The efficacy of DTC is expected to be the same of the approved co-administration of dutasteride and tamsulosin for the treatment of BPH symptoms because the products are bioequivalent. No clinical efficacy data were submitted for DTC.

6.1 Indication

The Applicant seeks the indication of DTC, "a combination of dutasteride, a 5α-reductase inhibitor, and tamsulosin, an alpha-adrenergic blocker, is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate." This is the same indication that was approved for Avodart co-administered with tamsulosin in NDA 21-319/S014 on June 19, 2008.

6.1.1 Methods

The following section summarizes the most pertinent efficacy findings of the Year 2 analysis of Study ARI40005. For more details, the reader is referred to the clinical and statistical reviews of Year 2 of Study ARI40005, which was submitted in efficacy supplement 014 to NDA 21-319.

6.1.2 Demographics

Study ARI40005 enrolled approximately 5000 men with symptomatic BPH from North America, Europe, South America, Africa, and Asia. A total of 1231 subjects were from North America (U.S., Canada, Mexico, and Puerto Rico) and 1892 subjects were from Western Europe (Belgium, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Portugal, Spain, and United Kingdom). Overall, the study population adequately represented the target population in the U.S.

The mean age at randomization was 66 years (± 7.0), with 59% being ≥ 65 years old. A majority of patients (88%) were White; Asians were the second largest ethnic group (7%). The mean body mass index (BMI) was 27.4 kg/mg^2 (± 4.0). The mean duration since first BPH-related symptoms and BPH diagnosis was 5.4 (±4.1) years and 3.9 (±4.8) years, respectively. The mean post-void residual volume was 68 mL (± 65 mL). Half of the subjects had a history of alpha-1 antagonist use, mostly (99%) for the treatment of BPH. Approximately 11% of subjects had a history of 5ARI treatment; another 20% had a history of phytotherapy use. The mean baseline IPSS, Qmax, prostate volume and PSA were balanced across the 3 treatment groups (see Table 10).

Table 10: Baseline efficacy variables (ITT)

Mean values (SD)	Co-administration N=1610	Dutasteride N=1623	Tamsulosin N=1611
IPSS	16.6 (6.35)	16.4 (6.03)	16.4 (6.10)
Qmax (mL/s)	10.9 (3.62)	10.6 (3.57)	10.7 (3.66)
Prostate volume (cc)	54.7 (23.51)	54.6 (23.02)	55.8 (24.18)
PSA (ng/mL)	4.0 (2.05)	3.9 (2.06)	4.0 (2.08)

Source: Primary Clinical Review of NDA 21-319/S014, p. 22

6.1.3 Subject Disposition

The trial enrolled 5064 subjects, 4844 of whom were randomized after a 4-week run-in period. The ITT population consisted of 4844 subjects (co-administration of dutasteride + tamsulosin: 1610 subjects, dutasteride: 1623 subjects, tamsulosin: 1611 subjects). Of the 4844 subjects randomized, 3822 (79%) completed 2 years of treatment, with similar completion rates among the 3 treatment groups (78-80%). More subjects in the co-administration group discontinued due to an adverse event, whereas more subjects in

the monotherapy groups discontinued due to lack of efficacy. The distribution of other reasons for discontinuation was comparable among the 3 treatment groups (Table 11).

Table 11: Subject disposition (ITT)

	Co-administration N = 1610 n (%)	**Dutasteride N = 1623 n (%)**	**Tamsulosin N = 1611 n (%)**	**Total N = 4844 n (%)**
Completed (Year 2)	1267 (79)	1301 (80)	11254 (78)	3822 (79)
Discontinued	343 (21)	322 (20)	357 (22)	1022 (21)
• AE	• 154 (10)	• 108 (7)	• 136 (8)	• 398 (8)
• Withdrew consent	• 71 (4)	• 95 (6)	• 74 (5)	• 240 (5)
• Lost to follow-up	• 30 (2)	• 30 (2)	• 29 (2)	• 89 (2)
• Protocol violation	• 24 (1)	• 17 (1)	• 27 (2)	• 68 (1)
• Lack of efficacy	• 36 (2)	• 45 (3)	• 53 (3)	• 134 (3)
• Other	• 28 (2)	• 27 (2)	• 38 (2)	• 93 (2)

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

6.1.4 Analysis of Primary Endpoint(s)

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 ($p < 0.001$). See Table 12.

Table 12: 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

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary endpoint was maximum urinary flow rate (Qmax) measured during uroflowmetry. Statistically significant improvement from baseline Qmax in the co-administration group compared to each monotherapy was seen from Month 6 ($p < 0.001$) to Month 24 ($p \leq 0.003$). At Month 24, the mean change from baseline Qmax was 2.4 mL/s for the co-administration group, 1.9 mL/s for dutasteride, and 0.9 mL/s for tamsulosin. The mean difference in the change from baseline Qmax between the co-administration group and dutasteride was 0.5 mL/s and between the co-administration group and tamsulosin was 0.9 mL/s.

7 Review of Safety

Safety Summary

The safety and tolerability of co-administration of dutasteride and tamsulosin are acceptable. There were no significant differences in deaths or non-fatal serious adverse events between the co-administration group compared to dutasteride or tamsulosin monotherapy in the cumulative database. The composite adverse event of cardiac failure occurred at a slightly higher incidence in the co-administration group. . There were no important differences between the safety findings of the Year 2 analysis and those reported after the Year 2 cut-off date for ARI40005 for the serious adverse events. As in the Year 2 analysis, the cumulative safety data indicated that, compared to each monotherapy, the co-administration of the 2 drugs was associated with a higher incidence of drug discontinuation due to an adverse event, most of which were reproductive/sexual and breast-related, and a statistically higher incidence of ejaculatory disorders.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The following sources were reviewed for safety assessment:

- Study ARI40005:
  a. Cumulative* safety information on deaths, non-fatal SAEs, adverse events leading to permanent drug discontinuation, and laboratory outliers
  b. Updated* safety information on *deaths* and *non-fatal SAEs* (and follow-up information on non-fatal SAEs that occurred during the 120-Day Safety Update of NDA 21-319/S014 and that were still ongoing by August 31, 2007, which was the cut-off date for the 120-Day Safety Update of NDA 21-319/S014)

  ***** *In this NDA submission, the safety information for ARI40005 was organized by 2 reporting time periods described below:*

  1. ***Cumulative****: time period from post-randomization of ARI40005 to the cut-off date for this NDA (i.e.* ***post-randomization of ARI40005 to 12/8/08****)*

  2. ***Updated****: time period following the 120-Day Safety Update of NDA 21-319/S014 to the cut-off date for this NDA (i.e.* ***9/1/07 to 12/8/08****)*

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

- 120-Day Safety Update

- NDA 21-319/Sequence 0022 submission dated July 27, 2009: This was a supplemental labeling request (SLR) for the addition of cardiac failure data from Trial ARI40005 and Trial ARI40006 (REDUCE) to the Avodart label. The submission contained summary cardiac safety data of ARI40006 and ARI40005 as of January 9, 2009, which was the completion date of the treatment phase for ARI40005. This submission will be referred to as the "SLR submission" for the remainder of this safety review. (b) (4)

(b) (4)

- Published literature

This reviewer approached the safety review in the following manner:

a. Assess and compare the type and frequency of adverse findings over approximately 4 years of ARI40005 among the 3 treatment groups (co-administration group, dutasteride and tamsulosin groups) by analyzing the cumulative safety information.
b. Assess for any major differences in the safety profile of the co-administration group in the first 2 years (reviewed in the clinical review of NDA 21-319/S014) versus the last 2 years of ARI40005 by analyzing the updated safety information.

Reviewer's comment: *Because study ARI40005 was ongoing at the time of this NDA submission, the cumulative and updated safety database is incomplete and has not been fully validated. The safety information submitted in this NDA (cumulative and updated safety information) included line listings, summary tables, case narratives, and CRFs. No datasets were submitted. This approach is acceptable, because the principal support of safety for DTC is based on the Year 2 safety data of ARI40005, which have already been analyzed and determined to be acceptable.*

7.1.2 Categorization of Adverse Events

All adverse events were coded to the MedDRA coding dictionary by Preferred Terms (PT) and System Organ Class (SOC), version 11.1. In the updated safety information, verbatim text was used for AE's with missing MedDRA Preferred Terms. The mapping of verbatim terms to MedDRA terms was reviewed and found to be acceptable.

7.1.3 Pooling of Data Across Clinical Trials to Estimate and Compare Incidence

Safety data are not pooled or integrated across the different studies because of major differences in the design, study population, and dosing schedule among the studies. The principal support for the safety of DTC is study ARI40005, which is the focus of this safety review.

7.2 Adequacy of Safety Assessments

The overall exposure and safety assessments were adequate to characterize the safety profile of the co-administration of dutasteride and tamsulosin compared to each monotherapy.

7.2.1 Overall Exposure at Appropriate Doses/Duration and Demographics of Target Population

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. The cumulative years of co-administration therapy exposure were 2771 person-years at the 2-year cutoff date. The cumulative duration of treatment exposures in the monotherapy groups was comparable to that in the co-administration group.

Reviewer's comment*: According to the SLR submission, 1096 co-administration subjects (68%), 1067 dutasteride subjects (66%), and 956 tamsulosin subjects (59%) completed 4 years of treatment in ARI40005*.

7.2.2 Explorations for Dose Response

DTC is a fixed-dose combination product and no other doses of dutasteride or tamsulosin were investigated in the clinical program of DTC or the co-administration dutasteride and tamsulosin.

7.2.4 Routine Clinical Testing

Protocol-specified clinical testing included: hematology, chemistry (including LFT's), urinalysis, and Prostate Specific Antigen (PSA) every 6 months during the study. All appropriate tests were incorporated into the protocol.

7.3 Major Safety Results

7.3.1 Deaths

The **cumulative** data of deaths in ARI40005 (post-randomization to December 8, 2008) by MedDRA System Organ Class (SOC) are summarized in Table 13. 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 13: 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

***Reviewer's comment**: A review of the summary data in the SLR submission did not reveal any significant difference from that presented in Table 13 above.*

During the **updated** safety period (9/1/07 to 12/8/08), 27 deaths occurred. Of these, 6 deaths were in the co-administration group, 10 in the dutasteride group, and 11 in the tamsulosin group. The most common causes of death were cardiac and neoplasm-related with a similar distribution of different causes of death across the 3 treatment groups. See Table 14.

Table 14: Cause of death by System Organ Class (updated, ITT)

System Organ Class	Co-administration N=1610 n	Dutasteride N=1623 n	Tamsulosin N=1611 n	Total N=4844
Any fatal AE	6	10	11	27
Cardiac	4	3	5	12
Neoplasms	0	2	2	4
Infections	1	2	0	3
Injury, poisoning and procedural complications	0	2	1	3
Nervous system disorders	1	0	1	2
Gastrointestinal disorders	0	0	1	1
Respiratory, thoracic, and mediastinal disorders	0	1	0	1
Unknown	0	0	1	1

Source: NDA 22-204, Module 5.3.5.1.22, Listing OL1, MO analysis

Reviewer's comment*: All narratives of fatal events in the updated safety database were reviewed and no deaths appeared to be drug-related.*

In the NDA 21-319/S014 safety review, which covered the first 2 years of ARI40005 and the 120-Day Safety Update, the all-cause death rate was approximately 1.8 % for each treatment arm (co-administration: 30 subjects, dutasteride: 28 subjects, tamsulosin: 29 subjects). More than 50% of the deaths were due to cardiac disorders or neoplasms. None of the deaths appeared to be drug-related. The safety profile of fatal SAEs in Year 3 and Year 4 (updated safety period) did not appear to differ from the Year 2 data of ARI40005.

7.3.2 Nonfatal Serious Adverse Events

In the **cumulative** database of non-fatal SAEs, 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 SAEs were in the SOCs cardiac disorders (4%) and neoplasms (3%). Non-fatal SAEs by SOC reported by ≥ 1% of subjects in any treatment group are shown in Table 15.

Table 15: 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

Table 16 shows the most common SAEs (≥ 10 subjects in any treatment group) by Preferred Term in the cumulative database. The most frequently reported SAEs were prostate cancer, coronary artery disease, myocardial infarction, and angina. No specific SAE Preferred Term was reported more frequently in the co-administration compared to each monotherapy, except for pneumonia.

Table 16: Common non-fatal SAEs (≥ 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

Reviewer's comment: *This reviewer reviewed the line listing of the cumulative SAE data by Preferred Term, with a focus on neurologic, cardiovascular, and investigations disorders. Overall, subjects in the co-administration group did not report a significantly*

higher incidence of any Preferred Term-specific SAE, except for pneumonia, compared to those in the monotherapy groups. Neither dutasteride nor tamsulosin are associated with increased risk of infection or pulmonary infection and there is no apparent biologic plausibility for the co-administration of these 2 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. A review of the pneumonia narratives indicated that none of those cases were likely to be drug-related. This reviewer does not consider the differences of pneumonia between the treatment groups to be clinically 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.

During the **updated** safety period (9/1/07 to 12/8/08), 257 patients (5%) experienced a non-fatal SAE. The incidence of non-fatal SAE was lower in the co-administration compared to each monotherapy groups (4% vs. 6%). The most common SAEs were in the SOCs neoplasms and cardiac (see Table 17).

Table 17: Non-fatal SAEs by System Organ Class (updated, ITT)

System Organ Class	Co-administration N=1610 n (%)	Dutasteride N=1623 n (%)	Tamsulosin N=1611 n (%)	Total N=4844 n (%)
Any non-fatal SAE	70 (4)	93 (6)	94 (6)	257 (5)
Neoplasms	16	16	16	48 (1)
Cardiac	13	20	14	47 (1)

Source: NDA 22-460, Module 5.3.5.1.22, Line Listing OL2, MO analysis

The most common non-fatal SAEs by PT (reported by ≥ 3 subjects in any treatment group) in the updated safety database are shown in Table 18. Compared to each monotherapy, co-administration of dutasteride and tamsulosin was not associated with a higher incidence of any specific non-fatal SAE.

Table 18: Common non-fatal SAEs (≥ 3 subjects/group) by Preferred Terms (updated, ITT)

Preferred Term	Co-administration N=1610	Dutasteride N=1623	Tamsulosin N=1611	Total N=4844
Coronary artery disease/cardiac infarction*	9	15	9	33
Prostate cancer	6	7	5	18
Cerebrovascular accident	3	3	7	13
Osteoarthritis	3	5	1	9
Bladder cancer	4	1	2	7
Pneumonia	3	1	3	7
Urinary retention	0	2	5	7
Atrial fibrillation	2	1	3	6
Gastrointestinal hemorrhage	1	4	1	6
Inguinal hernia	0	2	4	6
Colon cancer	0	3	2	5

Source: NDA 22-460, Module 5.3.5.1.22, Line Listing OL2, MO analysis
*This composite category includes: angina, coronary artery, and myocardial infarction

In this NDA submission, the Applicant provided **follow-up** data on non-fatal SAEs that occurred during the 120-Day Safety Update period for NDA 21-319/S014 that remained unresolved at the end of this Safety Update period (8/31/07). Follow up information was provided for 55 subjects (co-administration: 13, dutasteride: 24, tamsulosin: 18). A majority of these cases resolved (40 of 55). Eight patients died: 3 in the co-administration group (2 colon cancer, 1 pancreatic cancer), 4 in the dutasteride group (1 each of bronchial carcinoma, bladder cancer, gastrointestinal cancer metastatic, and sudden death), and 1 in the tamsulosin group (pyrexia/granulocytopenia). The remaining 7 cases were unresolved, but most were cases of malignancy (prostate, bladder). No overall unexpected or concerning outcomes were observed.

7.3.3 Dropouts and/or Discontinuations

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 are separated into SAEs and non-SAEs.

Cumulative SAEs leading to drug discontinuation: A total of 258 patients (5.3%) experienced an SAE which led to permanent drug discontinuation. The incidence of SAEs leading to drug discontinuation was highest in the tamsulosin group (6% vs. 5% in the other 2 treatment groups). The most common SAEs 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 SAEs leading to

drug discontinuation was not higher in the co-administration group compared to each monotherapy group for any specific SOC. See Table 19.

Table 19: Common SAEs (≥ 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

The most common SAEs (reported in ≥ 3 subjects in any treatment group) leading to permanent drug discontinuation were prostate cancer and myocardial infarction (composite term). More subjects in the co-administration group discontinued drug because of cerebrovascular accident, cardiac failure (composite term), and pneumonia. A review of the case narratives indicated that drug-causality was unlikely in these cases because of the presence of other compelling alternative explanations, such as significant co-morbidities.

Table 20: Common SAEs leading to drug discontinuation (≥ 3 subjects in any treatment group) by Preferred Term (cumulative, ITT)

Preferred Term	Co-administration N = 1610 n (%)	Dutasteride N = 1623 n (%)	Tamsulosin N = 1611 n (%)
Any SAEs leading to drug discontinuation	78 (5)	79 (5)	101 (6)
Prostate cancer	18 (1)	12	18 (1)
Myocardial infarction*	8	9	8
Cerebrovascular accidents	5	3	2
Cardiac failure**	5	3	1
Pneumonia	3	0	0
Urinary retention	2	4	9

Source: NDA 22-460, Module 5.3.5.1.22, Listing 5 and Table 5
*Includes Preferred Terms of myocardial infarction, acute myocardial infarction, acute coronary syndrome, coronary artery occlusion, and coronary artery thrombosis

**Includes PTs of cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, left ventricular failure acute, left ventricular chronic

According to Line Listing 5, 17 subjects experienced SAEs leading to drug discontinuation that were considered by the investigator to be treatment-related. These included 4 co-administration subjects (1 each of hypotension, gastric ulcer, loss of consciousness, and myeloid leukemia), 6 dutasteride subjects (1 each of jaundice, bradycardia, atrial-ventricular dissociation/ exacerbation of left ventricular failure, moderate syncope, heart attack, and coronary artery disease) and 7 tamsulosin subjects (1 each of myocardial infarction, hypertension, hepatitis, pancreatitis, circulatory collapse/syncope, dizziness, and tachycardia). All but the SAEs of coronary artery disease in the dutasteride subject, and hepatitis and tachycardia in the tamsulosin subjects occurred within the first 2 years of study ARI40005 and were reviewed previously.

Reviewer's comment: *This reviewer analyzed Listing 5 (listing of cumulative SAEs leading to drug withdrawal). The incidence of withdrawals in the co-administration group was similar between Year 3 and Year 4 (~1%), whereas it was slightly higher in Year 3 than Year 4 for dutasteride group (1.4% vs. 0.8%) and for tamsulosin group (2% vs. 0.6%).*

According to the clinical review of NDA 21-319/S014, the most common SAE's leading to drug withdrawal were prostate cancer (co-administration: 12 subjects, dutasteride: 3 subjects, tamsulosin: 12 subjects) and myocardial infarction (co-administration: 2 subjects, dutasteride: 6 subjects, tamsulosin: 9 subjects).

The incidence and types of SAEs leading to permanent drug discontinuation for the cumulative 4 years of ARI40005 did not appear to differ significantly from those observed in initial 2 years of ARI40005.

Cumulative <u>non-SAEs</u> 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-SAEs leading to drug discontinuation by SOC was reproductive and breast disorders and by PT was erectile dysfunction (see Table 21).

Table 21: 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

Reviewer's comment: *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.*

7.3.4 Significant Adverse Events

7.3.5 Submission Specific Primary Safety Concerns

In the clinical review of NDA 21-319/S014, cardiac failure and prostate cancer were identified as AEs of special interest because of the unexpected finding of higher incidence of these AEs in the co-administration group compared to both monotherapies (cardiac failure) or compared to dutasteride monotherapy (prostate cancer). See Table 22. The increased relative risks were not statistically significant and after a detailed

review, the clinical reviewer concluded that these AEs did not pose a significant safety concern for the co-administration regimen. Because study ARI40005 was ongoing, updated data on cardiac failure and prostate cancer were requested to assess whether these AEs would rise to a level of clinical safety concern with longer duration of use for the co-administration regimen.

Table 22: Relative Risk Estimate of Cardiac Failure and Prostate Cancer (Year 2)

AE	Relative Risk Estimate (95% CI) at Year 2	
	Co-administration vs. Dutasteride	Co-administration vs. Tamsulosin
Cardiac failure*	4.54 (0.98, 21.0)	2.29 (0.71, 7.44)
Prostate cancer	1.95 (0.94, 4.05)	0.82 (0.46, 1.46)

Source: Primary Clinical Review of NDA 21-319/S014, p. 46-7
*Cardiac failure is composite AE which includes the following Preferred Terms: cardiac failure congestive, cardiac failure, left ventricular failure, cardiac failure acute, cardiogenic shock, left ventricular failure acute, right ventricular failure, right ventricular failure acute

Cardiac failure: According to the Applicant, "cardiovascular events were evaluated prospectively as events of special interest in Study ARI40005…due to previous questions from 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 interests, 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. The table below shows the Year 4 CV data from trial ARI40005 contained in the SLR submission:

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

Table 23 summarizes the **cumulative** data on composite cardiac failure events. 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 23: 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
NDA 21-319/Sequence 0022, Module 5.3.5.1 and 5.3.6 (SLR submission), MO analysis
*Deaths = deaths directly associated with "cardiac failure"

In the SLR submission, the Applicant requested that the finding of 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. In support of this request, the Applicant presented the following data:

Study ARI40005: The incidence of cardiac failure (composite term) was 0.9% in the co-administration group (14 subjects) compared to 0.2% in the dutasteride group (4 subjects) and 0.6% in the tamsulosin group (10 subjects). The difference between the co-administration and dutasteride groups was statistically significant (RR 3.57 [95% CI: 1.17, 10.8]); the difference between co-administration and tamsulosin groups did not reach statistical significance (RR 1.36 [95% CI: 0.61, 3.07]). The imbalance in the

composite term cardiac failure was driven by the PTs “cardiac failure” and “congestive heart failure.” (See Table 24).

Table 24: Subjects with Cardiac Failure in ARI40005 (cumulative, ITT)

Composite Term MedDRA Preferred Term	Dut + Tam (N=1610) n (%)	Dutasteride (N=1623) n (%)	Tamsulosin (N=1611) n (%)
Any Cardiac Failure AE	14 (0.9)	4 (0.2)	10 (0.6)
Cardiac Failure	9 (0.6)	1 (<0.1)	6 (0.4)
Cardiac failure congestive	6 (0.4)	1 (<0.1)	2 (0.1)
Left ventricular failure	0	0	2 (0.1)
Cardio-pulmonary failure	0	1 (<0.1)	0
Congestive cardiomyopathy	0	0	1 (<0.1)
Acute left ventricular failure	0	1 (<0.1)	0

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

The time of onset of cardiac failure did not differ significantly among the 3 treatment groups (median time of onset ranged from 17 to 27 months). The treatment groups did not differ in demographic/baseline characteristics or in the incidence of events that may trigger cardiac failure (e.g., MI, myocardial ischemia, atrial fibrillation).

Study ARI40006: This 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 at elevated risk for prostate cancer. The study population of ARI40006 appeared to be similar to that of ARI40005 with respect to baseline demographics and cardiovascular risk profile. The 4-year incidence of composite cardiac failure was 0.7% (30 subjects) in the dutasteride group compared to 0.4% (15 subjects) in the placebo group and this difference was statistically significant (RR 2.04 [95% CI: 1.09, 3.78]). The imbalance in the composite term cardiac failure was driven by the Preferred Terms “cardiac failure” and “congestive heart failure.” (See Table 25).

Table 25: 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

The Kaplan-Meier curve for the time to first cardiac failure was similar for the 2 treatment groups for the first 9 months and diverged thereafter. The treatment groups did not differ in demographic/baseline characteristics or associated signs/symptoms of cardiac failure. According to the Applicant, 14/30 dutasteride subjects compared to 1/15 placebo subjects were taking an alpha-blocker around the time of the cardiac failure event.

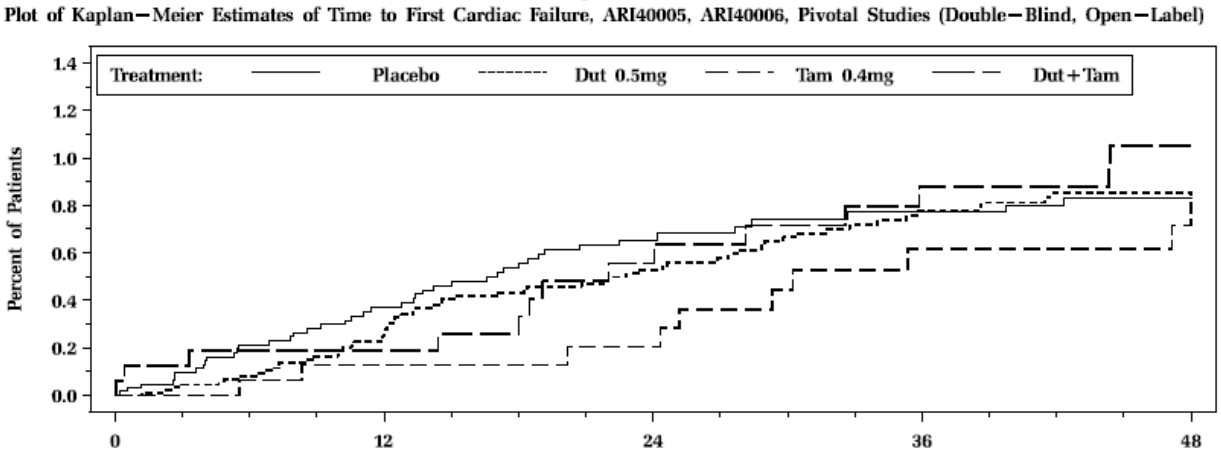
Pooled clinical trial data analyses: To date, the dutasteride clinical development have included 3 major programs:

1. Three placebo-controlled phase 3 trials for BPH (randomized, double-blind, placebo controlled trials of dutasteride vs. placebo for BPH treatment)
2. Trial ARI40005 for BPH (randomized, double-blind, parallel group trial of co-administration of dutasteride + tamsulosin vs. dutasteride vs. tamsulosin in BPH treatment)
3. Trial ARI40006 for reduction of risk of biopsy detectable prostate cancer (randomized, double-blind, placebo-controlled trial of dutasteride vs. placebo in risk of prostate cancer)

The Applicant conducted 2 integrated analyses across the dutasteride clinical programs to evaluate the composite event of cardiac failure. In the first analysis, placebo-controlled trial data from 4 years of ARI40006 and the first 2 years of phase 3 dutasteride BPH studies were integrated. Overall, the proportion of subjects with cardiac failure was 0.7% in both the dutasteride group (43/6272 subjects) and in placebo group 43/6284 subjects). In the second analysis, data from 4 years of ARI40006, 4 years of ARI40005, and 4 years of phase 3 dutasteride BPH studies (Years 1 & 2 were placebo-controlled, Years 3 & 4 were open-label in these studies) were integrated. The cumulative incidence of cardiac failure across all 4 years of dutasteride studies were the same for dutasteride and placebo groups at 0.7% (61/9047 in the dutasteride group, 43/6284 in the placebo group). Figure 1 shows the Kaplan-

Meier curve of time to first cardiac failure for all the pooled data from the 3 major clinical programs of dutasteride.

Figure 1: Kaplan-Meier estimates of time to first cardiac failure (pooled phase 3 BPH trials, ARI40005, ARI40006 over 4 years)



Placebo				
No. of Events/At Risk	22/6284	38/5563	41/3558	43/3164
Dut. 0.5mg				
No. of Events/At Risk	23/9047	42/7928	56/5952	61/5339
Tam. 0.4mg				
No. of Events/At Risk	2/1611	3/1466	8/1278	10/1105
Dut. + Tam.				
No. of Events/At Risk	3/1610	9/1425	12/1278	14/1195

Source: SLR submission (NDA 21-319/S0022, Module 5.3.6, Figure 11, p. 705)

Post-marketing analyses: The Applicant queried the FDA's AERS database (4Q2008) and searched for safety signals of cardiac failure using disproportionality analysis. No safety signals were noted for congestive heart failure or heart failure for dutasteride alone, tamsulosin alone, dutasteride + tamsulosin, finasteride alone, or finasteride + tamsulosin.

Applicant's conclusion: The Applicant concluded that integrated analyses did not demonstrate a difference between dutasteride monotherapy and placebo in the incidence of cardiac failure (composite term). However, an imbalance of composite cardiac failure events in ARI40006 and ARI40005 was observed when dutasteride was concomitantly dosed with an alpha-adrenergic antagonist, such as tamsulosin. No clear drug-causality or pathophysiologic explanation is apparent at this time.

Medical Officer's Assessment of Cardiac Failure:
The following section discusses the medical officer's assessment of cardiac failure based on evidence from controlled clinical trials, published literature and known mechanism of action.

A. Clinical Trials

Table 26 summarizes the study design, study population, and cardiac failure of the 3 major clinical programs of dutasteride.

Table 26: Study design, study population, and cardiac failure outcome of the 3 major clinical programs of dutasteride

Demographic/baseline variables	ARI40006	ARI40005	Pooled phase 3 BPH trials (3 trials)
Indication	Prostate ca	BPH	BPH
Study Design			
Study Design*	MC,R, DB, PC	MC, R, DB, PG	MC, R, DB, PC
Treatment Groups** (sample size)	Dut (4105), Plc (4126)	Dut + tam (1610), Dut (1623), Tam (1611)	Dut (2167), Plc (2158)
Placebo control	Yes	No	Yes
Duration of controlled study (years)	4	4	2
Study Population			
Ethnic- Caucasian (%)	~ 90	~ 90	~ 90
Median age (years)	63	66	66
Hypertension (%)	38	42-44	47 with CV dz
Coronary artery disease (%)	8	9-10	Data not available
Tobacco history (%)	53-55	48	12
Median or mean SBP/DBP	136/82	136/81	138/82
Concomitant medications during study (%): • Alpha blocker • ACE-I • Diuretics • Calcium channel blockers • Beta blockers	 • 28 (dut); 34 (plc) • 34-36 • 21-22 • 14-16 • 21-22	 • (50 previous use) • 37 • 22 • 18-21 • 24-26	 • Not permitted • 17 • 12 • 16-18 • 16-17
Cardiac Failure			
Subjects with cardiac failure (%)	Dut: 30/4105 (0.7) Plc: 15/4126 (0.4)	Dut + tam: 14/1610 (0.9) Dut: 4/1623 (0.2) Tam: 10/1611 (0.6)	Dut: 13/2167 (0.6) Plc: 28/2158 (1.3)

Source: Summary information from SLR submission and NDA 21-319/S014, Module 5.3.3.
*MC=multi-center; R=randomized; DB=double-blind; PC=placebo control; PG=parallel group
**Plc=placebo; Dut=dutasteride; Tam=tamsulosin

***Reviewer's comment**: The study populations in the 3 main clinical development programs for dutasteride (ARI40006, ARI40005, and pooled phase 3 studies) are comparable in their demographics/baseline characteristics, baseline risk factors for cardiac failure, and concomitant use of medications that may affect cardiac failure outcomes. As such, it may be reasonable to extrapolate the placebo data on cardiac failure in the placebo group from ARI40006 (0.4% over 4 years) and the placebo group from pooled phase 3 studies (1.3% over 2 year) to ARI40005.*

The study results of ARI40006 and those of the pooled phase 3 BPH studies are contradictory regarding the risk of cardiac failure of dutasteride compared to placebo.

***Reviewer's comment**: Cardiac failure was not pre-defined in the study protocols but was prospectively defined in the respective Statistical Analysis Plans of ARI40006 and ARI40005. The AEs in the pooled phase 3 BPH studies, which were originally coded using the MIDAS coding dictionary, was re-coded using the MedDRA coding dictionary in the post-hoc analysis.*

Individual case narratives of ARI40005 and ARI40006 were reviewed to determine whether 1) the case was coded properly, 2) any convincing evidence exists to exclude drug causality or, 3) there is a reasonably compelling alternative explanation for the event other than drug. The findings are presented below.

1. ARI40005: Case narratives were reviewed and miscoded cases (e.g., circulatory collapse secondary to aortic aneurysm rupture or fatal myocardial infarction coded as cardiac failure) were excluded from the total count. After excluding these cases, 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%). These subjects are discussed below:

    - *Co-administration (12 subjects, 0.8%)*: One subject "died on the street," which does not appear to be clinically consistent with CHF. Two subjects had CHF 12-13 days after the start of investigational product, which is most likely too short of duration of time for the drugs to cause CHF. Of the 9 remaining cases, 8 resolved on therapy. Eleven of the 12 subjects (the 12th subject had coronary artery disease) had ≥ 2 known independent risk factors for congestive heart failure, such as coronary artery disease (CAD), hypertension, diabetes, and significant history of alcohol use/smoking.
    - *Dutasteride (2 subjects, 0.1%)*: One subject with multiple risk factors for CHF died 1 year after the start of dutasteride treatment for "unknown reason"; it was unclear if this death was witnessed and an autopsy was not performed. The other subject with multiple risk factors (CAD, diabetes, hypertension, history of 45-pack year tobacco use) developed mild CHF on Day 832 which did not lead to drug discontinuation.
    - *Tamsulosin (8 subjects, 0.5%)*: One subject without relevant cardiovascular co-morbidity at baseline developed severe cardiac failure concurrently with grade III atrioventricular (AV) block resulting in severe bradycardia and loss of consciousness on Day 881. The subject received supportive medical treatment and an insertion of a permanent cardiostimulator. It is unclear to this reviewer whether this subject's cardiac failure was an event separate from or a consequence of the grade III AV block. Of the remaining 7 subjects, 6 had multiple risk factors for CHF. The 7th patient had no prior CV history (except erectile dysfunction) developed mild CHF at Month 9.

***Reviewer's comment**: In summary, this reviewer did not identify a case of cardiac failure, except for one tamsulosin patient with no prior cardiovascular history who developed mild CHF at Month 9, which could likely be drug-related. Most cardiac failure patients in ARI40005 had multiple established risk factors for CHF (e.g., coronary artery disease [CAD], hypertension, diabetes, significant tobacco/alcohol use, valvular disease, and obesity). Each risk factor independently increases the risk of CHF by 1.5-2.0 fold, and CAD alone increases the risk by 8-fold.[1] The development of CHF is much more likely to be attributable to these co-morbidities than to any of the 3 treatment regimens in ARI40005.*

Because of the lack of a placebo control in ARI40005, the risk of composite cardiac failure could not be quantified on absolute terms. As mentioned previously, the incidence of cardiac failure in the placebo group in ARI40006 was 0.4% over 4 years and 1.3% over 2 years in the pooled phase 3 BPH studies. In the Applicant's pooled placebo-controlled clinical trial data integrated analysis, the proportion of placebo subjects with composite cardiac failure events was **0.7%**. Because the study populations of these 2 clinical programs were similar to that of ARI40005, the 0.7% estimate may be reasonably extrapolated as a "background" incidence of cardiac failure in ARI40005. The incidence of cardiac failure for the co-administration (0.7%) in ARI40005 was the same as this 0.7% "background" estimate. Further, this reviewer does not consider the differences among the 3 treatment groups in the absolute number of subjects over 4 years (12 co-administration vs. 2 dutasteride vs. 8 tamsulosin) for a composite AE that is not uncommon in population of older men to be clinically meaningful.

2. ARI40006: This reviewer examined in detail the case narratives of cardiac failure in trial ARI40006 submitted in SLR submission. (b) (4)

(b) (4)

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. Two dutasteride subjects had cardiac events that were not assessable due to limited information (one unwitnessed death occurred at home that was considered to be from "acute cardiac failure"; another case of "cardiac insufficiency, described as cardiac complaints" was treated with surgery). One dutasteride subject had no relevant risk factors prior to the onset of cardiac failure on Day 742, 3 subjects had one CHF risk factor, and the

1 He J; Ogden LG; Bazzano LA; Vupputuri S; Loria C; Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001 Apr 9;161(7):996-1002.

remaining 20 subjects had at least 2 risk factors for CHF. In the placebo group, 13 of 14 subjects had ≥ 2 risk factors for CHF. This reviewer did not identify a case of cardiac failure that was probably drug-related or that was not confounded by significant co-morbidities, other than the one dutasteride subject who had no relevant risk factor who developed cardiac failure on Day 742.

Because there has been no known cardiovascular signal for dutasteride, which has been marketed worldwide since 2003, the Applicant conducted several exploratory analyses that may explain the imbalance in composite cardiac failure between dutasteride and placebo. According to the Applicant, one possible explanation is that 14 of 30 dutasteride subjects compared to 1 of 15 placebo subjects with cardiac failure had concomitant therapy with an alpha-adrenergic antagonist ("alpha-blocker"). This reviewer identified several reasons that would render it difficult to determine the role of alpha blocker in cardiac failure:

- Among the 14 dutasteride subjects and 1 placebo subject who were on concurrent alpha-blocker therapy who experienced cardiac failure, 10 dutasteride subjects and 1 placebo subject were also on other therapies that could contribute to cardiac failure (e.g., beta-blockers).
- Prior to the study start, the proportion of subjects on medications that may affect CHF outcomes (e.g., non-selective beta-blockers, ACE-I) were balanced between the 2 treatment groups, except for alpha-blockers. The use of **alpha-blockers** was **higher** in the **placebo group** compared to dutasteride group (34% vs. 28%). If alpha-blockers cause cardiac failure, one would expect a higher incidence of cardiac failure in the placebo group.
- Among subjects who had cardiac failure, those who were not on alpha blockers had a shorter median time of onset (450-500 days post-randomization) than those who were on alpha blockers (750-1200 days post-randomization). This would not support the role of alpha blockers in accelerating cardiac failure.
- The Applicant also calculated the crude incidence of composite cardiac failure by treatment group and by the use of alpha blocker prior to the onset of cardiac failure. The incidence of composite cardiac failure of the alpha-blocker only group (placebo with some alpha-blocker) was lower than that of placebo-only group (placebo with no alpha blocker). This analysis would not support the hypothesis that alpha-blockers alone increase the risk of cardiac failure over placebo in ARI400006.

Crude incidence of cardiac failure by use of alpha-blocker

Grouping	Crude Incidence (n/N)
Dutasteride with some alpha-blocker	1.0% (12/1148)
Dutasteride with no alpha-blocker	0.6% (18/2957)
Placebo with some alpha-blocker	<0.1% (1/1387)
Placebo with no alpha-blocker	0.5% (14/2739)

3. Drug-drug interaction: If dutasteride or tamsulosin alone does not appear to increase the risk of CHF, a drug-drug interaction may be responsible for the higher incidence of cardiac failure when these 2 drugs are concomitantly dosed. However, study ARIA1011 demonstrated that dutasteride and tamsulosin co-administered did not alter tamsulosin PK parameters or dutasteride PD parameters. Because of the long half life of dutasteride, no studies have been conducted to evaluate the effect of tamsulosin on dutasteride PK parameters. In the efficacy supplement supporting the co-administration of dutasteride and tamsulosin for the treatment of BPH symptoms (NDA 21-319/S014), the Applicant submitted sufficient evidence to indicate that the effect of tamsulosin on dutasteride PK would be highly unlikely.

B. Literature evidence:

1. The use of the alpha-blocker doxazosin monotherapy for hypertension was associated with a higher risk of CHF compared to diuretic monotherapy in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a comparative study evaluating 4 different antihypertensives (diuretics, alpha-blocker, ACE-I, and beta-blocker) on fatal coronary artery disease and nonfatal myocardial infarction in 41,000 hypertensive patients. The doxazosin arm was terminated prematurely after a planned interim analysis demonstrated that the risk of CHF (a secondary endpoint) was doubled in the doxazosin arm compared to the diuretic arm.[2] This finding triggered the convening of the FDA Cardio-Renal Advisory Committee in 2001 to consider if labeling changes for CHF would be appropriate for doxazosin and/or other alpha-blockers. The lack of a placebo control in ALLHAT and the fact that diuretic therapy was a well-recognized effective treatment for CHF made it difficult to establish whether the diuretic treatment was beneficial, doxazosin was or was not harmful, or some combination thereof. The Advisory Committee did not recommend a warning label for doxazosin until further data become available to fully interpret the results.[3] To date, there has been no class labeling for CHF for the alpha blockers. Cardura XL (but not Cardura IR), which was approved for the treatment of BPH in 2006, is the only alpha-blocker product with cardiac safety labeling. Specifically, under the General Precautions section of Cardura XL label:

> "**Patients with Coronary Insufficiency:** Patients with congestive heart failure, angina pectoris, or acute myocardial infarction within the last 6 months were excluded from the Phase 3 studies. If symptoms of angina pectoris should newly appear or worsen, CARDURA XL should be discontinued."

2 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin vs Chlorthalidone: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000;283:1967-1975.

3 McLellan F. US FDA weighs options for warning on antihypertensive drug. *Lancet* 2001; 357: 1775.

2. A search in PubMed and Embase did not retrieve any meaningful published literature on increased risk of CHF associated with dutasteride or finasteride treatment.

C. Biologic plausibility for cardiac failure:

1. Alpha-blockers induce 2 physiologic changes, volume expansion and compensatory heart rate increase, that may potentially lead to CHF. Volume expansion may trigger heart failure in a decompensated heart unable to accommodate the volume overload. Although edema and dyspnea are labeled adverse reactions for all alpha blockers, these 2 events alone do not qualify as CHF. The compensatory increase in heart rate due to alpha-blocker-induced peripheral vasodilation may also trigger heart failure in a damaged heart unable to accommodate the increased workload.
2. No currently known biologic plausibility exists for dutasteride or finasteride.

Reviewer's conclusions: Considering the totality of evidence, this reviewer addresses the following 3 key questions:

1. Compared to placebo, does dutasteride increase the risk of composite cardiac failure? Trial 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. Further, one cannot always equate frequency to causality. 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.

Reviewer's comment*: DRUP consulted the Division of Cardiovascular and Renal Products on October 26, 2009, to evaluate the cardiac failure data from trials ARI40005 and ARI40006. Because the comprehensive evaluation of the cardiac failure issue will require interdivisional discussions, it is premature at this time to conclude whether or not cardiac failure is a safety concern and to propose any potential risk management strategy for NDA 22-460.*

Prostate cancer:
Table 27 summarizes the cumulative experience with prostate cancer in ARI40005. The incidence of prostate cancer was higher in the tamsulosin group (3%) compared to dutasteride or co-administration groups (both 2%). Most cases of prostate cancer led to permanent drug discontinuation. There was no overall trend to the time of prostate cancer diagnosis. Comparing Years 3-4 to Years 0-2, more cases of prostate cancer were diagnosed in the dutasteride group, less in the co-administration group, and a similar number of cases in the tamsulosin group.

Table 27: Summary of prostate cancer (cumulative)

	Co-administration N=1610 n (%)	**Dutasteride N=1623 n (%)**	**Tamsulosin N=1611 n (%)**
Any prostate cancer	34 (2)	32 (2)	53 (3)
SAEs	21 (1.3)	16 (1)	24 (1.5)
Non-SAEs	13 (<1)	16 (<1)	29 (2)
Fatal	1	0	0
Leading to permanent drug discontinuation	26 (1.6)	24 (1.5)	40 (2.5)
Time of diagnosis • Year 0-2 • Year 3-4	 • 21 • 13	 • 12 • 20	 • 26 • 27

Source: NDA 22-460, Module 5.3.5.1.22, Listing 1 and Listing 2, MO analysis

Reviewer's comment*: No concerning trend in prostate cancer were noted for the co-administration group compared to each monotherapy group. In the MTOPS study (co-administration of finasteride + doxazosin in a similar BPH population), the 4-year incidence of prostate cancer in the placebo group was ~ 4%.*

Reviewer's comment: To the knowledge to this reviewer, there have been no reported cases of priapism, Intraoperative Floppy Iris Syndrome (IFIS) or breast cancer in controlled clinical trials of the co-administration of dutasteride and tamsulosin to date.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

No additional safety information on common adverse events of ARI40005 submitted for the co-administration of dutasteride and tamsulosin in NDA 21-319/S014 was submitted in this NDA. The reader is referred to the clinical review of NDA 21-319/S014 for detailed review of common AEs based on the Year 2 data of ARI40005. For ease of review, a summary of the most pertinent findings of common AEs in NDA 21-319/S014 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 ($p < 0.05$). See Table 28.

Table 28: 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

7.4.2 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. DRUP requested updated safety information on laboratory outliers as study ARI40005 is ongoing.

In the current NDA, the Applicant submitted cumulative data on laboratory outliers in order to put the data in full perspective of 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. Select laboratory tests are presented in Table 29.

Table 29: Laboratory outliers of selected laboratory tests (cumulative)

	Co-administration n/N (%)	Dutasteride n/N (%)	Tamsulosin n/N (%)
Any Outlier Value	129/1521 (8)	127/1532 (8)	135/1523 (9)
Hemoglobin < 0.75X LLN	6/1512 (<1)	7/1525 (<1)	4/1520 (<1)
Glucose > 1.75X UNL	62/1488 (4)	77/1508 (5)	68/1505 (5)
Total bilirubin > 2.5X ULN	1/1520	1/1532	1/1523
ALT > 3X ULN	5/1520	5/1532	6/1523
AST > 3X ULN	1/1519	4/1532	5/1523
Creatinine > 3X ULN	2/1520	2/1532	2/1523

Source: NDA 22-460, Module 5.3.5.1.22, Listing 9 and Table 9, MO analysis

A detailed review of line listing of laboratory outliers was conducted for subjects with significant liver function test (LFT) elevations (AST or ALT ≥ 5X ULN or total bilirubin > 2.5X ULN). A total of 9 subjects (co-administration: 2; dutasteride: 3; tamsulosin: 4) had laboratory values meeting these LFT criteria. Of these 9 subjects, 2 had concurrent significant elevations in transaminases and bilirubin. Subject 53490 (tamsulosin) had pancreatic cancer with liver metastases. Subject 51058 (dutasteride) has ALT 13X ULN, AST 8.7X ULN and total bilirubin 1.4X ULN at Month 12. These LFT abnormalities occurred one week after the subject started a second statin; the abnormalities resolved after the subject discontinued the second statin product.

***Reviewer's comment**: At this reviewer's request, the Applicant submitted a line listing of subjects with total bilirubin level ≥ 1.5X ULN (Amendment 0008 to NDA 22-460 dated June 23, 2009, Line Listing 14) up to December 8, 2008. A total of 43 patients (co-administration: 15; dutasteride: 14; tamsulosin: 14) had at least one total bilirubin level meeting the threshold value. Other than subject 53490 with pancreatic carcinoma and liver metastases described above, no subjects had concurrent AST/ALT ≥ 3X ULN and total bilirubin ≥ 1.5X ULN.*

7.4.3 Vital Signs

No additional vital sign information of ARI40005 beyond that submitted for the co-administration of dutasteride and tamsulosin in NDA 21-319/S014 was submitted in this NDA. According to the clinical review of NDA 21-319/S014 no safety concerns were identified for the co-administration group, compared to the monotherapy groups, in the analyses focused on central tendencies or vital sign outliers.

7.6 Additional Safety Evaluations

7.6.2 Human Reproduction and Pregnancy Data

During the **updated** reporting period, one partner pregnancy occurred in ARI40005. The subject's partner became pregnant approximately 31 months after the subject began taking his study medication (tamsulosin). The expected delivery due date was several weeks after the subject's last dose of study medication (April, 2008). As of July, 2008, the Applicant has not received a release of medical records to obtain follow-up information on the pregnancy or its outcome.

No partner pregnancies occurred in any other studies submitted in support of DTC.

7.6.3 Pediatrics and Assessment of Effects on Growth

Neither dutasteride nor tamsulosin, alone or in combination, or DTC has been investigated in the pediatric population. Dutasteride is contraindicated in children. A full pediatric waiver was requested and granted for DTC, as it was for the co-administration regimen in NDA 21-319/S014.

7.6.4 Overdose, Drug Abuse Potential, and Withdrawal and Rebound

Overdose: According the Applicant, as of December 8, 2008, 18 cases of dutasteride overdose and 1 case of dispensing error were reported to GSK's post-marketing safety database (Operating Companies Event Accession and Notification [OCEANS]). These 19 cases are described below:

Dutasteride:
No adverse events reported (10): One patient each reported taking 5 mg daily, 2.5 mg daily and 2 mg daily; another 5 patients reported taking 1 mg daily. Two reported the accidental ingestion of one extra pill. None of these patients reported adverse events.

Adverse events reported (6): A dispensing error was reported in a female patient who was given AVODART 0.5 mg twice daily instead of AVANDAMET®, and experienced stomach pains and elevated blood glucose.

One patient mistakenly took dutasteride 0.5 mg four times a day and developed "gallbladder sludge." Another patient took 2.5 mg daily for 6 months and reported decreased ejaculate volume, increased libido, hair regrowth, and slight somnolence. Three patients took dutasteride 0.5 mg twice daily; the reported events were feeling "abnormal," low blood sugar, and breast pain and enlargement.

Unknown (3): The remaining three reports (one case each of a suicide attempt, possible drug overdose, and intentional misuse) were poorly documented and could not be further evaluated.

Tamsulosin:
According to the FLOMAX label (4/09), one patient ingested thirty Flomax 0.4 mg capsules and reported a severe headache.

Dutasteride + Tamsulosin:
OCEANS has 7 overdose reports of persons taking dutasteride and tamsulosin. Three cases described accidental ingestions of one or two 0.5 mg dutasteride gel capsules on one occasion with no adverse event reported. Two reports described doubling of dutasteride capsules and no adverse events reported. Another case described a patient who took an unspecified overdose of his father's dutasteride and tamsulosin in a suicide attempt. He was hospitalized and improved and no AEs resulting from the overdose were noted. The final case described an attempted suicide by ingestion of 30 dutasteride capsules; the patient was hospitalized for 3 days with resolution of the unspecified events, which the reporting physician considered to be life-threatening. These same reports of overdose in persons taking dutasteride and tamsulosin from OCEANS also appeared in the FDA Adverse Event Reporting System (AERS).

Reviewer's comment: *The most important acute clinical sequela of DTC overdose would most likely be consequences of significant hypotension from the tamsulosin component.*

7.7 Additional Submissions / Safety Issues

The 120-Day Safety Update was received on July 16, 2009. This Safety Update included new SAE's 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 had a non-fatal SAE. Significant safety updates on previously reported SAEs were provided for 15 patients. No new safety findings were identified in the review of the 120-Day Safety Update.

Deaths
One death occurred in the co-administration group (acute myocardial infarction) and 2 deaths occurred in the tamsulosin group (gastrointestinal hemorrhage and traumatic subdural hematoma). This reviewer reviewed the case narratives and did not consider any of the deaths to be drug-related.

Reviewer's comment*: The acute MI occurred in an 81 year-old male subject after 4 years of treatment with the co-administration of dutasteride and tamsulosin and 13 days after his last dose of investigational product. An autopsy was not performed. Significant medical history included hypertension, hypercholesteremia and tobacco use. The subject was diagnosed with severe coronary artery disease and underwent cardiac catheterization with stent placement at approximately 1.5 years after the start of investigational product. The subject's fatal MI was most likely due to his underlying cardiac risk factors*.

Non-fatal SAEs
Nine (9) subjects in the co-administration group, 10 in the dutasteride group, and 9 in the tamsulosin group experienced at least one non-fatal SAE. Cardiac disorders and neoplasms were the most commonly reported SOC. One subject in the co-administration group experienced phlebectomy and one subject in the tamsulosin group experienced pleural effusion in which drug causality was considered "unknown" by the investigator. The remainder of the 26 cases was not considered to be drug-related. This reviewer reviewed all 28 case narratives and did not consider any of them drug-related.

Partner pregnancy
No new partner pregnancy occurred during the Safety Update period, and no follow-up information on previously reported pregnancies was received during the same time period.

Reviewer's comments: *No significant findings were noted in the review of the updates of previously reported SAE's for 15 subjects. According the Applicant, there were no new safety findings in the published literature or from spontaneously reported adverse events databases during the update period.*

8 Postmarketing Experience

DTC has not been marketed, however, postmarketing experience with concomitant dosing of dutasteride and tamsulosin are available. Dutasteride has been marketed in the U.S. since January, 2003, and is currently marketed in 75 countries. Based on sales data as of September, 2008, approximately 3.2 million patient-years of treatment have been sold worldwide. Tamsulosin has been marketed in Europe since 1995 and in the U.S. since 1997. The Applicant does not hold the safety database for tamsulosin.

In this NDA submission, the Applicant analyzed the following sources for post-marketing safety information on 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

Published literature
All of the 5 published reports of studies involving the concomitant use of dutasteride and tamsulosin were reviewed in NDA 21-319/S014.

GSK's Worldwide Safety Database (OCEANS)
OCEANS contains spontaneous adverse event reports from worldwide sources for GSK's marketed products (which include dutasteride but not tamsulosin) and serious adverse event reports from GSK-Applicanted clinical trials. Adverse events are coded using the MedDRA coding dictionary. Post-marketing adverse events in patients using dutasteride and tamsulosin are reported to GSK only if the reporter considers the event to be possibly related to dutasteride.

As of December 1, 2008, OCEANS had received 627 spontaneous adverse reports containing a total of 1464 AE's, which contained dutasteride as a suspect or concomitant drug AND tamsulosin as a suspect or concomitant drug. The most frequently reported events were dysuria (39 events), gynecomastia (32 events), erectile dysfunction (31 events), dizziness (26 events), rash (26 events), pharmaceutical product complaint (25 events), breast tenderness (24 events), pollakiuria (23 events), decreased libido (23 events), breast enlargement (22 events), nocturia (20 events), and fatigue (20 events). Two reports of women becoming pregnant while their partners were on dutasteride and tamsulosin did not describe any adverse event in these women; however, the outcomes of these pregnancies were not provided.

External post-marketing safety databases: FDA AERS and WHO Vigibase
The U.S. FDA AERS and WHO Vigibase are available publicly and contain reports of adverse events on the co-administration of dutasteride and tamsulosin reported to multiple manufacturers. Adverse events reported to the AERS database are coded using the MedDRA coding dictionary. Adverse events reported to the WHO Vigibase are coded using the WHO adverse reaction (WHOART) coding dictionary.

The Applicant analyzed the AERS (2nd quarter 2008) and Vigibase database (3rd quarter 2008) by using disproportionality analysis, which provides information about the relative reporting rates of adverse events to assist in detecting safety signals in the post-marketing setting. This method computes the Empiric Bayes Geometric Mean (EBGM) with associated two-side 90% confidence limits (EB05, EB95). EBGM values represent

relative reporting ratios of observed to expected cases. If the drug and the event were completely independent of one another, the EBGM (specifically EB05) would be 1. An EBGM of 2 indicates that the drug-event pair has been reported 2 times as frequently as expected if there was no association between the drug and the event. The FDA uses EB05 values ≥ 2 to define potential safety signals.[4]

Disproportionality Analysis of FDA AERS:
AERS (2nd quarter, 2008) contained 1832 reports containing dutasteride (no alpha blockers), 9357 reports containing tamsulosin (no 5ARIs), and 556 reports containing both dutasteride and tamsulosin. Table 30 shows the 10 most commonly reported drug-event pairs for the co-administration of dutasteride + tamsulosin where EB05 ≥ 2.

Table 30: AERS common drug-event pairs for co-administration of dutasteride and tamsulosin (Q2, 2008)

MedDRA Preferred Term	# Reports	EB05
Breast enlargement	15	27
Semen volume decreased	10	25
Breast tenderness	16	23
Nocturia	22	17
Urine flow decreased	10	15
Gynecomastia	20	14
Libido decreased	17	13
Breast mass	6	6
Pollakiuria	21	4
Dysuria	20	4

Source: NDA 22-460, Module 2.7.4, Summary of Clinical Safety, p. 29

According to the Applicant, when comparing the co-administration regimen to dutasteride or tamsulosin monotherapy, non-overlapping confidence intervals ((i.e. EB05 of co-administration > EB95 of each monotherapy) were observed for nocturia. When comparing co-administration to tamsulosin, non-overlapping confidence intervals (CIs) were observed for dysuria, pollakiuria, urine flow decreased, alopecia, erectile dysfunction, libido decreased, breast disorders, and drug administration error. When comparing co-administration to dutasteride, non-overlapping CIs were observed for aortic aneurysms (4 reports), head injury (6 reports), fatigue and insomnia.

Disproportionality Analysis of the WHO Vigibase
The WHO Vigibase (3rd quarter, 2008) contained 1046 reports containing dutasteride (no alpha blockers), 6129 reports containing tamsulosin (no 5ARI's), and 269 reports containing both dutasteride and tamsulosin. Table 31 shows the 10 most common drug-event pairs where EB05>1 for the co-administration of dutasteride + tamsulosin.

4 SzarfmanA, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Safety* 2002; 25:381-392.

Table 31: Vigibase common drug-event pairs for co-administration of dutasteride and tamsulosin (Q3, 2008)

MedDRA Preferred Term	# Reports	EB05
Breast enlargement	10	29
Breast pain	13	25
Libido decreased	13	14
Gynecomastia	14	10
Pollakiuria	11	4
Nocturia	6	3
Dysuria	6	2
Urine flow decreased	4	2
Alopecia	6	2
Urinary retention	7	2

Source: NDA 22-460, Module 2.7.4, Summary of Clinical Safety, p. 29

According to the Applicant, when comparing the co-administration to tamsulosin monotherapy, non-overlapping CIs were observed for libido decreased, breast disorders, and pollakiuria. No non-overlapping CIs were observed when comparing co-administration to dutasteride monotherapy.

Reviewer's comments: *A majority of the AE's listed in Tables 30 and 31 are consistent with the pharmacologic activity of or known safety profile of the dutasteride and tamsulosin or the underlying BPH disease. No new safety signals were detected during the review of the postmarketing data of the co-administration of dutasteride with tamsulosin.*

9 Appendices

9.2 Labeling Recommendations

The approved prescribing information of Avodart (6/08) and Flomax (4/09) formed the basis of the proposed label for DTC. Labeling for DTC will reflect the efficacy and safety findings previously determined for the co-administration regimen in NDA 21-319/S014. In reviewing the label, this reviewer verified that the information in the proposed DTC label is supported by data and that important safety information from dutasteride or tamsulosin monotherapy trials, which were placebo-controlled, are included in the DTC prescribing information. The following section discusses major clinical recommendations to the draft DTC label.

General comment:

- Because clinical safety and efficacy were evaluated with the co-administration regimen and not with DTC, the co-administration treatment group should be labeled as "co-administration" to differentiate it from the "combination" capsule (DTC).

Safety:
- Warnings and Precautions: "orthostatic hypotension" is a known significant safety issue because of the potential for life-threatening consequences from syncope and should be moved higher up in the order of safety concerns. "Drug drug interactions" should also be moved up in the order of safety concern because the anticipated increased risk of hypotension with the concomitant use of DTC with another alpha-adrenergic antagonist or PDE5-inhibitors.
- Postmarketing Experience: Additional important postmarketing experience with dutasteride and tamsulosin monotherapy should be included.

Drug-Drug Interactions:
- Information from drug-drug studies with tamsulosin monotherapy and moderate and strong CYP inhibitors should be added to the label.

Overdosage:
- Overdosage information for dutasteride monotherapy was added.

Clinical Pharmacology:
- Data from the drug-drug interaction studies of tamsulosin monotherapy and moderate/strong CYP inhibitors should be included.

Reviewer's comment**:** *The Division has not begun labeling discussions with the Applicant during this review cycle. The final approval of DTC will be contingent upon satisfactory labeling negotiations.*

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/

CHRISTINE P NGUYEN
06/10/2010

SURESH KAUL
06/11/2010

CLINICAL REVIEW

Application Type	N
Application Number(s)	22-460
Priority or Standard	S
Submit Date(s)	March 20, 2009
Received Date(s)	March 20, 2009
PDUFA Goal Date	January 20, 2010
Division / Office	Reproductive and Urologic Products
Reviewer Name(s)	Christine P. Nguyen
Review Completion Date	January 15, 2010
Established Name	Dutasteride/tamsulosin
(Proposed) Trade Name	Flodart
Therapeutic Class	5-alpha reductase inhibitor/alpha adrenergic antagonist
Applicant	GlaxoSmithKline
Formulation(s)	Oral capsule
Dosing Regimen	Fixed-dose combination dutasteride 0.5 mg/tamsulosin 0.4 mg once daily
Indication(s)	Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged

	prostate
Intended Population(s)	Men with symptomatic BPH and an enlarged prostate

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the **clinical perspective**, fixed-dose combination dutasteride 0.5 mg/tamsulosin 0.4 mg capsule (DTC) taken once daily should 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 the ongoing 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).

From a **regulatory perspective**, this NDA could only be **tentatively approved** at this time because the patent/exclusivity for tamsulosin does not expire until April 27, 2010. The final approval determination is contingent upon labeling negotiations, which will be addressed during the next review cycle.

1.2 Risk Benefit Assessment

The data to support the co-administration of dutasteride and tamsulosin came from one large, international, multicenter, randomized, double-blind, parallel group study of 4-year duration in men with moderate to severe BPH symptoms and an enlarged prostate (study ARI40005). The first 2 years of the trial were designed to evaluate the safety and efficacy of dutasteride and tamsulosin administered concomitantly ("co-administration" group) compared to each monotherapy in improving BPH symptoms. The last 2 years of the study were designed to determine the effects of the co-administration regimen on the time to event of acute urinary retention (AUR) or BPH-related prostate surgery. The Year 4 analyses of ARI40005 will be submitted in a separate submission.

Benefit: The co-administration of dutasteride and tamsulosin resulted in statistically significant improvement in the primary endpoint (International Prostate Symptom Score or IPSS) and the main secondary endpoint (maximum urinary flow rate or Qmax) compared to each monotherapy at 24 months. At Month 24, the mean difference between the co-administration and dutasteride groups was -1.3 units and between the co-administration therapy and tamsulosin was -1.8 units (see Table 1). Although Trial ARI40005 did not have a placebo-control group, there was sufficient evidence to reasonably conclude that dutasteride and tamsulosin monotherapy performed as expected. In summary, the benefit of the co-administration regimen over each monotherapy was established based on substantial evidence of effectiveness for the

products' intended use, as demonstrated by one large adequate and well-controlled clinical study, and satisfactory fulfillment of the Combination Drug Rule.
No clinical efficacy studies were conducted with DTC. The efficacy of DTC is expected to be comparable to that of the co-administration regimen because the 2 products were shown to be bioequivalent in study ARI109882.

Table 1: Change from baseline IPSS at Month 24 in ARI40005 (LOCF, ITT)

Time point	**Mean change from baseline IPSS (SE)**					
	N	Combination	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 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

Risk: The safety database of DTC includes: a) the clinical bridge to the safety database of ARI40005, which consisted of 4844 patients, 1610 of whom received at least one dose of the co-administration regimen and b) 110 healthy male subjects who received at least one dose of DTC. The study population in ARI40005 is representative of the target population of DTC.

The safety and tolerability of the co-administration regimen compared to each monotherapy was overall acceptable based on the Year 2 data of ARI40005. Compared to each monotherapy, the co-administration regimen was not associated with an excess of overall treatment-emergent adverse events, deaths, or non-fatal serious adverse events. No significant excesses in hepatic, hematologic, or renal toxicity were identified in the co-administration group compared to each monotherapy. Significantly more subjects in the co-administration group withdrew due to an adverse event (AE) or reported a drug-related adverse event, which was primarily sexual or breast-related. Among the common adverse events, the incidence of reproductive and breast disorders was higher in the co-administration group (20%) than dutasteride (16%) or tamsulosin (12%). Compared to each monotherapy, the incidence of ejaculation disorders was 3- to 5-fold higher for the co-administration group and this difference was statistically significant. Updated safety information on significant adverse events (from cut-off date of the 120-Day Safety Update of Year 2 of ARI40005 [September 1, 2007] to the December 8, 2008 cut off date of the DTC NDA) and preliminary ~ 4-year cumulative safety information from ARI40005 did not reveal any new trend or unexpected safety findings compared to the Year 2 data of ARI40005, with the exception of composite cardiac failure event.

Composite cardiac failure included all events coded to the MedDRA 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. The incidence of cardiac failure over 4 years was higher in the co-administration group (12 subjects, 0.7%) than tamsulosin (8 subjects, 0.5%) or dutasteride (2 subjects, 0.1%). A review of the case narratives indicated that all but one (1 tamsulosin subject) had more plausible alternative explanations for the adverse outcome or had clinical experience inconsistent with cardiac failure. The concomitant administration of dutasteride and tamsulosin does not alter tamsulosin pharmacokinetic or dutasteride pharmacodynamic parameters. The incidence of cardiac failure in the co-administration group (0.7%) was similar to that observed in the integrated analysis of placebo data from the major dutasteride trials whose study populations were similar to that of ARI40005. Cardiac failure is not a labeled adverse reaction of 5-alpha reductase inhibitors or alpha-adrenergic antagonists. At this time, this reviewer does not believe the totality of evidence indicates a significant cardiac failure signal for the co-administration regimen.

The cardiac failure data from Trial ARI40005 reviewed by DRUP (co-administration of dutasteride and tamsulosin for BPH treatment) and Trial ARI40006 reviewed by the Division of Oncology Products (dutasteride vs. placebo for reduction of the risk of prostate cancer) are currently being consulted to the Division of Cardiovascular and Renal Products. Because the comprehensive evaluation of the cardiac failure issue will require substantial interdivisional discussions, it is premature at this time to conclude whether or not cardiac failure is a safety concern and to propose any potential risk management strategy for NDA 22-460. The approvability of this NDA depends primarily on the Year 2 data of ARI40005 and will be handled separately from the cardiac failure issue.

***Reviewer's comment**: Cardiac failure is the subject of review in 3* (b) (4) *:*

1. *Supplement Labeling Request (SLR) to NDA 21-319 dated July 27, 2009, to include cardiac failure in the Warnings and Precautions section of the AVODART label*

(b) (4)

No unexpected safety findings were identified in healthy subjects receiving DTC.
Risk:benefit conclusion: The overall risk/benefit profile for the combination of dutasteride and tamsulosin was assessed in the efficacy supplement 014 to NDA 21-319 and was determined to be favorable. Since the approval of this efficacy supplement, no significant safety issues, other than the aforementioned cardiac failure, have been identified for the co-administration of dutasteride and tamsulosin. Cardiac failure will be addressed separately from this NDA. At this time, this reviewer does not believe the strength of the evidence of cardiac failure precludes the approval of this NDA. It is anticipated that the overall risk benefit profile for DTC will be comparable to the currently approved co-administration of dutasteride and tamsulosin because the 2 products are bioequivalent.

1.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No post-marketing risk evaluation and mitigation strategies are warranted for DTC at this time.

1.4 Recommendation for Postmarketing Requirements and Commitments

No new safety concerns have been identified to require actions other than routine post-marketing surveillance.

2 Introduction and Regulatory Background

2.1 Product Information

The dutasteride/tamsulosin combination capsule (DTC) is a hard shell capsule containing dutasteride intermediate (soft gelatin capsule containing 0.5 mg dutasteride) and tamsulosin hydrochloride product intermediate (pellet containing 0.4 mg tamsulosin hydrochloride). The manufacture of DTC involves the over-encapsulation of the intermediates of the 2 active ingredients. The drug substance and dose of each active ingredient are the same as those commercially available for dutasteride 0.5 mg and tamsulosin 0.4 mg that were used in study ARI40005.

The product information of dutasteride and tamsulosin monotherapies as well as for the co-administration of these 2 drugs is summarized Table 2 below.

Table 2: Summary of Product Information

Product	Dutasteride	Tamsulosin	Co-administration of dutasteride and tamsulosin
Trade name (U.S.)	Avodart	Flomax	Avodart + tamsulosin
Indication (s) (year of approval)	Treatment of BPH in men with an enlarged prostate to: • Improve symptoms (2001) • Reduce the risks of acute urinary retention and need for BPH-related surgery (2002)	The treatment of symptomatic BPH (1997)	Treatment of symptomatic BPH in men with an enlarged prostate (2008)
Dose and regimen	0.5 mg once daily	0.4 mg (up to 0.8 mg) once daily	0.5 mg dutasteride + 0.4 mg tamsulosin once daily
Intended population	Men with symptomatic BPH and an enlarged prostate	Men with BPH	Men with symptomatic BPH and an enlarged prostate
Sponsor	GSK	Boehringer Ingelheim	GSK

Source: Approved product labels of Avodart (6/2008) and Flomax (10/2009)

2.2 Currently Available Treatments for Proposed Indication

Benign prostatic hyperplasia (BPH) is a common medical condition among older men and affects approximately 50% of men after the age of 60 years. BPH can cause considerable disability, leading to obstructive and/or irritative voiding symptoms requiring medical or surgical treatment. The decision to treat is usually based on the type and severity of symptoms and the patient's tolerance for these symptoms. In general, men who develop significant upper tract changes (e.g., hydronephrosis, renal dysfunction) or significant lower tract changes (e.g., urinary retention, recurrent infection, bladder decompensation) require invasive therapy. Otherwise, symptomatic BPH may be treated medically with an alpha-adrenergic antagonist (doxazosin, alfuzosin, terazosin, tamsulosin, and silodosin), a 5α-reductase inhibitor (dutasteride, finasteride) or the combination of both (dutasteride + tamsulosin, finasteride + doxazosin). Treatment with a 5α-reductase inhibitor (5ARIs), alone or in combination, is typically reserved for men with symptomatic BPH associated with demonstrable prostatic enlargement. Table 3 summarizes the currently approved drug treatments for symptomatic BPH.

Table 3: FDA-approved pharmacologic treatments of BPH

Pharmacologic Class	Agents	Indication (s)	Typical onset of symptom relief	Proposed mechanism of action	Common adverse reactions
5α-reductase inhibitors	Finasteride Dutasteride	Treatment of symptomatic BPH; reduction in risks of AUR, BPH-related surgery	6-12 months	Decrease prostate volume	Sexual dysfunction (libido decreased, impotence, ejaculation disorders) Breast disorders
Alpha-adrenergic antagonists	Doxazosin Alfuzosin Terazosin Tamsulosin Silodosin	Treatment of symptomatic BPH	2-4 weeks	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	4 weeks	Combined mechanisms	Ejaculation disorder Sexual disorders Breast disorders

2.3 Availability of Proposed Active Ingredient in the United States

Both dutasteride 0.5 mg soft gelatin capsules and tamsulosin 0.4 mg capsules are approved and marketed in the U.S for the treatment of BPH.

2.4 Important Safety Issues With Consideration to Related Drugs

5 α-reductase inhibitors (5ARIs):

- 5ARIs may cause abnormalities of the external genitalia of a male fetus and are contraindicated in women who are or who may potentially become pregnant. These women are cautioned not to handle crushed or broken drug capsules because of the possibility of systemic drug absorption and the subsequent potential risk to a male fetus.
- 5ARIs decrease serum PSA levels by approximately 50% after 3 to 6 months of treatment and this suppression is maintained throughout the treatment period. This pharmacodynamic effect should be taken into consideration when interpreting PSA results for prostate cancer screening and monitoring. Any rise

in PSA levels after nadir may signal the presence of prostate cancer and should be evaluated accordingly.
- Common adverse reactions include impotence, decreased libido, decreased volume of ejaculate, ejaculation disorder, and breast disorders. The association between male breast cancer and long-term 5ARI use is currently unknown.

Alpha-adrenergic antagonists:
- Alpha-adrenergic antagonists cause peripheral adrenergic blockade, leading to peripheral vasodilatation and subsequent fall in blood pressure. Clinically significant outcomes are orthostatic hypotension and syncope. The hypotensive effects can be potentiated by the concomitant use of other alpha-adrenergic antagonists or phosphodiesterase-5 inhibitors (PDE5-Is). Alpha-adrenergic antagonists should not be used concomitantly with one another; alpha-adrenergic antagonist should be used with caution in combination with a PDE5-I.
- Rare but potentially serious adverse effects of alpha-adrenergic antagonist treatment include Intraoperative Floppy Iris Syndrome (IFIS) and priapism.
- Hypersensitivity reactions to tamsulosin have been observed in patients with sulfa allergy.
- Common adverse reactions include dizziness, somnolence, asthenia, nasal congestion, rhinitis, and abnormal ejaculation.

Co-administration of 5ARI and alpha-adrenergic antagonist:
In controlled studies, no unexpected clinical adverse experience was observed other than those already labeled for 5ARIs and alpha-adrenergic antagonists. The co-administration of these 2 products resulted at least an additive effect on ejaculatory disorders compared to each monotherapy.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

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. Tamsulosin (Flomax) 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 Avodart 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 Applicant of 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 support a marketing 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 DTC.

On September 19, 2008, the Applicant submitted pre-NDA questions concerning the content and format for the DTC NDA submission. The Division provided responses to these questions via written communication dated October 23, 2008.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Division of Scientific Investigation (DSI) was conducted a routine audit for study ARI109882, because this was the key BE study providing the clinical bridge to the pivotal safety and efficacy study ARI40005. DSI issued a "VAI – Voluntary Action Indicated" to the bioanalytical site and one of the 2 clinical sites. After evaluating the Applicant's responses, DSI concluded that "the inspectional findings should not have significant impact on the outcomes of study ARI109882." The clinical pharmacology team concurred that the deficiencies cited in the DSI audit would not likely alter the overall results of study ARI109882. From DSI's perspective, there are no outstanding issues for this application.

The Applicant has in place standard operating procedures that are consistent with the ICH Good Clinical Practice, including archiving of source data, data validation of CRF data, internal audits, and the use of a validated central laboratory.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all clinical studies submitted were conducted in compliance with Good Clinical Practices. In support of this, the Applicant submitted samples of informed consent, documents of IRB approval, and required case report forms.

3.3 Financial Disclosures

Form FDA 3454 (4/06), dated February 19, 2009, and signed by Craig A. Metz, Ph.D., Vice President, Regulatory Affairs, GlaxoSmithKline, was submitted. Financial disclosure documents were submitted for clinical investigators (principal and sub-investigators) of study 109882, the key BE study. Financial disclosures for study ARI40005, the primary study supporting the safety and efficacy of the co-administration of dutasteride and tamsulosin, was submitted previously in efficacy supplement 014 to NDA 21-319. This approach is acceptable, because the approval of this NDA is based on study 109882 with cross-referencing to study ARI40005.

All of the principal investigators (2) and sub-investigators (6) from 2 sites of study 109882 had no disclosures in the categories of compensation potentially affected by the outcome of the covered study [21 CFR 54.4(a)(3)(i), 54.2 (a)], significant payments of other sorts from the Applicant of the covered study [21 CFR 54.4 (a)(3)(ii), 54.2(f)], proprietary interest in the tested product [21 CFR 54.4(a)(3)(iii), 54.2(c)], or significant equity interest in the Applicant of the covered study product [21 CFR 54.4(a)(3)(iv), 54.2(b)].

In summary, adequate information was submitted to demonstrate compliance with financial disclosure requirements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

From the chemistry perspective, the chemistry team recommends approval of this NDA. The Office of Compliance issued an “Acceptable” recommendation for all the facilities involved in the manufacture and test of the drug substance and drug product. Because this application is tentative approved, labeling recommendations will be addressed in the next review cycle.

4.2 Clinical Microbiology

The clinical microbiology reviewer recommends approval of this NDA from a microbiology perspective.

4.3 Preclinical Pharmacology/Toxicology

No preclinical studies were conducted with DTC. No impurities were identified in the DTC product that warranted further preclinical evaluation. The Applicant relies on the

approved Avodart and Flomax package inserts to label preclinical findings for DTC. The preclinical pharmacology/toxicology team recommends approval of this NDA from a preclinical pharmacology/toxicology perspective. Because this application is tentatively approved, labeling recommendations will be addressed in the next review cycle.

4.4 Clinical Pharmacology

The clinical pharmacology team recommends the approval of this NDA from a clinical pharmacology perspective. Because this application is tentatively approved, labeling recommendations will be addressed in the next review cycle. This NDA for DTC relies on one key bioequivalence (BE) study (ARI109882) and 4 supporting biopharmaceutics studies to establish the BE of dutasteride and tamsulosin monotherapies co-administered (as in Trial ARI40005) to DTC. The BE assessment from Study ARI109882 is used to bridge the safety and efficacy data of Trial ARI40005 to DTC. The reader is referred to the clinical pharmacology review for a detailed review of the clinical pharmacology of DTC

4.4.1 Mechanism of Action

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

Dutasteride is an inhibitor of the 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. The Type 2 isoform is present in prostatic and other androgen-sensitive tissues and is believed to be important to prostatic enlargement. The Type 1 isoform is present in liver and skin and, to some extent, in the prostate. The clinical relevance of the Type 1 isoform in the prostate is unknown. 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.

4.4.2 Pharmacodynamics

No pharmacodynamic assessments were conducted with DTC. The following pharmacodynamic effects have been well-characterized for dutasteride and tamsulosin:

Dutasteride:
- Dutasteride decreases DHT levels in a dose-dependent manner. After daily dosing with dutasteride 0.5 mg, the maximum reduction in DHT is achieved within 2 weeks of therapy (median reduction of 90%) and is maintained throughout the treatment duration. The median increase in serum testosterone levels, ranging 18-22%, is seen after 8 weeks and is maintained throughout the treatment duration. Mean and median levels of serum testosterone remains within the physiologic range.
- Dutasteride 0.5 mg once daily decreases prostate-specific antigen (PSA) levels ~ 50% by 3 to 6 months of treatment.

Tamsulosin:
- Alpha-blockade results in peripheral vasodilation, which results in a fall in blood pressure.

4.4.3 Pharmacokinetics

The absorption and food effect data for DTC were obtained from Study ARI109882, the pivotal BE study. The Applicant relies on the approved Avodart and Flomax prescribing information to label the remainder of the pharmacokinetics of DTC.

The pharmacokinetics of dutasteride and tamsulosin from DTC are equivalent to the pharmacokinetics of dutasteride and tamsulosin when administered separately.

The PK parameters of dutasteride and tamsulosin observed after administration of DTC in a single dose, randomized, three-period partial cross-over study are summarized in the table below.

Geometric Means (%CV) of Serum Dutasteride and Tamsulosin Single-dose PK Parameters

Component	Condition	N	AUC (0-t) (ng·hr/mL)	C_{max} (ng/mL)	Tmax (hr)[a]	$t_{½}$ (hr)
Dutasteride	Fed	91	33.3 (78.6)	2.01 (35.5)	4.00 (1.00-6.03)	
	Fasted	46	29.2 (91.7)	2.02 (49.4)	2.00 (1.00-10.0)	
Tamsulosin	Fed	91	164 (52.6)	9.75 (44.7)	7.00 (2.00-24.0)	12.9 (28.7)
	Fasted	46	184 (46.1)	14.6 (35.3)	5.00 (2.00-8.00)	12.3 (29.6)

[a] Median (range)
Source: Primary Clinical Pharmacology review, NDA 22-460

Dutasteride:
Dutasteride has an absolute bioavailability of 60% and a Tmax ranging from 2-4 hours. Drug absorption is not significantly affected by food intake. Dutasteride has a large

volume of distribution (300-500 L) and is highly bound to plasma albumin (99.0%) and alpha-1-acid glycoprotein (96.6%). Dutasteride is extensively metabolized, primarily by the CPY3A4 and CYP3A5 isoenzymes; only a trace amount of dutasteride (<1%) is excreted unchanged in urine. Dutasteride and its metabolites are primarily excreted in feces. Approximately 55% of administered dutasteride dose is unaccounted for. The terminal half-life of dutasteride is approximately 5 weeks at steady state. No dose adjustment is anticipated in patients with renal impairment; caution should be used in hepatically impaired patients.

Tamsulosin:
Tamsulosin is almost completely absorbed (>90%) following oral intake under fasting conditions. Compared to fed conditions, administering tamsulosin under fasted conditions results in increased exposure (a 30% increase in AUC and 40-70% increase in Cmax) and a shorter time to Tmax. Tamsulosin has a volume of distribution of 16L and is extensively bound to plasma proteins (>90%), primarily to alpha-1 acid glycoprotein. Tamsulosin is extensively metabolized primarily by the CYP3A4 and CYP2D6 isoenzymes; less than 10% of the dose is excreted in the urine unchanged. The primary route of excretion for tamsulosin and its metabolites is via the kidney (76% of the administered dose). The apparent half-life is approximately 14 hours. Patients with renal impairment or mild/moderate hepatic dysfunction do not require an adjustment in tamsulosin dosing.

Reviewer's comment*: Because of the increased exposure in the fasted state, tamsulosin is to be administered 30 minutes after the same meal each day. The same dosing schedule was used in ARI40005, and the Applicant proposes that DTC be administered 30 minutes after the same meal each day.*

Drug-drug interaction between dutasteride and tamsulosin: Dutasteride administered with tamsulosin has no effect on the steady state PK of tamsulosin (Study ARIA1101 submitted in efficacy supplement 014 to NDA 21-319). The effect of tamsulosin on dutasteride PK parameters has not been evaluated. In efficacy supplement 014 to NDA 21-319, the Applicant submitted information which supported the probable lack of effect of tamsulosin on dutasteride pharmacokinetics

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4 summarizes the clinical studies conducted to support the safety and efficacy of DTC and which were analyzed in this clinical review.

Table 4: Clinical studies supporting DTC

Study/Design	Investigational products	Treatment duration	# subjects	Study outcomes
Pivotal clinical safety and efficacy: ARI40005/ Multicenter, randomized, double-blind, parallel group	1. Co-administration of dutasteride 0.5 mg + tamsulosin 0.4 mg once daily 2. Dutasteride 0.5 mg once daily + placebo 3. Tamsulosin 0.4 mg once daily + placebo	4 years	Total: 4844 Co-admi: 1610 Dut: 1623 Tam: 1611	IPSS Qmax
Pivotal Bioequivalence: ARI109882/ Two-center, randomized, open-label, 3-way partial crossover	DTC, fasted or fed Co-administration of dutasteride 0.5 mg + tamsulosin 0.4 mg, fasted or fed	Single dose	101 healthy male subjects	PK parameters

Source: NDA 22-460, Module 5.2

5.2 Review Strategy

The following approach was used to conduct the clinical review of this NDA:

1. The main focus of the clinical review was cumulative and updated safety information from the ongoing study ARI400005. This safety review is located in Section 7 (Review of Safety).
2. A detailed review of safety findings and a high-level review of PK findings of study ARI109882 were conducted. This review is found in Section 5.3 (Discussion of Individual Studies/Clinical Trials)
3. No clinical efficacy information for DTC was submitted. Clinical efficacy of DTC relies on the Year 2 findings of ARI40005, which is summarized in Section 6 (Review of Efficacy).
4. The safety data from the BE study (ARI109892) are not pooled with ARI40005 because of significant differences in study design, dosing, study population, and study outcomes.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study ARI40005: "A randomized, double-blind, parallel group study to investigate the efficacy and safety of treatment with Dutasteride (0.5mg) and Tamsulosin (0.4 mg), administered once daily for 4 years, alone and in combination, on the improvement of symptoms and clinical outcome in men with moderate to severe symptomatic benign prostatic hyperplasia"

Study ARI40005 was a 4-year, multicenter, randomized, double-blind, parallel group study to investigate the efficacy and safety of dutasteride and tamsulosin, alone and co-administered, on BPH outcomes in approximately 4,800 men with moderate to severe symptomatic BPH and an enlarged prostate. The first 2 years of the study was designed to evaluate the effect of dutasteride and tamsulosin co-administered compared to each monotherapy on BPH symptoms ("Year 2" study) as the primary outcome. The remaining 2 years were designed to evaluate clinical progression of BPH (i.e. time to acute urinary retention or BPH-related surgery) among the 3 treatment groups ("Year 4" study). The Year 2 data of ARI40005 provide the primary support for the clinical efficacy and safety of DTC. The review of ARI40005 is located in Section 6 and Section 7 of this clinical review.

5.3.2 Study ARI109882: "An Open-Label, Randomized, Single Dose Three-Period Partial Crossover Study to Determine the Bioequivalence and Food Effect of a Combination Capsule Formulation of Dutasteride and Tamsulosin Hydrochloride (0.5mg/0.4mg) Compared to Concomitant Dosing of AVODART® 0.5mg and Flomax 0.4mg Commercial Capsules in Healthy Male Subjects"

Primary Objective: 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 in fed state

Study design and conduct: 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 sequence 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 receiving treatment D. Each dosing session was separated by 4-week washout period. Table 5 describes the treatment groups.

Table 5: 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 (DTC) 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

Blood samples were collected for PK parameters of dutasteride and tamsulosin over a 72-hour period following dosing. The primary comparison for equivalence between DTC and the co-administration of dutasteride and tamsulosin was levels of drug exposure (AUC and Cmax) between treatment A and treatment B.

Changes in planned analysis: For dutasteride, $AUC_{(0-72)}$ could not be consistently determined because over 25% of the PK concentration from the last sample was not quantifiable or the actual sampling time of 72 hour sample was earlier than 72 hour. Therefore, $AUC_{(0-t)}$ was used as the primary PK parameter for dutasteride instead of $AUC_{(0-72)}$.

Study findings:

Subject Disposition and Demographics: One hundred one (101) subjects were enrolled and randomized. All subjects were male with a median age of 29.5 years. The most common ethnicity was Caucasian (77%), followed by Black (22%). Of 101 subjects, 81 (80%) completed the study. Twenty subjects (20%) withdrew prematurely and the most common reasons for withdrawal were consent withdrawal and protocol violation (7% each). See Table 6.

Table 6: Subject disposition

Disposition variables	N (%)
Number of subjects randomized	101
• Number of subjects completed	81 (80)
• Number of subjects withdrawn	20 (20)
* Adverse event	4 (4)
* Consent withdrawal	7 (7)
* Protocol violation	7 (7)
* Lost to follow up	1 (1)
* Investigator's discretion	1 (1)

Source: NDA 22-460, Study ARI109882, MO's analysis of ds.xpt

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 $AUC_{(0-t)}$ and Cmax between DTC 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 DTC to concomitantly dosed dutasteride and tamsulosin in the fasted state (D:C comparison). See table 7.

Table 7: Bioequivalence of DTC 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 = DTC in fed state (test)
Group C = co-administration of dutasteride + tamsulosin in fasted state (reference)
Group D = DTC in fasted state (test)

Food effect:
Dutasteride: There was no food effect on dutasteride PK with the exception of the mean Tmax occurring 1 hour later in the fed state compared to the fasted state (regimen B – D, A – C). This finding is not likely to be clinically significant.

Tamsulosin: Cmax and AUC values for treatment groups A and B (co-administration and DTC, respectively, in fed state) were 30% less than those for groups C and D (co-administration and DTC, respectively, in fasted state). Compared to fasted state, the Tmax of tamsulosin in fed state occurred approximately 1 to 1.5 hours later.

Reviewer's comment*: The food effect on tamsulosin has been adequately addressed in the proposed DTC product label, which recommends that DTC be taken 30 minutes after a meal.*

Safety Results

Exposure: The safety population, which consisted of all subjects who received at least one dose of study drug, included 101 subjects. All subjects were randomized to receive treatments A and B; half of the subjects were randomized to receive treatments C or D. Overall, 91 subjects received treatment A, 93 received treatment B, 46 received treatment C, and 46 received treatment D. A summary of the overall safety findings is provided in Table 8.

Table 8: Summary of exposure and safety findings by treatment

Treatment group*	A N = 91 n (%)	B N = 93 n (%)	C N = 46 n (%)	D N = 46 n (%)	Total N = 101 n (%)
# subjects with any AEs	21 (23)	24 (26)	14 (30)	15 (33)	50 (50)
Deaths/SAEs	0	0	0	0	0
AE's leading to withdrawal	1	1	0	2	4 (4)

Source: NDA 22-460, Module 5, Study ARI109882, MO analysis of ae.xpt
* A = co-administration of dutasteride + tamsulosin in fed state
B = DTC in fed state
C = co-administration of dutasteride + tamsulosin in fasted state
D = DTC in fasted state

Serious Adverse Events (SAEs): No deaths or non-fatal SAEs occurred.

AE's leading to study withdrawal: Four subjects (4%) withdrew prematurely due to adverse events, which are described below:

Subject 106 (randomized to DAB): received treatment D (DTC, fasted) prior to being withdrawn for liver function test (LFT) and creatine kinase (CK) elevations. These laboratory abnormalities were detected 27 days after receiving treatment D during the protocol-specified laboratory evaluation prior to session 2. Subject 106's laboratory abnormalities are summarized below:

Subject 106: Laboratory abnormalities

Laboratory Test	AST (IU/L)	ALT (IU/L)	Creatine kinase (IU/L)
Baseline (prior to any drug)	28	25	Not measured
Pre-dose session 2 (multiples of ULN) December 14, 2007	419 (10X)*	162 (3X)+	38,300 (165X)#
Follow up: • December 15, 2007 • December 17, 2007 • December 28, 2007	 • 475 • 301 • 36	 • 199 • 209 • 56	 • 40,360 • 12,010 • 215

Source: NDA 22-460, Module 5, study ARI109882, MO review of lab.xpt file
*Normal range: 10-42 IU/L
+Normal range: 0-55 IU/L
#Normal range: 21-232 IU/L

Reviewer's comment: *Because a review of subject 106's case narrative and CRF did not reveal a possible cause of laboratory abnormality, this reviewer requested the Applicant to clarify why creatine kinase (CK), which was not a protocol-specified laboratory test, was measured and to provide a possible explanation for the patient's laboratory abnormality. The Applicant stated that creatine kinase was measured because of the finding of LFT elevation. According to the Applicant, subject 106 "had begun intense training for boot camp just prior to checking in for the study, which the site investigator felt was responsible for his extreme laboratory elevations."*

Extent of acute CK elevation and its rapid reversal in an otherwise healthy young adult is indicative of rhabdomyolysis. Elevations of AST and ALT levels can occur concurrently with CK elevation. Immediately after muscle injury, the AST:ALT ratio is often > 3 but approaches 1 within a few days because of a faster decline in AST. This is consistent with subject 106's clinical experience. One of the possible etiologies includes significant physical exercise resulting in muscle trauma. Therefore, this reviewer considers the Applicant's response to be an acceptable explanation for subject 106's abnormal laboratory findings.

Subject 203 (randomized to CAB): received treatment C (co-administration, fasted) and treatment A (co-administration, fed) prior to being withdrawn for LFT elevation.

Subject 203: LFT abnormalities

Laboratory Test	AST (IU/L)	ALT (IU/L)	GGT (IU/L)
Baseline (prior to any drug)	24	37	39
Pre-dose session 3 (January 4, 2008)	168*	237+	116#
10 days of follow up (January 14, 2008)	43	64	Not done
After end of study (February 27, 2008)	Not done	Not done	34

*Normal range: 0-40 IU/L
+Normal range: 0-55 IU/L
#Normal range: 0-65 IU/L

Reviewer's comment: *This patient was withdrawn due to the prespecified withdrawal criteria of ALT or AST elevations ≥ 3X ULN.*

The case narrative and CRF of subject 203 were reviewed. The subject's other laboratory values, including total bilirubin, were normal. The subject had no history of liver disease or evidence of concomitant medications/herbs/supplements/alternative medicine or alcohol use. Although, the subject did not report any AEs prior to study withdrawal,an isolated elevation in ALT/AST < 5X ULN without any abnormality in total bilirubin can not rule out drug causality of the LFT elevation. However, a mild increase in transaminases would not likely represent a significant hepatic impairment.

Subject 150 (randomized to DBA): received treatment D (DTC, fasted) and treatment B (DTC, fed) prior to being withdrawn for dizziness. The subject was dosed with treatment B on December 15, 2007. He reported moderate dizziness with nausea on

January 12, 2008, and again reported mild dizziness on February 8, 2008, prior to being withdrawn from the study.

Reviewer's comment: *The long interval between dosing with treatment B and the onset of symptoms render it unlikely that the subject's dizziness/nausea were drug-related*.

Subject 218 (randomized to BDA): received treatment B (DTC, fed) and treatment D (DTC, fasted) prior to being withdrawn for orthostatic hypotension 4 hours after dosing with treatment D. The AE resolved after 2 hours. This was considered drug-related (most likely due to tamsulosin) and this reviewer concurs. Hypotension is a labeled adverse reaction in the Flomax prescribing information.

Common AE's: In all, 50 subjects (50%) reported at least one AE. Adverse events reported by ≥ 5 subjects included dizziness (22 subjects, 22%), headache (21 subjects, 21%), vertigo (9 subjects, 9%), and nausea (8 subjects, 8%). See Table 9. Orthostatic hypotension occurred in 2 subjects after being dosed in the fasted state (one after treatment D, second one after treatment C). These AEs are labeled adverse reactions in the Flomax prescribing information. Adverse events commonly associated with dutasteride, such as breast and sexual disorders, are not expected to occur frequently with single doses of drug separated by a 4- week washout interval.
The incidence of common AE's was higher in fasted than fed state. This is not unexpected as most common AEs were likely due to the tamsulosin component and tamsulosin exposure is higher in the fasted state. For a given food state (fed or fasting), slightly more subjects receiving DTC reported a common AEs than when receiving the co-administration of dutasteride and tamsulosin. Because this was a small, uncontrolled study, it is unclear if these small differences are clinically meaningful.

Table 9: Common AEs (≥ 5 subjects) by treatment group (Safety Population)

	Treatment A N = 91 n (%)	Treatment B N = 93 n (%)	Treatment C N = 46 n (%)	Treatment D N = 46 n (%)
Any AE	21 (23)	24 (26)	14 (30)	15 (33)
Dizziness	8 (9)	11 (12)	6 (13)	8 (17)
Headache	6 (7)	10 (11)	3 (7)	4 (9)
Nausea	2 (2)	4 (4)	2 (4)	2 (4)
Vertigo	0	2 (2)	3 (7)	4 (9)

Source: NDA 22-460, Module 5.3.1.2, Study ARI109882, MO's analysis of ae.xpt

Partner pregnancy: None.

Laboratory:
The listing of laboratory values of "potential clinical importance" was reviewed. In all, 24 subjects (24%) had at least laboratory value that was considered of "potential clinical importance," or PCI. Whether a laboratory value was considered to be of potential

clinical significance was left to an investigator's judgment. A majority of these PCI values (15 of 24, 63%) were borderline high bicarbonate levels at the Screening visit. No subjects other than subject 106 and subject 203 experienced LFT elevations. Subject 138 (randomized to BAD) experienced increased CK levels in conjunction with LFT elevations < 2X ULN as summarized in the table below:

Subject 138: Laboratory abnormalities

Laboratory Test	CK (IU/L)*	ALT (IU/L)+	AST (IU/L)#
Baseline	Not done	Normal	Normal
Pre-dose session 2 (12/14/07)		69	115
Follow-up			
• 12/15/07	4450	65	89
• 12/17/07	831	51	38

Source: NDA 22-460, Module 5.3.1.2, Study ARI109882, MO review of lab.xpt
* Normal range: 21-232 U/L
+Normal range: 10-60 U/L
#Normal range: 10-42 U/L

Reviewer's comment*: No adverse events were recorded for this subject, who completed the study. The Applicant stated that unscheduled CK levels were obtained due to ALT/AST elevations. The Applicant reported that subject had been lifting weights prior to the laboratory measurements. This reviewer does not consider subject 138's laboratory abnormalities to be drug-related.*

REVIEWER'S ASSESSMENT OF ARI109882: In the opinion of this reviewer, study ARI109882 demonstrated that DTC is bioequivalent to concomitantly dosed dutasteride and tamsulosin. No new or unexpected safety findings were observed in this small and uncontrolled study to alter the known risk/benefit of the combination therapy.

6 Review of Efficacy

Efficacy Summary

The efficacy of DTC is expected to be the same of the approved co-administration of dutasteride and tamsulosin for the treatment of BPH symptoms because the products are bioequivalent. No clinical efficacy data were submitted for DTC.

6.1 Indication

The Applicant seeks the indication of DTC, "a combination of dutasteride, a 5α-reductase inhibitor, and tamsulosin, an alpha-adrenergic blocker, is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate." This is the same indication that was approved for Avodart co-administered with tamsulosin in NDA 21-319/S014 on June 19, 2008.

6.1.1 Methods

The following section summarizes the most pertinent efficacy findings of the Year 2 analysis of Study ARI40005. For more details, the reader is referred to the clinical and statistical reviews of Year 2 of Study ARI40005, which was submitted in efficacy supplement 014 to NDA 21-319.

6.1.2 Demographics

Study ARI40005 enrolled approximately 5000 men with symptomatic BPH from North America, Europe, South America, Africa, and Asia. A total of 1231 subjects were from North America (U.S., Canada, Mexico, and Puerto Rico) and 1892 subjects were from Western Europe (Belgium, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Portugal, Spain, and United Kingdom). Overall, the study population adequately represented the target population in the U.S.

The mean age at randomization was 66 years (± 7.0), with 59% being ≥ 65 years old. A majority of patients (88%) were White; Asians were the second largest ethnic group (7%). The mean body mass index (BMI) was 27.4 kg/mg^2 (± 4.0). The mean duration since first BPH-related symptoms and BPH diagnosis was 5.4 (±4.1) years and 3.9 (±4.8) years, respectively. The mean post-void residual volume was 68 mL (± 65 mL). Half of the subjects had a history of alpha-1 antagonist use, mostly (99%) for the treatment of BPH. Approximately 11% of subjects had a history of 5ARI treatment; another 20% had a history of phytotherapy use. The mean baseline IPSS, Qmax, prostate volume and PSA were balanced across the 3 treatment groups (see Table 10).

Table 10: Baseline efficacy variables (ITT)

Mean values (SD)	Co-administration N=1610	Dutasteride N=1623	Tamsulosin N=1611
IPSS	16.6 (6.35)	16.4 (6.03)	16.4 (6.10)
Qmax (mL/s)	10.9 (3.62)	10.6 (3.57)	10.7 (3.66)
Prostate volume (cc)	54.7 (23.51)	54.6 (23.02)	55.8 (24.18)
PSA (ng/mL)	4.0 (2.05)	3.9 (2.06)	4.0 (2.08)

Source: Primary Clinical Review of NDA 21-319/S014, p. 22

6.1.3 Subject Disposition

The trial enrolled 5064 subjects, 4844 of whom were randomized after a 4-week run-in period. The ITT population consisted of 4844 subjects (co-administration of dutasteride + tamsulosin: 1610 subjects, dutasteride: 1623 subjects, tamsulosin: 1611 subjects). Of the 4844 subjects randomized, 3822 (79%) completed 2 years of treatment, with similar completion rates among the 3 treatment groups (78-80%). More subjects in the co-administration group discontinued due to an adverse event, whereas more subjects in

the monotherapy groups discontinued due to lack of efficacy. The distribution of other reasons for discontinuation was comparable among the 3 treatment groups (Table 11).

Table 11: Subject disposition (ITT)

	Co-administration N = 1610 n (%)	**Dutasteride N = 1623 n (%)**	**Tamsulosin N = 1611 n (%)**	**Total N = 4844 n (%)**
Completed (Year 2)	1267 (79)	1301 (80)	11254 (78)	3822 (79)
Discontinued	343 (21)	322 (20)	357 (22)	1022 (21)
• AE	• 154 (10)	• 108 (7)	• 136 (8)	• 398 (8)
• Withdrew consent	• 71 (4)	• 95 (6)	• 74 (5)	• 240 (5)
• Lost to follow-up	• 30 (2)	• 30 (2)	• 29 (2)	• 89 (2)
• Protocol violation	• 24 (1)	• 17 (1)	• 27 (2)	• 68 (1)
• Lack of efficacy	• 36 (2)	• 45 (3)	• 53 (3)	• 134 (3)
• Other	• 28 (2)	• 27 (2)	• 38 (2)	• 93 (2)

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

6.1.4 Analysis of Primary Endpoint(s)

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 ($p < 0.001$). See Table 12.

Table 12: 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

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary endpoint was maximum urinary flow rate (Qmax) measured during uroflowmetry. Statistically significant improvement from baseline Qmax in the co-administration group compared to each monotherapy was seen from Month 6 ($p < 0.001$) to Month 24 ($p \leq 0.003$). At Month 24, the mean change from baseline Qmax was 2.4 mL/s for the co-administration group, 1.9 mL/s for dutasteride, and 0.9 mL/s for tamsulosin. The mean difference in the change from baseline Qmax between the co-administration group and dutasteride was 0.5 mL/s and between the co-administration group and tamsulosin was 0.9 mL/s.

7 Review of Safety

Safety Summary

The safety and tolerability of co-administration of dutasteride and tamsulosin are acceptable. There were no significant differences in deaths or non-fatal serious adverse events between the co-administration group compared to dutasteride or tamsulosin monotherapy in the cumulative database. The composite adverse event of cardiac failure occurred at a slightly higher incidence in the co-administration group. . There were no important differences between the safety findings of the Year 2 analysis and those reported after the Year 2 cut-off date for ARI40005 for the serious adverse events. As in the Year 2 analysis, the cumulative safety data indicated that, compared to each monotherapy, the co-administration of the 2 drugs was associated with a higher incidence of drug discontinuation due to an adverse event, most of which were reproductive/sexual and breast-related, and a statistically higher incidence of ejaculatory disorders.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The following sources were reviewed for safety assessment:

- Study ARI40005:
  a. Cumulative* safety information on deaths, non-fatal SAEs, adverse events leading to permanent drug discontinuation, and laboratory outliers
  b. Updated* safety information on *deaths* and *non-fatal SAEs* (and follow-up information on non-fatal SAEs that occurred during the 120-Day Safety Update of NDA 21-319/S014 and that were still ongoing by August 31, 2007, which was the cut-off date for the 120-Day Safety Update of NDA 21-319/S014)

  ***** *In this NDA submission, the safety information for ARI40005 was organized by 2 reporting time periods described below:*
  1. ***Cumulative****: time period from post-randomization of ARI40005 to the cut-off date for this NDA (i.e.* ***post-randomization of ARI40005 to 12/8/08****)*
  2. ***Updated****: time period following the 120-Day Safety Update of NDA 21-319/S014 to the cut-off date for this NDA (i.e.* ***9/1/07 to 12/8/08****)*

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

- 120-Day Safety Update

- NDA 21-319/Sequence 0022 submission dated July 27, 2009: This was a supplemental labeling request (SLR) for the addition of cardiac failure data from Trial ARI40005 and Trial ARI40006 (REDUCE) to the Avodart label. The submission contained summary cardiac safety data of ARI40006 and ARI40005 as of January 9, 2009, which was the completion date of the treatment phase for ARI40005. This submission (b) (4) (b) (4)

- Published literature

This reviewer approached the safety review in the following manner:

a. Assess and compare the type and frequency of adverse findings over approximately 4 years of ARI40005 among the 3 treatment groups (co-administration group, dutasteride and tamsulosin groups) by analyzing the cumulative safety information.
b. Assess for any major differences in the safety profile of the co-administration group in the first 2 years (reviewed in the clinical review of NDA 21-319/S014) versus the last 2 years of ARI40005 by analyzing the updated safety information.

Reviewer's comment: *Because study ARI40005 was ongoing at the time of this NDA submission, the cumulative and updated safety database is incomplete and has not been fully validated. The safety information submitted in this NDA (cumulative and updated safety information) included line listings, summary tables, case narratives, and CRFs. No datasets were submitted. This approach is acceptable, because the principal support of safety for DTC is based on the Year 2 safety data of ARI40005, which have already been analyzed and determined to be acceptable.*

7.1.2 Categorization of Adverse Events

All adverse events were coded to the MedDRA coding dictionary by Preferred Terms (PT) and System Organ Class (SOC), version 11.1. In the updated safety information, verbatim text was used for AE's with missing MedDRA Preferred Terms. The mapping of verbatim terms to MedDRA terms was reviewed and found to be acceptable.

7.1.3 Pooling of Data Across Clinical Trials to Estimate and Compare Incidence

Safety data are not pooled or integrated across the different studies because of major differences in the design, study population, and dosing schedule among the studies. The principal support for the safety of DTC is study ARI40005, which is the focus of this safety review.

7.2 Adequacy of Safety Assessments

The overall exposure and safety assessments were adequate to characterize the safety profile of the co-administration of dutasteride and tamsulosin compared to each monotherapy.

7.2.1 Overall Exposure at Appropriate Doses/Duration and Demographics of Target Population

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. The cumulative years of co-administration therapy exposure were 2771 person-years at the 2-year cutoff date. The cumulative duration of treatment exposures in the monotherapy groups was comparable to that in the co-administration group.

Reviewer's comment*: According to the SLR submission, 1096 co-administration subjects (68%), 1067 dutasteride subjects (66%), and 956 tamsulosin subjects (59%) completed 4 years of treatment in ARI40005*.

7.2.2 Explorations for Dose Response

DTC is a fixed-dose combination product and no other doses of dutasteride or tamsulosin were investigated in the clinical program of DTC or the co-administration dutasteride and tamsulosin.

7.2.4 Routine Clinical Testing

Protocol-specified clinical testing included: hematology, chemistry (including LFT's), urinalysis, and Prostate Specific Antigen (PSA) every 6 months during the study. All appropriate tests were incorporated into the protocol.

7.3 Major Safety Results

7.3.1 Deaths

The **cumulative** data of deaths in ARI40005 (post-randomization to December 8, 2008) by MedDRA System Organ Class (SOC) are summarized in Table 13. 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 13: 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

Reviewer's comment*: A review of the summary data in the SLR submission did not reveal any significant difference from that presented in Table 13 above.*

During the **updated** safety period (9/1/07 to 12/8/08), 27 deaths occurred. Of these, 6 deaths were in the co-administration group, 10 in the dutasteride group, and 11 in the tamsulosin group. The most common causes of death were cardiac and neoplasm-related with a similar distribution of different causes of death across the 3 treatment groups. See Table 14.

Table 14: Cause of death by System Organ Class (updated, ITT)

System Organ Class	Co-administration N=1610 n	Dutasteride N=1623 n	Tamsulosin N=1611 n	Total N=4844
Any fatal AE	6	10	11	27
Cardiac	4	3	5	12
Neoplasms	0	2	2	4
Infections	1	2	0	3
Injury, poisoning and procedural complications	0	2	1	3
Nervous system disorders	1	0	1	2
Gastrointestinal disorders	0	0	1	1
Respiratory, thoracic, and mediastinal disorders	0	1	0	1
Unknown	0	0	1	1

Source: NDA 22-204, Module 5.3.5.1.22, Listing OL1, MO analysis

Reviewer's comment*: All narratives of fatal events in the updated safety database were reviewed and no deaths appeared to be drug-related.*

In the NDA 21-319/S014 safety review, which covered the first 2 years of ARI40005 and the 120-Day Safety Update, the all-cause death rate was approximately 1.8 % for each treatment arm (co-administration: 30 subjects, dutasteride: 28 subjects, tamsulosin: 29 subjects). More than 50% of the deaths were due to cardiac disorders or neoplasms. None of the deaths appeared to be drug-related. The safety profile of fatal SAEs in Year 3 and Year 4 (updated safety period) did not appear to differ from the Year 2 data of ARI40005.

7.3.2 Nonfatal Serious Adverse Events

In the **cumulative** database of non-fatal SAEs, 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 SAEs were in the SOCs cardiac disorders (4%) and neoplasms (3%). Non-fatal SAEs by SOC reported by ≥ 1% of subjects in any treatment group are shown in Table 15.

Table 15: 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

Table 16 shows the most common SAEs (≥ 10 subjects in any treatment group) by Preferred Term in the cumulative database. The most frequently reported SAEs were prostate cancer, coronary artery disease, myocardial infarction, and angina. No specific SAE Preferred Term was reported more frequently in the co-administration compared to each monotherapy, except for pneumonia.

Table 16: Common non-fatal SAEs (≥ 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

Reviewer's comment: *This reviewer reviewed the line listing of the cumulative SAE data by Preferred Term, with a focus on neurologic, cardiovascular, and investigations disorders. Overall, subjects in the co-administration group did not report a significantly*

higher incidence of any Preferred Term-specific SAE, except for pneumonia, compared to those in the monotherapy groups. Neither dutasteride nor tamsulosin are associated with increased risk of infection or pulmonary infection and there is no apparent biologic plausibility for the co-administration of these 2 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. A review of the pneumonia narratives indicated that none of those cases were likely to be drug-related. This reviewer does not consider the differences of pneumonia between the treatment groups to be clinically 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.

During the **updated** safety period (9/1/07 to 12/8/08), 257 patients (5%) experienced a non-fatal SAE. The incidence of non-fatal SAE was lower in the co-administration compared to each monotherapy groups (4% vs. 6%). The most common SAEs were in the SOCs neoplasms and cardiac (see Table 17).

Table 17: Non-fatal SAEs by System Organ Class (updated, ITT)

System Organ Class	Co-administration N=1610 n (%)	Dutasteride N=1623 n (%)	Tamsulosin N=1611 n (%)	Total N=4844 n (%)
Any non-fatal SAE	70 (4)	93 (6)	94 (6)	257 (5)
Neoplasms	16	16	16	48 (1)
Cardiac	13	20	14	47 (1)

Source: NDA 22-460, Module 5.3.5.1.22, Line Listing OL2, MO analysis

The most common non-fatal SAEs by PT (reported by ≥ 3 subjects in any treatment group) in the updated safety database are shown in Table 18. Compared to each monotherapy, co-administration of dutasteride and tamsulosin was not associated with a higher incidence of any specific non-fatal SAE.

Table 18: Common non-fatal SAEs (≥ 3 subjects/group) by Preferred Terms (updated, ITT)

Preferred Term	Co-administration N=1610	Dutasteride N=1623	Tamsulosin N=1611	Total N=4844
Coronary artery disease/cardiac infarction*	9	15	9	33
Prostate cancer	6	7	5	18
Cerebrovascular accident	3	3	7	13
Osteoarthritis	3	5	1	9
Bladder cancer	4	1	2	7
Pneumonia	3	1	3	7
Urinary retention	0	2	5	7
Atrial fibrillation	2	1	3	6
Gastrointestinal hemorrhage	1	4	1	6
Inguinal hernia	0	2	4	6
Colon cancer	0	3	2	5

Source: NDA 22-460, Module 5.3.5.1.22, Line Listing OL2, MO analysis
*This composite category includes: angina, coronary artery, and myocardial infarction

In this NDA submission, the Applicant provided **follow-up** data on non-fatal SAEs that occurred during the 120-Day Safety Update period for NDA 21-319/S014 that remained unresolved at the end of this Safety Update period (8/31/07). Follow up information was provided for 55 subjects (co-administration: 13, dutasteride: 24, tamsulosin: 18). A majority of these cases resolved (40 of 55). Eight patients died: 3 in the co-administration group (2 colon cancer, 1 pancreatic cancer), 4 in the dutasteride group (1 each of bronchial carcinoma, bladder cancer, gastrointestinal cancer metastatic, and sudden death), and 1 in the tamsulosin group (pyrexia/granulocytopenia). The remaining 7 cases were unresolved, but most were cases of malignancy (prostate, bladder). No overall unexpected or concerning outcomes were observed.

7.3.3 Dropouts and/or Discontinuations

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 are separated into SAEs and non-SAEs.

Cumulative SAEs leading to drug discontinuation: A total of 258 patients (5.3%) experienced an SAE which led to permanent drug discontinuation. The incidence of SAEs leading to drug discontinuation was highest in the tamsulosin group (6% vs. 5% in the other 2 treatment groups). The most common SAEs 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 SAEs leading to

drug discontinuation was not higher in the co-administration group compared to each monotherapy group for any specific SOC. See Table 19.

Table 19: Common SAEs (≥ 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

The most common SAEs (reported in ≥ 3 subjects in any treatment group) leading to permanent drug discontinuation were prostate cancer and myocardial infarction (composite term). More subjects in the co-administration group discontinued drug because of cerebrovascular accident, cardiac failure (composite term), and pneumonia. A review of the case narratives indicated that drug-causality was unlikely in these cases because of the presence of other compelling alternative explanations, such as significant co-morbidities.

Table 20: Common SAEs leading to drug discontinuation (≥ 3 subjects in any treatment group) by Preferred Term (cumulative, ITT)

Preferred Term	Co-administration N = 1610 n (%)	Dutasteride N = 1623 n (%)	Tamsulosin N = 1611 n (%)
Any SAEs leading to drug discontinuation	78 (5)	79 (5)	101 (6)
Prostate cancer	18 (1)	12	18 (1)
Myocardial infarction*	8	9	8
Cerebrovascular accidents	5	3	2
Cardiac failure**	5	3	1
Pneumonia	3	0	0
Urinary retention	2	4	9

Source: NDA 22-460, Module 5.3.5.1.22, Listing 5 and Table 5
*Includes Preferred Terms of myocardial infarction, acute myocardial infarction, acute coronary syndrome, coronary artery occlusion, and coronary artery thrombosis

**Includes PTs of cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, left ventricular failure acute, left ventricular chronic

According to Line Listing 5, 17 subjects experienced SAEs leading to drug discontinuation that were considered by the investigator to be treatment-related. These included 4 co-administration subjects (1 each of hypotension, gastric ulcer, loss of consciousness, and myeloid leukemia), 6 dutasteride subjects (1 each of jaundice, bradycardia, atrial-ventricular dissociation/ exacerbation of left ventricular failure, moderate syncope, heart attack, and coronary artery disease) and 7 tamsulosin subjects (1 each of myocardial infarction, hypertension, hepatitis, pancreatitis, circulatory collapse/syncope, dizziness, and tachycardia). All but the SAEs of coronary artery disease in the dutasteride subject, and hepatitis and tachycardia in the tamsulosin subjects occurred within the first 2 years of study ARI40005 and were reviewed previously.

Reviewer's comment: *This reviewer analyzed Listing 5 (listing of cumulative SAEs leading to drug withdrawal). The incidence of withdrawals in the co-administration group was similar between Year 3 and Year 4 (~1%), whereas it was slightly higher in Year 3 than Year 4 for dutasteride group (1.4% vs. 0.8%) and for tamsulosin group (2% vs. 0.6%).*

According to the clinical review of NDA 21-319/S014, the most common SAE's leading to drug withdrawal were prostate cancer (co-administration: 12 subjects, dutasteride: 3 subjects, tamsulosin: 12 subjects) and myocardial infarction (co-administration: 2 subjects, dutasteride: 6 subjects, tamsulosin: 9 subjects).

The incidence and types of SAEs leading to permanent drug discontinuation for the cumulative 4 years of ARI40005 did not appear to differ significantly from those observed in initial 2 years of ARI40005.

Cumulative <u>non-SAEs</u> 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-SAEs leading to drug discontinuation by SOC was reproductive and breast disorders and by PT was erectile dysfunction (see Table 21).

Table 21: 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

Reviewer's comment: *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.*

7.3.4 Significant Adverse Events

7.3.5 Submission Specific Primary Safety Concerns

In the clinical review of NDA 21-319/S014, cardiac failure and prostate cancer were identified as AEs of special interest because of the unexpected finding of higher incidence of these AEs in the co-administration group compared to both monotherapies (cardiac failure) or compared to dutasteride monotherapy (prostate cancer). See Table 22. The increased relative risks were not statistically significant and after a detailed

review, the clinical reviewer concluded that these AEs did not pose a significant safety concern for the co-administration regimen. Because study ARI40005 was ongoing, updated data on cardiac failure and prostate cancer were requested to assess whether these AEs would rise to a level of clinical safety concern with longer duration of use for the co-administration regimen.

Table 22: Relative Risk Estimate of Cardiac Failure and Prostate Cancer (Year 2)

AE	Relative Risk Estimate (95% CI) at Year 2	
	Co-administration vs. Dutasteride	Co-administration vs. Tamsulosin
Cardiac failure*	4.54 (0.98, 21.0)	2.29 (0.71, 7.44)
Prostate cancer	1.95 (0.94, 4.05)	0.82 (0.46, 1.46)

Source: Primary Clinical Review of NDA 21-319/S014, p. 46-7
*Cardiac failure is composite AE which includes the following Preferred Terms: cardiac failure congestive, cardiac failure, left ventricular failure, cardiac failure acute, cardiogenic shock, left ventricular failure acute, right ventricular failure, right ventricular failure acute

Cardiac failure: According to the Applicant, "cardiovascular events were evaluated prospectively as events of special interest in Study ARI40005…due to previous questions from 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 interests, 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. The table below shows the Year 4 CV data from trial ARI40005 contained in the SLR submission:

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

Table 23 summarizes the **cumulative** data on composite cardiac failure events. 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 23: 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
NDA 21-319/Sequence 0022, Module 5.3.5.1 and 5.3.6 (SLR submission), MO analysis
*Deaths = deaths directly associated with "cardiac failure"

In the SLR submission, the Applicant requested that the finding of 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. In support of this request, the Applicant presented the following data:

Study ARI40005: The incidence of cardiac failure (composite term) was 0.9% in the co-administration group (14 subjects) compared to 0.2% in the dutasteride group (4 subjects) and 0.6% in the tamsulosin group (10 subjects). The difference between the co-administration and dutasteride groups was statistically significant (RR 3.57 [95% CI: 1.17, 10.8]); the difference between co-administration and tamsulosin groups did not reach statistical significance (RR 1.36 [95% CI: 0.61, 3.07]). The imbalance in the

composite term cardiac failure was driven by the PTs “cardiac failure” and “congestive heart failure.” (See Table 24).

Table 24: Subjects with Cardiac Failure in ARI40005 (cumulative, ITT)

Composite Term MedDRA Preferred Term	Dut + Tam (N=1610) n (%)	Dutasteride (N=1623) n (%)	Tamsulosin (N=1611) n (%)
Any Cardiac Failure AE	14 (0.9)	4 (0.2)	10 (0.6)
Cardiac Failure	9 (0.6)	1 (<0.1)	6 (0.4)
Cardiac failure congestive	6 (0.4)	1 (<0.1)	2 (0.1)
Left ventricular failure	0	0	2 (0.1)
Cardio-pulmonary failure	0	1 (<0.1)	0
Congestive cardiomyopathy	0	0	1 (<0.1)
Acute left ventricular failure	0	1 (<0.1)	0

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

The time of onset of cardiac failure did not differ significantly among the 3 treatment groups (median time of onset ranged from 17 to 27 months). The treatment groups did not differ in demographic/baseline characteristics or in the incidence of events that may trigger cardiac failure (e.g., MI, myocardial ischemia, atrial fibrillation).

Study ARI40006: This 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 at elevated risk for prostate cancer. The study population of ARI40006 appeared to be similar to that of ARI40005 with respect to baseline demographics and cardiovascular risk profile. The 4-year incidence of composite cardiac failure was 0.7% (30 subjects) in the dutasteride group compared to 0.4% (15 subjects) in the placebo group and this difference was statistically significant (RR 2.04 [95% CI: 1.09, 3.78]). The imbalance in the composite term cardiac failure was driven by the Preferred Terms “cardiac failure” and “congestive heart failure.” (See Table 25).

Table 25: 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

The Kaplan-Meier curve for the time to first cardiac failure was similar for the 2 treatment groups for the first 9 months and diverged thereafter. The treatment groups did not differ in demographic/baseline characteristics or associated signs/symptoms of cardiac failure. According to the Applicant, 14/30 dutasteride subjects compared to 1/15 placebo subjects were taking an alpha-blocker around the time of the cardiac failure event.

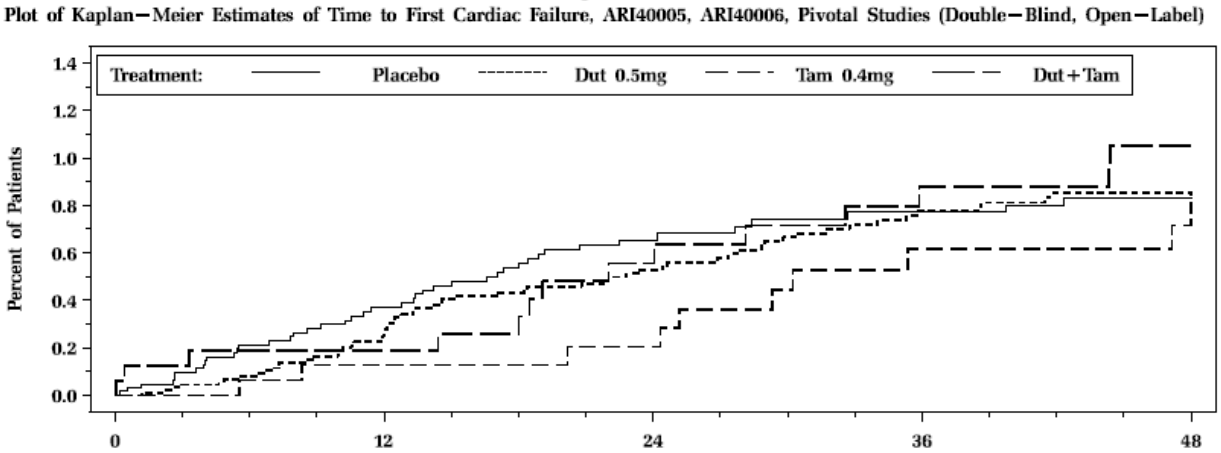
Pooled clinical trial data analyses: To date, the dutasteride clinical development have included 3 major programs:

1. Three placebo-controlled phase 3 trials for BPH (randomized, double-blind, placebo controlled trials of dutasteride vs. placebo for BPH treatment)
2. Trial ARI40005 for BPH (randomized, double-blind, parallel group trial of co-administration of dutasteride + tamsulosin vs. dutasteride vs. tamsulosin in BPH treatment)
3. Trial ARI40006 for reduction of risk of biopsy detectable prostate cancer (randomized, double-blind, placebo-controlled trial of dutasteride vs. placebo in risk of prostate cancer)

The Applicant conducted 2 integrated analyses across the dutasteride clinical programs to evaluate the composite event of cardiac failure. In the first analysis, placebo-controlled trial data from 4 years of ARI40006 and the first 2 years of phase 3 dutasteride BPH studies were integrated. Overall, the proportion of subjects with cardiac failure was 0.7% in both the dutasteride group (43/6272 subjects) and in placebo group 43/6284 subjects). In the second analysis, data from 4 years of ARI40006, 4 years of ARI40005, and 4 years of phase 3 dutasteride BPH studies (Years 1 & 2 were placebo-controlled, Years 3 & 4 were open-label in these studies) were integrated. The cumulative incidence of cardiac failure across all 4 years of dutasteride studies were the same for dutasteride and placebo groups at 0.7% (61/9047 in the dutasteride group, 43/6284 in the placebo group). Figure 1 shows the Kaplan-

Meier curve of time to first cardiac failure for all the pooled data from the 3 major clinical programs of dutasteride.

Figure 1: Kaplan-Meier estimates of time to first cardiac failure (pooled phase 3 BPH trials, ARI40005, ARI40006 over 4 years)



Placebo				
No. of Events/At Risk	22/6284	38/5563	41/3558	43/3164
Dut. 0.5mg				
No. of Events/At Risk	23/9047	42/7928	56/5952	61/5339
Tam. 0.4mg				
No. of Events/At Risk	2/1611	3/1466	8/1278	10/1105
Dut. + Tam.				
No. of Events/At Risk	3/1610	9/1425	12/1278	14/1195

Source: SLR submission (NDA 21-319/S0022, Module 5.3.6, Figure 11, p. 705)

Post-marketing analyses: The Applicant queried the FDA's AERS database (4Q2008) and searched for safety signals of cardiac failure using disproportionality analysis. No safety signals were noted for congestive heart failure or heart failure for dutasteride alone, tamsulosin alone, dutasteride + tamsulosin, finasteride alone, or finasteride + tamsulosin.

Applicant's conclusion: The Applicant concluded that integrated analyses did not demonstrate a difference between dutasteride monotherapy and placebo in the incidence of cardiac failure (composite term). However, an imbalance of composite cardiac failure events in ARI40006 and ARI40005 was observed when dutasteride was concomitantly dosed with an alpha-adrenergic antagonist, such as tamsulosin. No clear drug-causality or pathophysiologic explanation is apparent at this time.

Medical Officer's Assessment of Cardiac Failure:
The following section discusses the medical officer's assessment of cardiac failure based on evidence from controlled clinical trials, published literature and known mechanism of action.

A. Clinical Trials

Table 26 summarizes the study design, study population, and cardiac failure of the 3 major clinical programs of dutasteride.

Table 26: Study design, study population, and cardiac failure outcome of the 3 major clinical programs of dutasteride

Demographic/baseline variables	ARI40006	ARI40005	Pooled phase 3 BPH trials (3 trials)
Indication	Prostate ca	BPH	BPH
Study Design			
Study Design*	MC,R, DB, PC	MC, R, DB, PG	MC, R, DB, PC
Treatment Groups** (sample size)	Dut (4105), Plc (4126)	Dut + tam (1610), Dut (1623), Tam (1611)	Dut (2167), Plc (2158)
Placebo control	Yes	No	Yes
Duration of controlled study (years)	4	4	2
Study Population			
Ethnic- Caucasian (%)	~ 90	~ 90	~ 90
Median age (years)	63	66	66
Hypertension (%)	38	42-44	47 with CV dz
Coronary artery disease (%)	8	9-10	Data not available
Tobacco history (%)	53-55	48	12
Median or mean SBP/DBP	136/82	136/81	138/82
Concomitant medications during study (%): • Alpha blocker • ACE-I • Diuretics • Calcium channel blockers • Beta blockers	 • 28 (dut); 34 (plc) • 34-36 • 21-22 • 14-16 • 21-22	 • (50 previous use) • 37 • 22 • 18-21 • 24-26	 • Not permitted • 17 • 12 • 16-18 • 16-17
Cardiac Failure			
Subjects with cardiac failure (%)	Dut: 30/4105 (0.7) Plc: 15/4126 (0.4)	Dut + tam: 14/1610 (0.9) Dut: 4/1623 (0.2) Tam: 10/1611 (0.6)	Dut: 13/2167 (0.6) Plc: 28/2158 (1.3)

Source: Summary information from SLR submission and NDA 21-319/S014, Module 5.3.3.
*MC=multi-center; R=randomized; DB=double-blind; PC=placebo control; PG=parallel group
**Plc=placebo; Dut=dutasteride; Tam=tamsulosin

***Reviewer's comment**: The study populations in the 3 main clinical development programs for dutasteride (ARI40006, ARI40005, and pooled phase 3 studies) are comparable in their demographics/baseline characteristics, baseline risk factors for cardiac failure, and concomitant use of medications that may affect cardiac failure outcomes. As such, it may be reasonable to extrapolate the placebo data on cardiac failure in the placebo group from ARI40006 (0.4% over 4 years) and the placebo group from pooled phase 3 studies (1.3% over 2 year) to ARI40005.*

The study results of ARI40006 and those of the pooled phase 3 BPH studies are contradictory regarding the risk of cardiac failure of dutasteride compared to placebo.

***Reviewer's comment**: Cardiac failure was not pre-defined in the study protocols but was prospectively defined in the respective Statistical Analysis Plans of ARI40006 and ARI40005. The AEs in the pooled phase 3 BPH studies, which were originally coded using the MIDAS coding dictionary, was re-coded using the MedDRA coding dictionary in the post-hoc analysis.*

Individual case narratives of ARI40005 and ARI40006 were reviewed to determine whether 1) the case was coded properly, 2) any convincing evidence exists to exclude drug causality or, 3) there is a reasonably compelling alternative explanation for the event other than drug. The findings are presented below.

1. ARI40005: Case narratives were reviewed and miscoded cases (e.g., circulatory collapse secondary to aortic aneurysm rupture or fatal myocardial infarction coded as cardiac failure) were excluded from the total count. After excluding these cases, 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%). These subjects are discussed below:

    - *Co-administration (12 subjects, 0.8%)*: One subject "died on the street," which does not appear to be clinically consistent with CHF. Two subjects had CHF 12-13 days after the start of investigational product, which is most likely too short of duration of time for the drugs to cause CHF. Of the 9 remaining cases, 8 resolved on therapy. Eleven of the 12 subjects (the 12th subject had coronary artery disease) had ≥ 2 known independent risk factors for congestive heart failure, such as coronary artery disease (CAD), hypertension, diabetes, and significant history of alcohol use/smoking.
    - *Dutasteride (2 subjects, 0.1%)*: One subject with multiple risk factors for CHF died 1 year after the start of dutasteride treatment for "unknown reason"; it was unclear if this death was witnessed and an autopsy was not performed. The other subject with multiple risk factors (CAD, diabetes, hypertension, history of 45-pack year tobacco use) developed mild CHF on Day 832 which did not lead to drug discontinuation.
    - *Tamsulosin (8 subjects, 0.5%)*: One subject without relevant cardiovascular co-morbidity at baseline developed severe cardiac failure concurrently with grade III atrioventricular (AV) block resulting in severe bradycardia and loss of consciousness on Day 881. The subject received supportive medical treatment and an insertion of a permanent cardiostimulator. It is unclear to this reviewer whether this subject's cardiac failure was an event separate from or a consequence of the grade III AV block. Of the remaining 7 subjects, 6 had multiple risk factors for CHF. The 7th patient had no prior CV history (except erectile dysfunction) developed mild CHF at Month 9.

***Reviewer's comment**: In summary, this reviewer did not identify a case of cardiac failure, except for one tamsulosin patient with no prior cardiovascular history who developed mild CHF at Month 9, which could likely be drug-related. Most cardiac failure patients in ARI40005 had multiple established risk factors for CHF (e.g., coronary artery disease [CAD], hypertension, diabetes, significant tobacco/alcohol use, valvular disease, and obesity). Each risk factor independently increases the risk of CHF by 1.5-2.0 fold, and CAD alone increases the risk by 8-fold.[1] The development of CHF is much more likely to be attributable to these co-morbidities than to any of the 3 treatment regimens in ARI40005.*

Because of the lack of a placebo control in ARI40005, the risk of composite cardiac failure could not be quantified on absolute terms. As mentioned previously, the incidence of cardiac failure in the placebo group in ARI40006 was 0.4% over 4 years and 1.3% over 2 years in the pooled phase 3 BPH studies. In the Applicant's pooled placebo-controlled clinical trial data integrated analysis, the proportion of placebo subjects with composite cardiac failure events was **0.7%**. Because the study populations of these 2 clinical programs were similar to that of ARI40005, the 0.7% estimate may be reasonably extrapolated as a "background" incidence of cardiac failure in ARI40005. The incidence of cardiac failure for the co-administration (0.7%) in ARI40005 was the same as this 0.7% "background" estimate. Further, this reviewer does not consider the differences among the 3 treatment groups in the absolute number of subjects over 4 years (12 co-administration vs. 2 dutasteride vs. 8 tamsulosin) for a composite AE that is not uncommon in population of older men to be clinically meaningful.

2. ARI40006: This reviewer examined in detail the case narratives of cardiac failure in trial ARI40006 submitted in SLR submission. (b) (4)

(b) (4)

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. Two dutasteride subjects had cardiac events that were not assessable due to limited information (one unwitnessed death occurred at home that was considered to be from "acute cardiac failure"; another case of "cardiac insufficiency, described as cardiac complaints" was treated with surgery). One dutasteride subject had no relevant risk factors prior to the onset of cardiac failure on Day 742, 3 subjects had one CHF risk factor, and the

1 He J; Ogden LG; Bazzano LA; Vupputuri S; Loria C; Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001 Apr 9;161(7):996-1002.

remaining 20 subjects had at least 2 risk factors for CHF. In the placebo group, 13 of 14 subjects had ≥ 2 risk factors for CHF. This reviewer did not identify a case of cardiac failure that was probably drug-related or that was not confounded by significant co-morbidities, other than the one dutasteride subject who had no relevant risk factor who developed cardiac failure on Day 742.

Because there has been no known cardiovascular signal for dutasteride, which has been marketed worldwide since 2003, the Applicant conducted several exploratory analyses that may explain the imbalance in composite cardiac failure between dutasteride and placebo. According to the Applicant, one possible explanation is that 14 of 30 dutasteride subjects compared to 1 of 15 placebo subjects with cardiac failure had concomitant therapy with an alpha-adrenergic antagonist ("alpha-blocker"). This reviewer identified several reasons that would render it difficult to determine the role of alpha blocker in cardiac failure:

- Among the 14 dutasteride subjects and 1 placebo subject who were on concurrent alpha-blocker therapy who experienced cardiac failure, 10 dutasteride subjects and 1 placebo subject were also on other therapies that could contribute to cardiac failure (e.g., beta-blockers).
- Prior to the study start, the proportion of subjects on medications that may affect CHF outcomes (e.g., non-selective beta-blockers, ACE-I) were balanced between the 2 treatment groups, except for alpha-blockers. The use of **alpha-blockers** was **higher** in the **placebo group** compared to dutasteride group (34% vs. 28%). If alpha-blockers cause cardiac failure, one would expect a higher incidence of cardiac failure in the placebo group.
- Among subjects who had cardiac failure, those who were not on alpha blockers had a shorter median time of onset (450-500 days post-randomization) than those who were on alpha blockers (750-1200 days post-randomization). This would not support the role of alpha blockers in accelerating cardiac failure.
- The Applicant also calculated the crude incidence of composite cardiac failure by treatment group and by the use of alpha blocker prior to the onset of cardiac failure. The incidence of composite cardiac failure of the alpha-blocker only group (placebo with some alpha-blocker) was lower than that of placebo-only group (placebo with no alpha blocker). This analysis would not support the hypothesis that alpha-blockers alone increase the risk of cardiac failure over placebo in ARI400006.

Crude incidence of cardiac failure by use of alpha-blocker

Grouping	Crude Incidence (n/N)
Dutasteride with some alpha-blocker	1.0% (12/1148)
Dutasteride with no alpha-blocker	0.6% (18/2957)
Placebo with some alpha-blocker	<0.1% (1/1387)
Placebo with no alpha-blocker	0.5% (14/2739)

3. Drug-drug interaction: If dutasteride or tamsulosin alone does not appear to increase the risk of CHF, a drug-drug interaction may be responsible for the higher incidence of cardiac failure when these 2 drugs are concomitantly dosed. However, study ARIA1011 demonstrated that dutasteride and tamsulosin co-administered did not alter tamsulosin PK parameters or dutasteride PD parameters. Because of the long half life of dutasteride, no studies have been conducted to evaluate the effect of tamsulosin on dutasteride PK parameters. In the efficacy supplement supporting the co-administration of dutasteride and tamsulosin for the treatment of BPH symptoms (NDA 21-319/S014), the Applicant submitted sufficient evidence to indicate that the effect of tamsulosin on dutasteride PK would be highly unlikely.

B. Literature evidence:

1. The use of the alpha-blocker doxazosin monotherapy for hypertension was associated with a higher risk of CHF compared to diuretic monotherapy in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a comparative study evaluating 4 different antihypertensives (diuretics, alpha-blocker, ACE-I, and beta-blocker) on fatal coronary artery disease and nonfatal myocardial infarction in 41,000 hypertensive patients. The doxazosin arm was terminated prematurely after a planned interim analysis demonstrated that the risk of CHF (a secondary endpoint) was doubled in the doxazosin arm compared to the diuretic arm.[2] This finding triggered the convening of the FDA Cardio-Renal Advisory Committee in 2001 to consider if labeling changes for CHF would be appropriate for doxazosin and/or other alpha-blockers. The lack of a placebo control in ALLHAT and the fact that diuretic therapy was a well-recognized effective treatment for CHF made it difficult to establish whether the diuretic treatment was beneficial, doxazosin was or was not harmful, or some combination thereof. The Advisory Committee did not recommend a warning label for doxazosin until further data become available to fully interpret the results.[3] To date, there has been no class labeling for CHF for the alpha blockers. Cardura XL (but not Cardura IR), which was approved for the treatment of BPH in 2006, is the only alpha-blocker product with cardiac safety labeling. Specifically, under the General Precautions section of Cardura XL label:

> "**Patients with Coronary Insufficiency:** Patients with congestive heart failure, angina pectoris, or acute myocardial infarction within the last 6 months were excluded from the Phase 3 studies. If symptoms of angina pectoris should newly appear or worsen, CARDURA XL should be discontinued."

2 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin vs Chlorthalidone: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000;283:1967-1975.

3 McLellan F. US FDA weighs options for warning on antihypertensive drug. *Lancet* 2001; 357: 1775.

2. A search in PubMed and Embase did not retrieve any meaningful published literature on increased risk of CHF associated with dutasteride or finasteride treatment.

C. Biologic plausibility for cardiac failure:

1. Alpha-blockers induce 2 physiologic changes, volume expansion and compensatory heart rate increase, that may potentially lead to CHF. Volume expansion may trigger heart failure in a decompensated heart unable to accommodate the volume overload. Although edema and dyspnea are labeled adverse reactions for all alpha blockers, these 2 events alone do not qualify as CHF. The compensatory increase in heart rate due to alpha-blocker-induced peripheral vasodilation may also trigger heart failure in a damaged heart unable to accommodate the increased workload.
2. No currently known biologic plausibility exists for dutasteride or finasteride.

Reviewer's conclusions: Considering the totality of evidence, this reviewer addresses the following 3 key questions:

1. Compared to placebo, does dutasteride increase the risk of composite cardiac failure? Trial 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. Further, one cannot always equate frequency to causality. 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.

Reviewer's comment*: DRUP consulted the Division of Cardiovascular and Renal Products on October 26, 2009, to evaluate the cardiac failure data from trials ARI40005 and ARI40006. Because the comprehensive evaluation of the cardiac failure issue will require interdivisional discussions, it is premature at this time to conclude whether or not cardiac failure is a safety concern and to propose any potential risk management strategy for NDA 22-460.*

Prostate cancer:
Table 27 summarizes the cumulative experience with prostate cancer in ARI40005. The incidence of prostate cancer was higher in the tamsulosin group (3%) compared to dutasteride or co-administration groups (both 2%). Most cases of prostate cancer led to permanent drug discontinuation. There was no overall trend to the time of prostate cancer diagnosis. Comparing Years 3-4 to Years 0-2, more cases of prostate cancer were diagnosed in the dutasteride group, less in the co-administration group, and a similar number of cases in the tamsulosin group.

Table 27: Summary of prostate cancer (cumulative)

	Co-administration N=1610 n (%)	**Dutasteride N=1623 n (%)**	**Tamsulosin N=1611 n (%)**
Any prostate cancer	34 (2)	32 (2)	53 (3)
SAEs	21 (1.3)	16 (1)	24 (1.5)
Non-SAEs	13 (<1)	16 (<1)	29 (2)
Fatal	1	0	0
Leading to permanent drug discontinuation	26 (1.6)	24 (1.5)	40 (2.5)
Time of diagnosis • Year 0-2 • Year 3-4	 • 21 • 13	 • 12 • 20	 • 26 • 27

Source: NDA 22-460, Module 5.3.5.1.22, Listing 1 and Listing 2, MO analysis

Reviewer's comment*: No concerning trend in prostate cancer were noted for the co-administration group compared to each monotherapy group. In the MTOPS study (co-administration of finasteride + doxazosin in a similar BPH population), the 4-year incidence of prostate cancer in the placebo group was ~ 4%.*

Reviewer's comment: To the knowledge to this reviewer, there have been no reported cases of priapism, Intraoperative Floppy Iris Syndrome (IFIS) or breast cancer in controlled clinical trials of the co-administration of dutasteride and tamsulosin to date.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

No additional safety information on common adverse events of ARI40005 submitted for the co-administration of dutasteride and tamsulosin in NDA 21-319/S014 was submitted in this NDA. The reader is referred to the clinical review of NDA 21-319/S014 for detailed review of common AEs based on the Year 2 data of ARI40005. For ease of review, a summary of the most pertinent findings of common AEs in NDA 21-319/S014 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 ($p < 0.05$). See Table 28.

Table 28: 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

7.4.2 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. DRUP requested updated safety information on laboratory outliers as study ARI40005 is ongoing.

In the current NDA, the Applicant submitted cumulative data on laboratory outliers in order to put the data in full perspective of 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. Select laboratory tests are presented in Table 29.

Table 29: Laboratory outliers of selected laboratory tests (cumulative)

	Co-administration n/N (%)	Dutasteride n/N (%)	Tamsulosin n/N (%)
Any Outlier Value	129/1521 (8)	127/1532 (8)	135/1523 (9)
Hemoglobin < 0.75X LLN	6/1512 (<1)	7/1525 (<1)	4/1520 (<1)
Glucose > 1.75X UNL	62/1488 (4)	77/1508 (5)	68/1505 (5)
Total bilirubin > 2.5X ULN	1/1520	1/1532	1/1523
ALT > 3X ULN	5/1520	5/1532	6/1523
AST > 3X ULN	1/1519	4/1532	5/1523
Creatinine > 3X ULN	2/1520	2/1532	2/1523

Source: NDA 22-460, Module 5.3.5.1.22, Listing 9 and Table 9, MO analysis

A detailed review of line listing of laboratory outliers was conducted for subjects with significant liver function test (LFT) elevations (AST or ALT ≥ 5X ULN or total bilirubin > 2.5X ULN). A total of 9 subjects (co-administration: 2; dutasteride: 3; tamsulosin: 4) had laboratory values meeting these LFT criteria. Of these 9 subjects, 2 had concurrent significant elevations in transaminases and bilirubin. Subject 53490 (tamsulosin) had pancreatic cancer with liver metastases. Subject 51058 (dutasteride) has ALT 13X ULN, AST 8.7X ULN and total bilirubin 1.4X ULN at Month 12. These LFT abnormalities occurred one week after the subject started a second statin; the abnormalities resolved after the subject discontinued the second statin product.

***Reviewer's comment**: At this reviewer's request, the Applicant submitted a line listing of subjects with total bilirubin level ≥ 1.5X ULN (Amendment 0008 to NDA 22-460 dated June 23, 2009, Line Listing 14) up to December 8, 2008. A total of 43 patients (co-administration: 15; dutasteride: 14; tamsulosin: 14) had at least one total bilirubin level meeting the threshold value. Other than subject 53490 with pancreatic carcinoma and liver metastases described above, no subjects had concurrent AST/ALT ≥ 3X ULN and total bilirubin ≥ 1.5X ULN.*

7.4.3 Vital Signs

No additional vital sign information of ARI40005 beyond that submitted for the co-administration of dutasteride and tamsulosin in NDA 21-319/S014 was submitted in this NDA. According to the clinical review of NDA 21-319/S014 no safety concerns were identified for the co-administration group, compared to the monotherapy groups, in the analyses focused on central tendencies or vital sign outliers.

7.6 Additional Safety Evaluations

7.6.2 Human Reproduction and Pregnancy Data

During the **updated** reporting period, one partner pregnancy occurred in ARI40005. The subject's partner became pregnant approximately 31 months after the subject began taking his study medication (tamsulosin). The expected delivery due date was several weeks after the subject's last dose of study medication (April, 2008). As of July, 2008, the Applicant has not received a release of medical records to obtain follow-up information on the pregnancy or its outcome.

No partner pregnancies occurred in any other studies submitted in support of DTC.

7.6.3 Pediatrics and Assessment of Effects on Growth

Neither dutasteride nor tamsulosin, alone or in combination, or DTC has been investigated in the pediatric population. Dutasteride is contraindicated in children. A full pediatric waiver was requested and granted for DTC, as it was for the co-administration regimen in NDA 21-319/S014.

7.6.4 Overdose, Drug Abuse Potential, and Withdrawal and Rebound

Overdose: According the Applicant, as of December 8, 2008, 18 cases of dutasteride overdose and 1 case of dispensing error were reported to GSK's post-marketing safety database (Operating Companies Event Accession and Notification [OCEANS]). These 19 cases are described below:

Dutasteride:
No adverse events reported (10): One patient each reported taking 5 mg daily, 2.5 mg daily and 2 mg daily; another 5 patients reported taking 1 mg daily. Two reported the accidental ingestion of one extra pill. None of these patients reported adverse events.

Adverse events reported (6): A dispensing error was reported in a female patient who was given AVODART 0.5 mg twice daily instead of AVANDAMET®, and experienced stomach pains and elevated blood glucose.

One patient mistakenly took dutasteride 0.5 mg four times a day and developed "gallbladder sludge." Another patient took 2.5 mg daily for 6 months and reported decreased ejaculate volume, increased libido, hair regrowth, and slight somnolence. Three patients took dutasteride 0.5 mg twice daily; the reported events were feeling "abnormal," low blood sugar, and breast pain and enlargement.

Unknown (3): The remaining three reports (one case each of a suicide attempt, possible drug overdose, and intentional misuse) were poorly documented and could not be further evaluated.

Tamsulosin:
According to the FLOMAX label (4/09), one patient ingested thirty Flomax 0.4 mg capsules and reported a severe headache.

Dutasteride + Tamsulosin:
OCEANS has 7 overdose reports of persons taking dutasteride and tamsulosin. Three cases described accidental ingestions of one or two 0.5 mg dutasteride gel capsules on one occasion with no adverse event reported. Two reports described doubling of dutasteride capsules and no adverse events reported. Another case described a patient who took an unspecified overdose of his father's dutasteride and tamsulosin in a suicide attempt. He was hospitalized and improved and no AEs resulting from the overdose were noted. The final case described an attempted suicide by ingestion of 30 dutasteride capsules; the patient was hospitalized for 3 days with resolution of the unspecified events, which the reporting physician considered to be life-threatening. These same reports of overdose in persons taking dutasteride and tamsulosin from OCEANS also appeared in the FDA Adverse Event Reporting System (AERS).

Reviewer's comment: *The most important acute clinical sequela of DTC overdose would most likely be consequences of significant hypotension from the tamsulosin component.*

7.7 Additional Submissions / Safety Issues

The 120-Day Safety Update was received on July 16, 2009. This Safety Update included new SAE's 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 had a non-fatal SAE. Significant safety updates on previously reported SAEs were provided for 15 patients. No new safety findings were identified in the review of the 120-Day Safety Update.

Deaths
One death occurred in the co-administration group (acute myocardial infarction) and 2 deaths occurred in the tamsulosin group (gastrointestinal hemorrhage and traumatic subdural hematoma). This reviewer reviewed the case narratives and did not consider any of the deaths to be drug-related.

Reviewer's comment*: The acute MI occurred in an 81 year-old male subject after 4 years of treatment with the co-administration of dutasteride and tamsulosin and 13 days after his last dose of investigational product. An autopsy was not performed. Significant medical history included hypertension, hypercholesteremia and tobacco use. The subject was diagnosed with severe coronary artery disease and underwent cardiac catheterization with stent placement at approximately 1.5 years after the start of investigational product. The subject's fatal MI was most likely due to his underlying cardiac risk factors*.

Non-fatal SAEs
Nine (9) subjects in the co-administration group, 10 in the dutasteride group, and 9 in the tamsulosin group experienced at least one non-fatal SAE. Cardiac disorders and neoplasms were the most commonly reported SOC. One subject in the co-administration group experienced phlebectomy and one subject in the tamsulosin group experienced pleural effusion in which drug causality was considered "unknown" by the investigator. The remainder of the 26 cases was not considered to be drug-related. This reviewer reviewed all 28 case narratives and did not consider any of them drug-related.

Partner pregnancy
No new partner pregnancy occurred during the Safety Update period, and no follow-up information on previously reported pregnancies was received during the same time period.

Reviewer's comments: *No significant findings were noted in the review of the updates of previously reported SAE's for 15 subjects. According the Applicant, there were no new safety findings in the published literature or from spontaneously reported adverse events databases during the update period.*

8 Postmarketing Experience

DTC has not been marketed, however, postmarketing experience with concomitant dosing of dutasteride and tamsulosin are available. Dutasteride has been marketed in the U.S. since January, 2003, and is currently marketed in 75 countries. Based on sales data as of September, 2008, approximately 3.2 million patient-years of treatment have been sold worldwide. Tamsulosin has been marketed in Europe since 1995 and in the U.S. since 1997. The Applicant does not hold the safety database for tamsulosin.

In this NDA submission, the Applicant analyzed the following sources for post-marketing safety information on 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

Published literature
All of the 5 published reports of studies involving the concomitant use of dutasteride and tamsulosin were reviewed in NDA 21-319/S014.

GSK's Worldwide Safety Database (OCEANS)
OCEANS contains spontaneous adverse event reports from worldwide sources for GSK's marketed products (which include dutasteride but not tamsulosin) and serious adverse event reports from GSK-Applicanted clinical trials. Adverse events are coded using the MedDRA coding dictionary. Post-marketing adverse events in patients using dutasteride and tamsulosin are reported to GSK only if the reporter considers the event to be possibly related to dutasteride.

As of December 1, 2008, OCEANS had received 627 spontaneous adverse reports containing a total of 1464 AE's, which contained dutasteride as a suspect or concomitant drug AND tamsulosin as a suspect or concomitant drug. The most frequently reported events were dysuria (39 events), gynecomastia (32 events), erectile dysfunction (31 events), dizziness (26 events), rash (26 events), pharmaceutical product complaint (25 events), breast tenderness (24 events), pollakiuria (23 events), decreased libido (23 events), breast enlargement (22 events), nocturia (20 events), and fatigue (20 events). Two reports of women becoming pregnant while their partners were on dutasteride and tamsulosin did not describe any adverse event in these women; however, the outcomes of these pregnancies were not provided.

External post-marketing safety databases: FDA AERS and WHO Vigibase
The U.S. FDA AERS and WHO Vigibase are available publicly and contain reports of adverse events on the co-administration of dutasteride and tamsulosin reported to multiple manufacturers. Adverse events reported to the AERS database are coded using the MedDRA coding dictionary. Adverse events reported to the WHO Vigibase are coded using the WHO adverse reaction (WHOART) coding dictionary.

The Applicant analyzed the AERS (2nd quarter 2008) and Vigibase database (3rd quarter 2008) by using disproportionality analysis, which provides information about the relative reporting rates of adverse events to assist in detecting safety signals in the post-marketing setting. This method computes the Empiric Bayes Geometric Mean (EBGM) with associated two-side 90% confidence limits (EB05, EB95). EBGM values represent

relative reporting ratios of observed to expected cases. If the drug and the event were completely independent of one another, the EBGM (specifically EB05) would be 1. An EBGM of 2 indicates that the drug-event pair has been reported 2 times as frequently as expected if there was no association between the drug and the event. The FDA uses EB05 values ≥ 2 to define potential safety signals.[4]

Disproportionality Analysis of FDA AERS:
AERS (2nd quarter, 2008) contained 1832 reports containing dutasteride (no alpha blockers), 9357 reports containing tamsulosin (no 5ARIs), and 556 reports containing both dutasteride and tamsulosin. Table 30 shows the 10 most commonly reported drug-event pairs for the co-administration of dutasteride + tamsulosin where EB05 ≥ 2.

Table 30: AERS common drug-event pairs for co-administration of dutasteride and tamsulosin (Q2, 2008)

MedDRA Preferred Term	# Reports	EB05
Breast enlargement	15	27
Semen volume decreased	10	25
Breast tenderness	16	23
Nocturia	22	17
Urine flow decreased	10	15
Gynecomastia	20	14
Libido decreased	17	13
Breast mass	6	6
Pollakiuria	21	4
Dysuria	20	4

Source: NDA 22-460, Module 2.7.4, Summary of Clinical Safety, p. 29

According to the Applicant, when comparing the co-administration regimen to dutasteride or tamsulosin monotherapy, non-overlapping confidence intervals ((i.e. EB05 of co-administration > EB95 of each monotherapy) were observed for nocturia. When comparing co-administration to tamsulosin, non-overlapping confidence intervals (CIs) were observed for dysuria, pollakiuria, urine flow decreased, alopecia, erectile dysfunction, libido decreased, breast disorders, and drug administration error. When comparing co-administration to dutasteride, non-overlapping CIs were observed for aortic aneurysms (4 reports), head injury (6 reports), fatigue and insomnia.

Disproportionality Analysis of the WHO Vigibase
The WHO Vigibase (3rd quarter, 2008) contained 1046 reports containing dutasteride (no alpha blockers), 6129 reports containing tamsulosin (no 5ARI's), and 269 reports containing both dutasteride and tamsulosin. Table 31 shows the 10 most common drug-event pairs where EB05>1 for the co-administration of dutasteride + tamsulosin.

4 SzarfmanA, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Safety* 2002; 25:381-392.

Table 31: Vigibase common drug-event pairs for co-administration of dutasteride and tamsulosin (Q3, 2008)

MedDRA Preferred Term	# Reports	EB05
Breast enlargement	10	29
Breast pain	13	25
Libido decreased	13	14
Gynecomastia	14	10
Pollakiuria	11	4
Nocturia	6	3
Dysuria	6	2
Urine flow decreased	4	2
Alopecia	6	2
Urinary retention	7	2

Source: NDA 22-460, Module 2.7.4, Summary of Clinical Safety, p. 29

According to the Applicant, when comparing the co-administration to tamsulosin monotherapy, non-overlapping CIs were observed for libido decreased, breast disorders, and pollakiuria. No non-overlapping CIs were observed when comparing co-administration to dutasteride monotherapy.

Reviewer's comments: *A majority of the AE's listed in Tables 30 and 31 are consistent with the pharmacologic activity of or known safety profile of the dutasteride and tamsulosin or the underlying BPH disease. No new safety signals were detected during the review of the postmarketing data of the co-administration of dutasteride with tamsulosin.*

9 Appendices

9.2 Labeling Recommendations

The approved prescribing information of Avodart (6/08) and Flomax (4/09) formed the basis of the proposed label for DTC. Labeling for DTC will reflect the efficacy and safety findings previously determined for the co-administration regimen in NDA 21-319/S014. In reviewing the label, this reviewer verified that the information in the proposed DTC label is supported by data and that important safety information from dutasteride or tamsulosin monotherapy trials, which were placebo-controlled, are included in the DTC prescribing information. The following section discusses major clinical recommendations to the draft DTC label.

General comment:

- Because clinical safety and efficacy were evaluated with the co-administration regimen and not with DTC, the co-administration treatment group should be labeled as "co-administration" to differentiate it from the "combination" capsule (DTC).

Safety:

- Warnings and Precautions: “orthostatic hypotension” is a known significant safety issue because of the potential for life-threatening consequences from syncope and should be moved higher up in the order of safety concerns. “Drug drug interactions” should also be moved up in the order of safety concern because the anticipated increased risk of hypotension with the concomitant use of DTC with another alpha-adrenergic antagonist or PDE5-inhibitors.
- Postmarketing Experience: Additional important postmarketing experience with dutasteride and tamsulosin monotherapy should be included.

Drug-Drug Interactions:

- Information from drug-drug studies with tamsulosin monotherapy and moderate and strong CYP inhibitors should be added to the label.

Overdosage:

- Overdosage information for dutasteride monotherapy was added.

Clinical Pharmacology:

- Data from the drug-drug interaction studies of tamsulosin monotherapy and moderate/strong CYP inhibitors should be included.

Reviewer’s comment**:** *The Division has not begun labeling discussions with the Applicant during this review cycle. The final approval of DTC will be contingent upon satisfactory labeling negotiations.*

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/

CHRISTINE P NGUYEN
01/19/2010

SURESH KAUL
01/19/2010

GEORGE S BENSON
01/19/2010

Deputy Division Director Summary Review for Regulatory Action

Date	January 19, 2010
From	George S. Benson, MD
Subject	Division Deputy Director Summary Review
NDA/BLA #	NDA 22-460/S000
Applicant Name	GlaxoSmithKline
Date of Submission	March 20, 2009
PDUFA Goal Date	January 20, 2010
Proprietary Name / Established Name	Pending 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	Tentative 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
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 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.

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 combination dutasteride/tamsulosin. 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.

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.

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 coadministered 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, 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 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 this NDA submission, the cumulative and 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

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 – congestive 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 recently 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 recently due to discrepancies in the investigator identification information.

According to the sponsor, "cardiovascular events were evaluated prospectively as events of special interest in Study ARI40005…due to previous questions from 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 and this difference was statistically significant (RR 2.04 [95% CI: 1.09, 3.78]). (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 has 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 concluded that their analysis did demonstrate 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. The review of the SLR can not be completed without reviewing complete data sets for the 4 year data from ARI40005 and ARI40006. As discussed above, this is complicated by the fact that the NDA's which contain these datasets have been withdrawn with the sponsor's intention of resubmitting both NDA's in the near future. The issue is further complicated by the fact that there is no placebo control group in ARI40005 and no alpha blocker comparator arm in ARI40006. A consultation has been requested from the Cardiorenal Division but has not been completed at the time of the writing of this review. The Warning/Precaution concerning cardiac failure with dutasteride and alpha blockers would affect multiple FDA review Divisions and multiple drugs. The review of this issue remains ongoing. To date, I do not find the data to support the proposed cardiac failure labeling to be compelling.

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 increase in erectile and ejaculatory adverse events can be adequately managed in labeling.

9. Advisory Committee Meeting

No Advisory Committee meeting was convened. 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 the two proprietary names proposed by the sponsor to date. At the time of the writing of this review, the sponsor is considering alternate proprietary names to submit for DMEPA's review.

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

DDMAC reviewed the sponsor's proposed physician's label. Their comments and recommendations will be considered for incorporation into the label. The label will not be finalized during this review cycle.

Division of Risk Management (DRISK):

DRISK's comments and recommendations will be considered for incorporation into the Patient Package Insert (PPI). The PPI will not be finalized during this review cycle.

12. Labeling

Labeling in Physicians Labeling Rule format was submitted and reviewed. During the 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. NDA 22-460 can not be approved until the tamsulosin patent expires. Labeling will be negotiated with the sponsor during the next review cycle.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action:

I believe that a tentative approval action should be taken. The new Boehringer Ingelheim tamsulosin patent expiration date is April 27, 2010, and NDA 22-460 can not be approved until the tamsulosin patent expires. A tentative approval action was recommended by the cross discipline team leader and primary medical officer as well as the clinical pharmacology, chemistry, statistical, and DSI reviewers. Labeling will be negotiated with the sponsor during the next review cycle and DMEPA will continue tradename discussions with the sponsor.

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 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.

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

None.

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
01/19/2010

Cross-Discipline Team Leader Review

Date	**January 14, 2010**
From	**Suresh Kaul, MD, MPH**
Subject	**Cross-Discipline Team Leader Review**
NDA #	**22-460**
Applicant	**GlaxoSmithKline**
Date of Submission	**March 20th, 2009**
PDUFA Goal Date	**January 20th 2010**
Proprietary Name / Established (USAN) names	**PENDING dutasteride/tamsulosin**
Dosage forms / Strength	**Fixed-dose combination dutasteride 0.5 mg/tamsulosin 0.4 mg once daily**
Proposed Indication(s)	**Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate**
Recommended:	***Tentative Approval***

Cross Discipline Team Leader Review

1. Introduction

This drug product has received a **tentative approval action** because one of the components (tamsulosin) of this combination capsule is under a current exclusivity for six months which will expire on April 27th, 2010. Therefore, a final approval can only be granted by the Agency only after April 27th, 2010.

The dutasteride/tamsulosin combination capsule (DTC) is a capsule containing dutasteride (soft gelatin capsule containing 0.5 mg dutasteride) and tamsulosin hydrochloride product (pellet containing 0.4 mg tamsulosin hydrochloride). The manufacture of DTC involves over-encapsulation of the intermediates of the 2 active ingredients. The drug substance and dose of each active ingredient are the same as those commercially available for dutasteride 0.5 mg (Avodart) and tamsulosin 0.4 mg (Flomax) that were used in study ARI40005.

The applicant has submitted (1) 2 year data from a single pivotal clinical safety and efficacy study (AR140005) and (2) data from a bioequivalence study (AR1109882), both adequate and well controlled clinical trials conducted in the US as the primary support for dutasteride/tamsulosin combination capsule.

The Primary Medical Reviewer, Dr. Christine Nguyen did not identify any issues during this review that would preclude approval of dutasteride and tamsulosin combination capsule (DTC) for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with enlarged prostate.

2. Background

2.1 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.

2.2 Proposed Indication and Currently Available Treatments

Benign prostatic hyperplasia (BPH) is a common medical condition among older men and affects approximately 50% of men after the age of 60 years. BPH can cause considerable disability, leading to obstructive and/or irritative voiding symptoms requiring medical or surgical treatment. The decision to treat is usually based on the type and severity of symptoms and the patient's tolerance for these symptoms. In general, men who develop significant upper tract changes (e.g., hydronephrosis, renal dysfunction) or significant lower tract changes (e.g., urinary retention, recurrent infection, bladder decompensation) require invasive therapy. Otherwise, symptomatic BPH may be treated medically with an alpha-adrenergic antagonist (doxazosin, alfuzosin, terazosin, silodosin and tamsulosin), a 5α-reductase inhibitor (dutasteride, finasteride) or the combination of both (dutasteride + tamsulosin, finasteride + doxazosin). Treatment with a 5α-reductase inhibitor (5ARIs), alone or in combination, is typically reserved for men with symptomatic BPH associated with demonstrable prostatic enlargement.

2.3 REGULATORY HISTORY

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. Tamsulosin (Flomax) 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 Avodart 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 Applicant of 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 support a marketing 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 DTC.

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

3. CMC/Device

Dr. Yichun Sun, the chemistry reviewer and Dr. Moo-Jhong Rhee from Branch III, Division of Pre-Marketing assessment II, Office of NDQA have the following recommendation.

A. Recommendation and Conclusion on Approvability
This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels have an issue on the established name and strengths. Also pending is the final recommendation of Establishment Evaluation.

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.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
None

CTDL Comment:
After having an extensive discussion with the chemistry reviewer Dr. Yichun Sun, it is clear that there are no outstanding issues as regards the chemistry of the combination pill is concerned. However, the inspection report from the Office of Compliance for the manufacturing sites that was successfully completed is still pending. Additionally, the established drug name and the drug strength need to be separated in the final negotiated label. With an approvable action from Office of Compliance, the chemistry review team intends to amend their recommendation for approval.

Addendum:
Dr. Yichun Sun, Chemistry Reviewer, in his memo dated January 11, 2010, wrote the following:

Recommendation for Tentative Approval
At the time when the CMC review #1 was written, there were two pending issues: one was the Establishment Evaluation, and the other issue involved the container label. 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 about the container label are still pending. However, since this NDA is to be "Tentative 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.

Therefore, this application is recommended for tentative approval from the CMC perspective with pending review on container labels.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review team, Laurie McLeod-Flynn and Lynnda Reid, made the following recommendations in their final reviews dated November 18th, 2009.

Recommendations
A. Recommendation on approvability: There is no impediment to approval from a pharmacology/toxicology perspective.
B. Recommendation for nonclinical studies: None at this time.
C. Recommendations on labeling
Proposed labeling: Sections 8 and 13 were revised.

Dr. McLeod-Flynn further concludes that 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.

***CTDL Comment**: I fully concur with Dr. McLeod-Flynn's recommendation.*

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review team, Chongwoo Yu and Myong-Jin Kim, made the following recommendation in their review dated January 7th, 2010:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed NDA 22-460 submitted on March 20, 2009. The overall Clinical Pharmacology information submitted to support this NDA is acceptable.

CTDL Comment:
After receiving an acceptable action for analytical site inspection from the Division of Scientific Investigation (DSI), the Clinical-Pharmacology review team wrote an addendum dated January 15th,2010, to their recommendation.

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.

POSTMARKETING REQUIREMENTS/COMMITMENTS:
None

Bio-Equalence:
Dr. Chongwoo Yu in his review wrote:
Tamsulosin administered as a combination capsule, dutasteride/tamssulosin at steady state was BE to when tamsulosin was coadministered as Flomax® with Avodart® (dutasteride) at steady-state (Study ARI111402).

Dutasteride administered as a combination capsule, dutasteride/tamssulosin, containing (b) (4) mg MDC in the soft gelatin capsule was BE to when dutasteride was administered as Avodart® ((b) (4) mg MDC) under fasted conditions (Study ARI103880).

Tamsulosin administered as tamsulosin HCl capsules containing MR pellets, (b) (4)% w/w ((b) (4)) was BE to tamsulosin administered as Flomax® 0.4 mg MR capsules (Boehringer Ingelheim Pharmaceuticals Inc., USA) under fed conditions (Study 163/07).

Tamsulosin administered as tamsulosin HCl capsules containing MR pellets, (b) (4)% w/w ((b) (4)) was BE to tamsulosin administered as Flomax® 0.4 mg MR capsules (Boehringer Ingelheim Pharmaceuticals Inc., USA) under fed conditions (Study 186/07).

PK parameters:
Singe Dose PK:
Following a single dose of the combination capsule under fed state, dutasteride had a median Tmax of 3.00 hr (range: 1.00-10.00 hr). A mean Cmax value of 2.14 ng/ml was observed for dutasteride. Dutasteride had a mean AUC (0-t) value of 39.6 ng·hr/ml. Selected dutasteride PK parameters are summarized in Table 1.

Table: 1. Summary of Serum Dutasteride PK Parameters Following a Single Dose of combination capsule Under Fed State (Study ARI109882)

Parameter	N	Arithmetic Mean (SD)
AUC(0-t) (ng·hr/ml)	92	39.6 (23.1)
C_{max} (ng/ml)	92	2.14 (0.77)
T_{max} (hr)	92	3.00 (1.00, 10.00)[1]

Following a single dose of dutasteride/tamssulosin under fed state, tamsulosin had a median Tmax of 6.00 hr (range: 2.00 – 24.00 hr). A mean t1/2 value of 13.5 hr, a mean Cmax value of 11.3 hr, and a mean AUC(0-t) value of 187.2 ng·hr/ml for tamsulosin was observed. Selected PK parameters are summarized in Table 2.

Table: 2. Summary of Serum Tamsulosin PK Parameters Following a Single Dose of combination capsule Under Fed State (Study ARI109882)

Parameter	N	Arithmetic Mean (SD)
AUC(0-t) (ng·hr/ml)	92	187.2 (95.7)
C_{max} (ng/ml)	92	11.3 (4.44)

T_{max} (hr)	92	6.00 (2.00, 24.00)[1]
$t_{½}$ (hr)	91	13.5 (3.92)

Multiple Dose PK:
The PK parameters of tamsulosin were characterized following once daily oral administration under fasted state in an open-label, randomized, repeat dose, 3-period crossover study to determine the BE of 3 different formulations of tamsulosin at steady state in healthy male volunteers study (Study ARI111402) are summarized below in Table 3.

Table 3: Summary of Serum Tamsulosin PK Parameters Following Multiple Doses of dutasteride/tamsulosin under Fasted State (Study ARI111402)

Parameter	N	Day 1 Arithmetic Mean (SD)	Day 7 Arithmetic Mean (SI
AUC(0-24) (ng·hr/ml)	23	138.7 (33.0)	188.9 (56.2)
C_{max} (ng/ml)	23	14.4 (3.3)	17.2 (4.2)
C_{min} (ng/ml)	23	NC	3.11 (1.59)
T_{max} (hr)	23	5.00 (3.00, 7.00)[1]	5.00 (3.00, 7.00)[1]
$t_{½}$ (hr)	23	NC	13.9 (2.67)

CTDL Comment:

I agree with the clinical Pharmacology reviewer's assessment.

6. Clinical Microbiology

The microbiology review was done during this review cycle. The microbiology reviewer Dr. Pawar recommends approval of the application from a microbiology perspective.

No phase 4 microbiology commitments are requested.

CTDL Comment:
During the review cycle the microbiology reviewer pointed out the following deficiency that needed to be corrected by the sponsor prior to the approval.

The agency agrees that the (b) (4) in your capsule is a deterrent to the proliferation of microorganisms but this does not address the issue of possible contamination by adventitious microorganisms during the manufacturing process. Therefore, the product specification should continue to include the following wording: "meets the requirements of USP <1111>, <61> and <62> if tested" in your batch release criteria as stated in the original comment.

Sponsor in their submission of December 3rd, 2009, considered the agency's request related to the drug product microbiological attributes and agreed with the Agency's proposal to add the microbial limit tests and criteria to the regulatory specification for dutasteride and tamsulosin Combination Capsules. The specification criteria will be "the product meets the requirements of USP <1111>, <61> and <62> if tested".

Further, a microbiological quality control testing site was added by the sponsor because of the addition of MLT (microbial limits testing) to the DP (drug product) specifications. The newly added site is (b) (4). There was an FDA inspection for this site in July 2009 under NDA 22-417, and it received NAI and was deemed acceptable.

7. Clinical/Statistical- Efficacy

7.1 Clinical Program for Efficacy

No new clinical efficacy information for DTC was submitted. However, clinical efficacy of DTC relies on the Year 2 findings of study **ARI40005**.

7.2 Design, Primary Objective and Efficacy Assessment

Study ARI40005: "A randomized, double-blind, parallel group study to investigate the efficacy and safety of treatment with Dutasteride (0.5mg) and Tamsulosin (0.4 mg), administered once daily for 4 years, alone and in combination, on the improvement of symptoms and clinical outcome in men with moderate to severe symptomatic benign prostatic hyperplasia"

Study ARI40005, a 4-year, multicenter, randomized, double-blind, parallel group study to investigate the efficacy and safety of dutasteride and tamsulosin, alone and co-administered, on BPH outcomes in approximately 4,800 men with moderate to severe symptomatic BPH and an enlarged prostate. The first 2 years of the study were designed to evaluate the effect of dutasteride and tamsulosin co-administered compared to each monotherapy on BPH symptoms ("Year 2" study) as the primary outcome. The remaining 2 years were designed to evaluate clinical progression of BPH (i.e. time to acute urinary retention or BPH-related surgery) among the 3 treatment groups ("Year 4" study). The Year 2 data of ARI40005 provides primary support for the clinical efficacy and safety of DTC.

Analysis of Primary Endpoint(s)

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 ($p < 0.001$). See Table 4.

Table 4: Change from baseline IPSS at Month 24 in ARI40005 (LOCF, ITT)

Time point	Mean change from baseline IPSS (SE)					
	N	Combination	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 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

No clinical efficacy studies were conducted with DTC. However, the efficacy of DTC is expected to be comparable to that of the co-administration regimen because the 2 products were shown to be bioequivalent in study ARI109882. Dr. Nguyen in her review writes that the co-administration of dutasteride and tamsulosin resulted in statistically significant improvement in the primary endpoint (International Prostate Symptom Score or IPSS) and the main secondary endpoint (maximum urinary flow rate or Qmax) compared to each monotherapy at 24 months.

CTDL Comment:
I agree with Dr. Nguyen's assessment.

Analysis of Secondary Endpoints(s)

The key secondary endpoint was maximum urinary flow rate (Qmax) measured during uroflowmetry. Statistically significant improvement from baseline Qmax in the co-administration group compared to each monotherapy was seen from Month 6 ($p < 0.001$) to Month 24 ($p \leq 0.003$). At Month 24, the mean change from baseline Qmax was 2.4 mL/s for the co-administration group, 1.9 mL/s for dutasteride, and 0.9 mL/s for tamsulosin. The mean difference in the change from baseline Qmax between the co-administration group and dutasteride was 0.5 mL/s and between the co-administration group and tamsulosin was 0.9 mL/s.

Disposition of Subjects in Study ARI40005
The trial enrolled 5064 subjects, 4844 of whom were randomized after a 4-week run-in period. The ITT population consisted of 4844 subjects (co-administration of dutasteride + tamsulosin: 1610 subjects, dutasteride: 1623 subjects, tamsulosin: 1611 subjects). Of the 4844 subjects

randomized, 3822 (79%) completed 2 years of treatment, with similar completion rates among the 3 treatment groups (78-80%). More subjects in the co-administration group discontinued due to an adverse event, whereas more subjects in the monotherapy groups discontinued due to lack of efficacy. The distribution of other reasons for discontinuation was comparable among the 3 treatment groups (Table 5).

Table 5: Subject disposition (ITT)

	Co-administration N = 1610 n (%)	**Dutasteride N = 1623 n (%)**	**Tamsulosin N = 1611 n (%)**	**Total N = 4844 n (%)**
Completed (Year 2)	1267 (79)	1301 (80)	11254 (78)	3822 (79)
Discontinued	343 (21)	322 (20)	357 (22)	1022 (21)
• AE	• 154 (10)	• 108 (7)	• 136 (8)	• 398 (8)
• Withdrew consent	• 71 (4)	• 95 (6)	• 74 (5)	• 240 (5)
• Lost to follow-up	• 30 (2)	• 30 (2)	• 29 (2)	• 89 (2)
• Protocol violation	• 24 (1)	• 17 (1)	• 27 (2)	• 68 (1)
• Lack of efficacy	• 36 (2)	• 45 (3)	• 53 (3)	• 134 (3)
• Other	• 28 (2)	• 27 (2)	• 38 (2)	• 93 (2)

Source: Primary Clinical Review of NDA 21-319/S014

Study ARI109882: "An open-label, randomized, single dose three-period partial crossover study to **determine the Bioequivalence** and food effect of a combination capsule formulation of Dutasteride and Tamsulosin Hydrochloride (0.5mg/0.4mg) compared to concomitant dosing of AVODART® 0.5mg and Flomax 0.4mg Commercial Capsules in Healthy Male Subjects"

Primary Objective: 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 in fed state

Study design and conduct: 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 sequence 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 receiving treatment D. Each dosing session was separated by 4-week washout period. Table 6: describes the treatment groups.

Table 6: 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 (DTC) 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

Blood samples were collected for PK parameters of dutasteride and tamsulosin over a 72-hour period following dosing. The primary comparison for equivalence between DTC and the co-administration of dutasteride and tamsulosin was levels of drug exposure (AUC and Cmax) between treatment A and treatment B.

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 $AUC_{(0-t)}$ and Cmax between DTC 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.

Table 7: Bioequivalence of DTC 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 = DTC in fed state (test)
Group C = co-administration of dutasteride + tamsulosin in fasted state (reference)
Group D = DTC in fasted state (test)

CTDL Comment:
Dr. Christine Nguyen in her review wrote, that bioequivalence was observed when comparing PK parameters of DTC to concomitantly dosed dutasteride and tamsulosin in the fasted state (D:C comparison). I concur with Dr. Nguyen.

Additionally, there was no food effect on dutasteride PK with the exception of the mean Tmax occurring 1 hour later in the fed state compared to the fasted state (regimen B – D, A – C). This finding is not likely to be clinically significant.

The food effect on tamsulosin has been adequately addressed in the proposed DTC product label, which recommends that DTC be taken 30 minutes after a meal.

7.3 Disposition of Subjects in Study ARI109882

One hundred one (101) subjects were enrolled and randomized. All subjects were male with a median age of 29.5 years. The most common ethnicity was Caucasian (77%), followed by Black (22%). Of 101 subjects, 81 (80%) completed the study. Twenty subjects (20%) withdrew prematurely and the most common reasons for withdrawal were consent withdrawal and protocol violation (7% each). See Table 8.

Table 8: Subject disposition

Disposition variables	N (%)
Number of subjects randomized	101
• Number of subjects completed	81 (80)
• Number of subjects withdrawn	20 (20)
* Adverse event	4 (4)
* Consent withdrawal	7 (7)
* Protocol violation	7 (7)
* Lost to follow up	1 (1)
* Investigator's discretion	1 (1)

Source: NDA 22-460, Study ARI109882, MO's analysis of ds.xpt

CTDL Comment:
The percentage of patients who withdrew from the study as a result of adverse event is relatively low.

7.4 Statistical Review:

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

CTDL Comment:
I concur with the assessment of statistical reviewer's Kate Dwyer and Mahboob Sobhan from the Division of Biometrics III.

8. Safety

There were no important differences between the safety findings of the Year 2 analysis and those reported after the Year 2 cut-off date for ARI40005 for the serious adverse events.

There were no significant differences in deaths or non-fatal serious adverse events between the co-administration group compared to dutasteride or tamsulosin monotherapy in the cumulative database. However, the adverse event of cardiac failure occurred at a higher incidence in the co-administration group than each of the monotherapies (see section 8.6).

For Year 2 analysis, the cumulative safety data indicated that, compared to each monotherapy, the co-administration of the 2 drugs was associated with a higher incidence of drug discontinuation due to an adverse event, most of which were reproductive/sexual and breast-related, and a statistically higher incidence of ejaculatory disorders

8.1 Safety Populations and Overall Exposure

The overall exposure and safety assessments were adequate to characterize the safety profile of the co-administration of dutasteride and tamsulosin compared to each monotherapy.

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.

***CTDL comment**: According to Dr. Nguyen, (68%)of subjects in co-administration group, (66%)in dutasteride group, and (59%) in tamsulosin group completed 4 years of treatment in study ARI40005*.

8.2 Demographics

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. The cumulative years of co-administration therapy exposure were 2771 person-years at the 2-year cutoff date. The cumulative duration of treatment exposures in the monotherapy groups was comparable to that in the co-administration group.

***CDTL Comment**:*
Per Dr. Nguyen's review, 1096 co-administration subjects (68%), 1067 dutasteride subjects (66%), and 956 tamsulosin subjects (59%) completed 4 years of treatment in ARI40005.
I concur with the primary reviewer's assessment.

8.3 Discontinuation due to Adverse Events

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 are separated into SAEs and non-SAEs.

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

CTDL Comment:
I agree with the Primary Medical Reviewer's assessment, in which she states that most of the adverse events that lead to discontinuation were not higher in the combination group when compared to each monotherapy.

8.4 Deaths

The **cumulative** data of deaths in ARI40005 (post-randomization to December 8, 2008) are summarized in Table 9. 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 9: 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

CTDL Comment:
The number of deaths was about 2% in the total population under this drug development program and most of the deaths were from either cardiac cause or due to neoplasms. Cardiac causes included ACS, Coronary insufficiency, Myocardial infarction and Cardiac failure. There was a similar distribution among the three groups and none of the deaths were related directly to the drug.

8.5 Common Adverse Events

Approximately 64% of patients reported at least 1 adverse event. The most commonly reported AEs (≥ 5% in any treatment group) were infections, reproductive and breast disorders, and gastrointestinal disorders. The 3 most common AEs 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 ($p < 0.05$).

8.6 Safety Issues of Particular Interest

Cardiac failure: Cardiovascular events were evaluated prospectively as events of special interest in Study ARI40005 due to previous questions from 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 proportion of subjects with any cardiovascular adverse event of interest was similar among the 3 treatment groups, with the exception of cardiac failure.

Table: 10. 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

Table: 10 above summarizes the **cumulative** data on composite cardiac failure events. 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: 11. 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

Source: NDA 22-460, Module 5.3.5.1.22, Listings 3 & 4, cardiac failure case narratives, MO analysis
NDA 21-319/Sequence 0022, Module 5.3.5.1 and 5.3.6 (SLR submission), MO analysis

Dr. Nguyen in her review comments as follows: The incidence of cardiac failure was 0.9% in the co-administration group (14 subjects) compared to 0.2% in the dutasteride group (4 subjects) and 0.6% in the tamsulosin group (10 subjects). The difference between the co-administration and dutasteride groups was statistically significant (RR 3.57 [95% CI: 1.17, 10.8]); the difference between co-administration and tamsulosin groups did not reach statistical significance (RR 1.36 [95% CI: 0.61, 3.07]). The imbalance in the composite term cardiac failure was driven by the PTs "cardiac failure" and "congestive heart failure."

CTDL Comment:
I agree with the assessment of Dr. Nguyen. Additionally, the clinical review team reviewed the case narratives provided in this submission for all cardiac failure patients and concluded that advanced age, prior history of CHF, known risk factors that are associated with CHF, i.e., acute coronary syndrome, ischemic heart disease, HTN and MI or being on multiple concurrent medications (frequently seen in older patients), and most of all accompanying co-morbid medical conditions, could very well have contributed to a higher incidence of cardiac failure in patients who received an alpha blocker including tamsulosin. It is premature to associate the use of tamsulosin (an alpha adrenergic receptor inhibitor) to a higher incidence of cardiac failure from the limited controlled available data at this time.

Therefore, in my opinion, there is no substantial evidence that indicates a safety signal for cardiac failure for the combination drug product (dutasteride/tamsulosin).

9. Advisory Committee Meeting

An Advisory Committee was not held for this application.

10. Pediatrics

The Applicant requested a full waiver of the requirement to conduct assessments of dutasteride/tamsulosin in pediatric patients.

The Division recommended a full waiver because studies would be highly impracticable to conduct and because disease/condition does not exist in normal children. Also, dutasteride is contraindicated in children.

On September 23, 2009, the Pediatric Review Committee (PeRC) PREA Subcommittee agreed with the Division to grant a full waiver for this product.

11. Other Relevant Regulatory Issues

Division of Scientific Investigation (DSI)

Site inspections (one analytical site and two clinical sites) by the Division of Scientific Investigation (DSI) were conducted during the review cycle. Out of the two clinical sites that were inspected by the DSI, the site at Indiana had no deficiencies at all. However, for the second clinical site at Austin, TX, Form 483 was issued by the DSI for minor observation. A response to this Form 483 by the sponsor on January 8th, 2010 indicates no areas of concern at this time. Therefore, both clinical site inspections are acceptable to the clinical and Clinical-Pharmacology review teams.

The DSI team had also issued Form 483 to the sponsor for their bio-analytical site inspection. A response to this Form 483 was received a by the DSI on January 8th, 2010. The DSI review team found some inconsistencies in data integration and sample integrity, but nothing that would rise to the level of non-approvability of the dutasteride/tamsulosin combination product at this time.

Following evaluation of Form FDA-483 items and written responses from GSK and Covance-Austin, **DSI concludes that the inspectional findings should not have significant impact on the outcomes of study ARI109882.**

Form 483 issued by the DSI to GSK and a review of their response:

Study # ARI109882: "An Open-Label, Randomized, Single Dose, Three-Period Partial Crossover Study to Determine the Bio-equivalence and Food Effect of a Combination Capsule Formulation of Dutasteride and Tamsulosin Hydrochloride (0.5 mg / 0.4 mg) Compared to Concomitant Dosing of AVODART~ 0.5 mg and Flomax 0.4 mg Commercial Capsules in Healthy Male Subjects"

Study ARI10 98 82 was conducted at two clinical facilities (Contract Research Organizations) in the US. The first facility was in Covance GFI Research at 800 St. Mary's Drive, Evansville, IN 47714, and the second facility in Covance Research at 313 E. Anderson Lane, Austin, TX 78752. The analytical portion of the study was conducted at Glaxo-Smith-Kline, 3030 E. Cornwallis Road, Research Triangle Park, NC 27709

Clinical Site 1: Covance GFI Research at 800 St. Mary's Drive, Evansville, IN 47714 (Evansville Facility)
Following inspection at the clinical site 1 (June 29 - July 01, 2009), No Form FDA-483 was issued.

Clinical Site 2: Covance Research at 313 E. Anderson Lane, Austin, TX 78752 (Austin Facility)
Following inspection at the clinical site 2 (July 13-21, 2009), a one-item Form FDA-483 was issued (Attachment 1). The Covance's response (dated August 10, 2009) was received by DSI on August 20, 2009 (Attachment 2). The Form FDA-483 observation (in bold type), the firm's response, and our evaluations follow.

1. Failure to prepare or maintain adequate and accurate case respect to observations and data pertinent to the Specifically for protocol GSK ARI109882, study # 207897:

A. The randomization schedule for subject 206 is incorrect in that it documents treatment B (dutasteride 0.5 mg/tamsulosin 0.4 mg combination capsule) for dosing Period 2 on 08 Dec 2007 was given when in fact subject 206 was actually given treatment A (Flomax 0.4 mg and Avodart 0.5 mg individual capsules).
B. The source document for subject 211 documents a 6 hour supine BP of 125/74 mmHg on 10 Nov 2007, yet a BP of 128/74 mmHg. was documented on the eCRF for 6 hours post dose reading.
C. The source document for subject 243 documents the 48 hour blood collection on 10 Dec 2007 at 0916. A 48 hours Post Dose time of 10: 16 was reported on the eCRF on 10 Dec 2007.
D. The source document for subject 245 72 hours post dose on 5 Feb 2008 is missing from the subject file.
E. The source document for subject 246 72 hours post dose on 5 Feb 2008 is missing from the subject file.
F. Source document for subject 246 documents the 2 hour blood collection on 05 Jan 2008 at 1122. A 2 hours Post Dose time of 11: 21 was documented on the eCRF on 5 Jan 2008.

Regarding Item lA, Covance explained in their written response (Attachment 2) that the dose administrator inadvertently marked Treatment B on the source records. Correct dose was actually administered as reflected in the study protocol and report (i.e., no mistake in the study report). Covance also said that they provided evidence obtained from their pharmacy to the FDA investigator during the inspection to support that this is a documentation error in the source records. *The FDA investigator accepted Covance's explanation.*

Covance also acknowledged the Form FDA-483 observations 1B, 1C and 1F. Covance said that they already informed GSK of these reporting errors. These errors are minor and those should not impact the study outcomes.

For items 1D and 1E of the Form FDA-483, Covance stated that the source documents were misfiled. Covance is committed to provide a copy of this source document to FDA upon retrieval.

Analytical site: GlaxoSmithKline, 3030 E. Research Triangle Park, NC 27709 (GSK).

Following inspection of the analytical site (December 7 - 10, 2009) , Form FDA-483 was issued (Attachment 3). The GSK's response (dated January 08, 2010) was received by DSI on January 11, 2010 (Attachment 4). The Form FDA-483 observation (in bold type), GSK's written response, and our evaluations follow.

1. Audit trail feature in Analyst v.1.4.1 was disabled. Only PDF files of chromatograms and final run results were available; the electric data files were not archived and not stored in a secure environment.

As cited in the 483 observation above, the audit trail feature in Analyst v. 1.4.1 was disabled and only PDF files of chromatograms and final run results were available. This is objectionable because any changes in the integration of chromatograms cannot be verified to assure that changes were not made to bias results of QCs, calibration standards, and/or subject samples. The available electronic data files were not reliable, as they were not archived and not stored in a secure environment.

During the inspection, GSK informed FDA investigators that all chromatograms within an analytical run were integrated using the same integration parameters, and GSK did not manually reintegrate any chromatograms from all the analytical runs (i.e., no samples including calibration standards, QCs, and subject samples were manually re-integrated). GSK also said their procedure allowed minor changes in integration parameters between runs to optimize integration, but the same parameters were used for all samples in the same run. To verify that information, GSK was asked by FDA investigator to list the integration parameters used in all the dutasteride and tamsulosin analytical runs. For dutasteride, 81 out of 93 runs used the same integration parameters (i. e., global integration parameters); 12 runs used integration parameters slightly different from global integration parameter. For tamsulosin, 79 out of 94 runs used global integration parameters; 15 runs used integration parameters slightly different from the global integration parameters (see Attachment 5). For dutasteride and tamsulosin runs with integration parameters different from the global integration parameters (i.e., modified integration parameters), GSK was asked by the FDA investigators to reintegrate chromatograms in the entire runs using the global integration parameters. QCs results from these runs generated using modified integration parameters were compared to results generated using global integration parameters. Overall, DSI found that the QC results are similar regardless of whether global or modified integration parameters were used. Moreover, there was no change in run acceptance when modified integration parameters were used. Based on these findings, DSI is of the opinion that data were not biased by changing integration parameters. Source records in analytical runs were also checked during the inspection to confirm that no manual integration was conducted for all chromatograms generated in the study. *No problem was noted*.

In the written response, GSK said they have now changed their practices and have enabled the Analyst audit trail feature to prompt for reasons for changes during quantitation. They now obtain the PDF copy of the Analyst audit trail, and archived all PDF copies along with the proprietary Analyst files such that they can be made available during inspection.

Overall DSI considers that this Form FDA-483 observation has been resolved.

2. Failure to use suitable quality control samples (QCs) that are representative of the dutasteride concentrations in serum samples of study subjects. Specifically, QC concentrations used were D .3, 3, 8, and 40 ng/mL, but ~99% of dutasteride concentrations were ~ 3 ng/mL. The mean Cmax values of Treatment A, B, C, and D determined in the study were all ~2.1 ng/mL.

As cited in the above 483 observation, only two (0.3 ng/mL and 3 ng/mL) of the four dutasteride QC concentrations are representative of the dutasteride concentrations obtained in

study subjects. Normally, three QC concentrations in duplicate (i.e., n=2 at each of three QC concentration representative of low, mid, and high dutasteride concentration observed in study samples) should be used to monitor performance of each analytical run. However, upon review of all the QC results showed that almost all QCs at 0.3 and 3 ng/mL met the acceptance criteria (i.e. ~15% deviation from the nominal value). In addition, in the Form FDA-483 response, GSK also reported that a high degree of accuracy of the QC data from 0.3 ng/mL (2.6% bias) to 3 ng/mL (0.9% bias) was observed using a linear regression equation. The result suggested that the response of the standard curve was linear over 0.3 and 3 ng/mL. *Consequently, DSI is of the opinion that this Form FDA-483 observation should not significantly affect the study outcomes.*

3. Failure to provide sufficient long term frozen storage stability data to assure sample integrity over the period when study serum samples were collected after first dosing at the clinical sites to the end of samples analysis.

GSK did not conduct any long term frozen storage stability experiment for FLODART (combination of dutasteride and tamsulosin). Instead, QC samples were prepared at GSK and stored with the subject samples in the same -30°C freezer. According to GSK, the QC samples were used as internal controls to support study sample integrity over the frozen storage period prior to sample analysis. However, during the inspection, DSI uncovered that the QC samples were not prepared at the same time when study samples were collected at the clinical sites, but were prepared later at GSK around the time when shipments of the QCs samples were not adequate to cover the period when study serum samples were collected after first dosing at the clinical sites to the end of sample analysis (about 125 days). Moreover, study samples were not stored in -30°C freezer but in -20°C freezer at the clinical site. However, this stability issue only affects sample integrity of only 71 samples. *In light of small sample number, there should not be significant impact on the study outcome.*

4. Failure to perform sufficient assessments of Incurred Sample Reproducibility (ISR). Only 4% of dutasteride/tamsulosin samples were re-analyzed for ISR.

The SOP for ISR in effect at the time was not adequate. However, GSK has now revised their SOP (becoming effective January 2010), requiring 10% (5% for ~2000 samples) of total study samples excluding samples from control or placebo subjects*. However, ISR results (Attachment 6) from the 4% study samples indicated that significant ISR problem is unlikely.*

5. Many study samples (~100) collected in this study were hemolyzed, but no experiment was conducted to investigate the effect of hemolysis on the accuracy of the UPLC-MS/MS method.

GSK acknowledged that the effect of hemolysis was not directly evaluated during the method validation for dutasteride and tamsulosin. GSK revised their SOP (becomes effective January 2010) to evaluate this effect in future studies. *Following, a review of the GSK's response, we agree that this observation should not have a significant impact on study outcomes.*

6. No selectivity experiment on selected OTC drugs and concomitant medications was attempted (see Table 8, clinical pharmacology study report ARI109882), although SOP (# SOP-DMD- 0007 v05) stated that these experiments should be conducted.

Per SOP at the time when the study was conducted (SOP-DMD-0007 v05, effective date October 15, 2007) selectivity experiment on selected OTC drugs and concomitant medications should be studied. Table 8 of clinical pharmacology study report ARI109882 reveals subjects were administered OTC drugs and other medications, but no experiment to evaluate assay interference was conducted. In their response, GSK only said that they will evaluate the OTC drugs and concomitant medications in future studies, and that based on molecular structures of OTC drugs and concomitant medications, assay interference is unlikely. *During the inspection, DSI noticed no significant interference on analytic and internal standard peaks upon review of study chromatograms.*

7. SOP (# SOP-DMD-0007 v05) allows calibration standards with concentrations greater than LLOQ to be acceptable even of deviations from nominal values are ~ 15% (i.e., accept deviations up to 20% instead of ~ 15%).

Per GSK's SOP at the time when the study was conducted, the acceptance criterion for all the calibration standards was f20%. However, FDA guidance for industry (Bio-analytical Method Validation), recommends that a calibration standard should not be accepted if the deviation is /15% from the nominal value (/20% deviation for LLOQ). In their response GSK reported that only 45 out of 2805 standards other than LLOQ had deviations /15% from the nominal values. *Consequently, this finding should not have significant impact on the study outcomes.*

8. No temperature monitoring procedure in effect during the study covering areas such as temperature monitoring, alarm checks and calibration for freezers used to store study samples received and analyzed. Specifically:

A. The firm does not conduct periodic alarm checks on freezers utilized to store study samples and QC samples to provide assurance that freezer set points for alarms continue to operate adequately.
B. The firm does not perform preventive maintenance or calibration of the centrifuge utilized during the processing of study samples.
C. SOP for freezer maintenance was not maintained during the study period.

In their response, GSK has agreed to revise their current procedures to correct the findings cited specifically above in 8A, 8B, and 8C. *During the inspection, continuous temperature records for the freezers were reviewed and no significant problem was noted.*

9. Documentation was incomplete. For example:

A. No documentation of handling of stability samples (e.g., freeze-thaw, bench-top experiments).
B. Failure to retain PDF files of original chromatograms, results) in a precision

validation run (Run G198745HUSEVALB001) injected.

C. Pipetting error by Zymark Rapid Plate in Run # ARI109882HUSE053 was not documented in the source data.

In their response, GSK stated that processes are now put in place to correct the documentation issues cited above. *This observation is unlikely to have significant impact on the study outcome.*

Conclusion:
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.

Division of Medication Errors and Prevention (DMEPA)
The review team from DMEPA made the following recommendation for the proprietary name (b) (4).

The Proprietary Name Risk Assessment did not find the name to be promotional. However, the (b) (4)

Thus, the Division of Medication Error Prevention and Analysis (DMEPA) does not recommend the use of the proprietary name, (b) (4), for this product at this time.

The DMEPA reviewer also had the following draft comments for the container label:

Container Label (30 and 90 count bottles)

1. Relocate and increase the prominence of the strength statement on the principle display panel (i.e. 0.5 mg/0.4 mg), to appear below the dosage form statement. As currently presented is difficult to read.
2. Delete the statement 'Each capsule contains…' from the principal display panel to allow for the implementation of comment 1.
3. Relocate the net quantity statement away from the strength statement (e.g. below the 'Rx only' statement). To achieve this we recommend you consider reducing the size of the double arrow graphic.

Container Label (7 count bottles)

1. Relocate and increase the prominence of the strength statement on the principle display panel (i.e. 0.5 mg/0.4 mg), to appear below the dosage form statement. As currently presented is difficult to read.

Division of Drug Advertising, Marketing and Communication (DDMAC)
Each of the DDMAC comments were considered individually and discussed within the clinical review team and most of the DDMAC recommendations were incorporated into the label and will be negotiated with the sponsor toward an agreeable label.

Division of Risk Management (DRISK)

The patient labeling reviewer, Melisa Hulett from the Division of Risk Management reviewed a substantially completed PPI and made some label changes. During their review the following changes to the PPI were made.

• simplified wording and clarified concepts where possible
• ensured that the PPI is consistent with the PI
• removed unnecessary or redundant information
• ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Labeling

A substantially complete label will be sent to the sponsor and discussions will be held with the sponsor to reach an agreement towards a final label.

Key issues/labeling changes:
Safety:

- Warnings and Precautions: "orthostatic hypotension" is a known significant safety issue because of the potential for life-threatening consequences from syncope. "Drug drug interactions" moved up in the order of safety concern because the anticipated increased risk of hypotension with the concomitant use of DTC with another alpha-adrenergic antagonist or PDE5-inhibitors.
- Postmarketing Experience: Additional important postmarketing experience with dutasteride and tamsulosin monotherapy included.

Drug-Drug Interactions:

- Information from drug-drug studies with tamsulosin monotherapy and moderate and strong CYP inhibitors added to the label.

Overdosage:

- Overdosage information for dutasteride monotherapy was added.

Clinical Pharmacology:

- Data from the drug-drug interaction studies of tamsulosin monotherapy and moderate/strong CYP inhibitors was included in the label.

1. Recommendations

12.1 Recommended Regulatory Action

In my opinion, the sponsor has provided sufficient evidence for efficacy (NDA 21-319), safety data and 120 day safety update in support of this NDA. Therefore, an approval should be granted for dutasteride/tamsulosin combination pill. However, since tamsulosin exclusivity is valid until April 27, 2010, a tentative approval may be granted at this time.

12.2 Risk Benefit Assessment

The overall risk/benefit profile for the combination of dutasteride and tamsulosin is determined to be favorable. Since the approval of the efficacy supplement, no significant safety issues, other than the cardiac failure, have been identified for the co-administration of dutasteride and tamsulosin. A detailed review of cardiac failure cases revealed no significant increase with tamsulosin when compared to dutastride or to the combination pill. It is anticipated that the overall risk benefit profile for DTC is comparable to the currently approved co-administration of dutasteride and tamsulosin because the 2 products are bioequivalent.

12.3 Recommendation for Post marketing Requirement

None

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/

SURESH KAUL
01/19/2010

GEORGE S BENSON
01/19/2010

Sponsor's responses to DRUP's questions during NDA review. Review of this submission is contained in the primary clinical review of NDA 22-460.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22460	ORIG 1	GLAXOSMITHKLINE INC	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/

CHRISTINE P NGUYEN
08/25/2009

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-460 **Applicant: GSK** **Stamp Date: March 20, 2009**

Drug Name: Flodart **NDA Type: N**

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD-compliant
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	The Division waived this requirement, because there was only one study supporting the safety of the co-administration of dutasteride and tamsulosin in the BPH population (Study ARI40005).
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	The Division waived this requirement, because there was only one study supporting the efficacy of the co-administration of dutasteride and tamsulosin the BPH population (Study ARI40005)
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If	505			Tamsulosin (Flomax)

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	Application is a 505(b)(2) and if appropriate, what is the reference drug?	(b)(2)			
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?			X	Dutasteride-tamsulosin combination capsule (DTC) is a fixed-dose combination product
EFFICACY					
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? • Pivotal Study #1: Safety and efficacy study ARI40005 titled "A randomised, double-blind, parallel group, study to investigate the efficacy and safety of treatment with Dutasteride (0.5mg) and Tamsulosin (0.4mg), administered once daily for 4 years, alone and in combination, on the improvement of symptoms and clinical outcome in men with moderate to severe symptomatic benign prostatic hyperplasia (Year 2 analysis)" • Pivotal Study #2: Bioequivalence study ARI109882 titled "An Open-Label, Randomized, Single Dose Three-Period Partial Crossover Study to Determine the Bioequivalence and Food Effect of a Combination Capsule Formulation of Dutasteride and Tamsulosin Hydrochloride (0.5mg/0.4mg) Compared to Concomitant Dosing of AVODART® 0.5mg and Flomax 0.4mg Commercial Capsules in Healthy Male Subjects" **Indication**: Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate	X			The Division concurred that the clinical safety and efficacy for DTC may be supported by cross-referencing to the Year 2 data from Study ARI40005 submitted to efficacy supplement 014 to NDA 21-319.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	The Division did not request a thorough QT study.
20.	Has the applicant presented a safety assessment based on all	X			

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	current worldwide knowledge regarding this product?				
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the sponsor submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?		X		The sponsor should clarify the version of MedDRA coding dictionary and provide the mapping of verbatim terms to preferred terms.
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			The Division concurred with the sponsor's proposal to submit narratives for serious adverse events (including deaths) and only those withdrawals due to a serious event.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Sponsor requests a full pediatric waiver. BPH has no pediatric correlate and, dutasteride is contraindicated in the pediatric population.
ABUSE LIABILITY					

[2] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	The Division did not request datasets from study ARI40005 in this NDA submission. Only subject listings and summaries and case narratives were requested to evaluate the updated safety information from the Year 2 data of Study ARI40005.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The following comments should be conveyed to the sponsor in the 74-Day letter:

1. Provide the version of MedDRA coding dictionary used to code the adverse events.

2. Provide the mapping of investigator verbatim terms to the MedDRA Preferred Terms and from the MedDRA Preferred Terms to the investigator verbatim terms.
3. Provide the correct titles for Listing 8 and Table 8 in Module 5.3.5.1.22. Currently Listing 8 is titled "Summary of Non-Fatal Serious AEs and Study Drug Discontinued" and Table 8 is titled "Summary of Non-Fatal Serious AEs (Post-Randomization) and Study Drug Permanently Discontinued." Listing 8 and Table 8 appear to be a listing and summary, respectively, of all non-fatal SAEs from post-randomization to December 8, 2008, whether or not these SAEs led to permanent drug discontinuation.
4. Clarify if there is any difference between adverse event listings/tables in Module 5.3.5.1.22 that are labeled "Post-Randomization" versus "Cumulative"; both of these terms appear to describe the time period from post-randomization to December 8, 2008.

CHRISTINE P. NGUYEN, MD	May 5, 2009
Reviewing Medical Officer	Date
SURESH KAUL, MD, MPH	May 5, 2009
Clinical Team Leader	Date

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

The document contained in this section summarizes the clinical presentation and discussion at the Filing Meeting on May 4, 2009 for NDA 22-460.

NDA 22-240 FILING MEETING
May 4, 2009

NDA Dates

74-Day Letter date:	June 2, 2009
Mid-cycle date:	August 27, 2009
PDFUDA date:	January 20, 2010

Product

Established Name:	Dutasteride/tamsulosin combination capsule (DTC)
Proposed Trade Name:	Flodart
Therapeutic Class:	5-alpha reductase inhibitor (dutasteride)/alpha-adrenergic antagonist (tamsulosin)
Dose/Dosage form:	0.5 mg dutasteride/0.4 mg tamsulosin once daily/fixed-dose combination capsule
Indication:	Treatment of symptomatic BPH in men with an enlarged prostate
Sponsor:	GlaxoSmithKline (GSK)

Product Background

Product	Dutasteride	Tamsulosin	Co-administration of dutasteride and tamsulosin
Trade name (U.S.)	AVODART	Flomax	
Indication (s) (year of approval)	Treatment of BPH in men with an enlarged prostate to: • Improve symptoms (2001) • Reduce the risks of acute urinary retention and need for BPH-related surgery (2002)	The treatment of symptomatic BPH (1997)	Treatment of symptomatic BPH in men with an enlarged prostate (2008)
Dose and Regimen	0.5 mg once daily	0.4 mg (up to 0.8 mg) once daily	0.5 mg dut + 0.4 mg tamsulosin once daily
Intended population	Men with BPH and an enlarged prostate	Men with BPH	Men with BPH and an enlarged prostate
Sponsor	GSK	Boehringer Ingelheim	GSK

Co-administration of dutasteride and tamsulosin (efficacy supplement 014 to NDA 21-319 [AVODART])

- Safety and efficacy supported by findings from one single large, multinational phase 3 study in approximately 4,800 men with moderate to severe BPH (**Study ARI40005**)

- Efficacy:

Study ARI40005 Year 2 (LOCF)	**Co-administration of dutasteride + tamsulosin**	**Dutasteride**	**Tamsulosin**
Mean change from baseline **IPSS**	-6.2	-4.9	-4.3
Mean difference IPSS of co-administration therapy compared from monotherapy (95% CI)		-1.3 (-0.9, -1.7)	-1.8 (-1.4, -2.2)
Mean change from baseline **Qmax** (mL/sec)	2.4	1.9	0.9
Mean difference Qmax of co-administration therapy compared from monotherapy (95% CI)		0.5 (0.2, 0.8)	1.5 (1.2, 1.9)

- Safety: By Year 2, the safety profile of the co-administration of dutasteride + tamsulosin was acceptable compared to each monotherapy (no increased incidences of deaths, non-fatal SAEs, laboratory abnormalities, etc.). The co-administration group had a higher incidence of withdrawal due to AE's (mostly breast/reproductive AEs), more drug-related AEs, statistically significant higher incidence of ejaculatory disorders (3- to 5-fold higher than each monotherapy).

NDA 22-460 submission: Fixed-dose dutasteride 0.5 mg/tamsulosin 0.4 mg combination capsule (DTC)

Rationale for Combination Therapy and Combination Capsule:

1. provide symptomatic relief superior to either monotherapy through different mechanisms of action of the 2 medications
2. provide the rapid symptom improvement associated with tamsulosin
3. maintain long-term benefits of reduced risks of AUR and BPH-related surgery with dutasteride
4. reduce the pill burden

Clinical program of DTC:

- Clinical safety and efficacy of DTC **cross-referenced to Year 2 data** of **ARI40005** (co-administration of dutasteride and tamsulosin)

- **Bioequivalence study ARI109882** (open-label, randomized, single dose, 3-period, 4-treatment partial block crossover) of DTC vs. dutasteride + tamsulosin co-administered to bridge the efficacy and safety data of co-administration of dutasteride and tamsulosin (ARI40005) to DTC

- Updated safety information of ARI40005 from cut-off date of the 120-Day Safety Update for NDA 21-319/S014 to December 8, 2008

- No additional efficacy information with DTC was submitted.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

Discussion at the Filing Meeting:

1. NDA 22-460 is **fileable** from the clinical, clinical-pharmacology, chemistry, pharm/tox, and biostatistics perspectives.
2. Consults to OSE and DDMAC have been requested. The clinical pharmacology team requests a DSI consult for the pivotal bioequivalence study (ARI109882); the chemistry team requests inspections of the drug substance manufacturing sites and Microbiology consult.
3. The sponsor's request for a full pediatric waiver will be sent to PeRC for consideration.
4. Comments from the clinical and chemistry teams will be conveyed to the sponsor in the 74-Day Letter. The clinical-pharmacology, pharm/tox, and biostatistics teams have no comments at this time.

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

/s/

Christine Nguyen
5/5/2009 05:06:28 PM
MEDICAL OFFICER

Suresh Kaul
5/7/2009 01:50:34 PM
MEDICAL OFFICER

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-460 **Applicant: GSK** **Stamp Date: March 20, 2009**

Drug Name: Flodart **NDA Type: N**

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD-compliant
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	The Division waived this requirement, because there was only one study supporting the safety of the co-administration of dutasteride and tamsulosin in the BPH population (Study ARI40005).
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	The Division waived this requirement, because there was only one study supporting the efficacy of the co-administration of dutasteride and tamsulosin the BPH population (Study ARI40005)
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If	505			Tamsulosin (Flomax)

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	Application is a 505(b)(2) and if appropriate, what is the reference drug?	(b)(2)			
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?			X	Dutasteride-tamsulosin combination capsule (DTC) is a fixed-dose combination product
EFFICACY					
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? • Pivotal Study #1: Safety and efficacy study ARI40005 titled "A randomised, double-blind, parallel group, study to investigate the efficacy and safety of treatment with Dutasteride (0.5mg) and Tamsulosin (0.4mg), administered once daily for 4 years, alone and in combination, on the improvement of symptoms and clinical outcome in men with moderate to severe symptomatic benign prostatic hyperplasia (Year 2 analysis)" • Pivotal Study #2: Bioequivalence study ARI109882 titled "An Open-Label, Randomized, Single Dose Three-Period Partial Crossover Study to Determine the Bioequivalence and Food Effect of a Combination Capsule Formulation of Dutasteride and Tamsulosin Hydrochloride (0.5mg/0.4mg) Compared to Concomitant Dosing of AVODART® 0.5mg and Flomax 0.4mg Commercial Capsules in Healthy Male Subjects" **Indication**: Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate	X			The Division concurred that the clinical safety and efficacy for DTC may be supported by cross-referencing to the Year 2 data from Study ARI40005 submitted to efficacy supplement 014 to NDA 21-319.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	The Division did not request a thorough QT study.
20.	Has the applicant presented a safety assessment based on all	X			

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	current worldwide knowledge regarding this product?				
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the sponsor submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?		X		The sponsor should clarify the version of MedDRA coding dictionary and provide the mapping of verbatim terms to preferred terms.
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			The Division concurred with the sponsor's proposal to submit narratives for serious adverse events (including deaths) and only those withdrawals due to a serious event.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Sponsor requests a full pediatric waiver. BPH has no pediatric correlate and, dutasteride is contraindicated in the pediatric population.
ABUSE LIABILITY					

[2] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	The Division did not request datasets from study ARI40005 in this NDA submission. Only subject listings and summaries and case narratives were requested to evaluate the updated safety information from the Year 2 data of Study ARI40005.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The following comments should be conveyed to the sponsor in the 74-Day letter:

1. Provide the version of MedDRA coding dictionary used to code the adverse events.

2. Provide the mapping of investigator verbatim terms to the MedDRA Preferred Terms and from the MedDRA Preferred Terms to the investigator verbatim terms.
3. Provide the correct titles for Listing 8 and Table 8 in Module 5.3.5.1.22. Currently Listing 8 is titled "Summary of Non-Fatal Serious AEs and Study Drug Discontinued" and Table 8 is titled "Summary of Non-Fatal Serious AEs (Post-Randomization) and Study Drug Permanently Discontinued." Listing 8 and Table 8 appear to be a listing and summary, respectively, of all non-fatal SAEs from post-randomization to December 8, 2008, whether or not these SAEs led to permanent drug discontinuation.
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CHRISTINE P. NGUYEN, MD	May 5, 2009
Reviewing Medical Officer	Date
SURESH KAUL, MD, MPH	May 5, 2009
Clinical Team Leader	Date

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

/s/

Christine Nguyen
5/5/2009 05:06:28 PM
MEDICAL OFFICER

Suresh Kaul
5/7/2009 01:50:34 PM
MEDICAL OFFICER