DEPUTY DIRECTOR/CROSS-DISCIPLINE TEAM LEADER REVIEW

Date	**June 18, 2008**
From	**George S. Benson, MD**
Subject	**Deputy Director/Cross-Discipline Team Leader Review**
NDA # **Supp #**	**21319** **014**
Proprietary/ Established names	**Dutasteride/Avodart**
Dosage forms/strength	**0.5 mg capsule**
Proposed indication	**"AVODART in combination with the alpha-blocker tamsulosin is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH)"**
Recommendation	**Approval**

Table of contents:

1. Introduction

Two classes of drugs [5-alpha reductase inhibitors (5ARIs) and alpha-adrenergic antagonists] have been approved for the treatment of the symptoms of benign prostatic hyperplasia (BPH). In 2003, the sponsor of Avodart (dutasteride) (a 5ARI) initiated discussions with the Division of Reproductive and Urologic Products concerning conducting a clinical trial to determine whether the co-administration of dutasteride and tamsulosin (an alpha-adrenergic antagonist currently also approved for treating the symptoms of BPH) would result in greater symptomatic improvement than that seen with the administration of either drug alone.

The use of a combination of a 5ARI and an alpha-adrenergic antagonist has been previously evaluated in the Medical Therapy of Prostatic Symptoms (MTOPS) trial. This study evaluated the combination of finasteride and doxazosin and led to the approval of finasteride in combination with doxazosin for the reduction in the risk of symptomatic progression of BPH in April, 2004.

NDA 21319 (S014), which was submitted on August 20, 2007, included the two year results of a 4 year large, multicenter, randomized, double-blind, parallel group study (Study ARI40005) in which 4844 subjects were randomized [co-administration of dutasteride and tamsulosin (1610 subjects); dutasteride alone (1623 subjects); tamsulosin alone (1611 subjects)]. The primary efficacy endpoint for the two year study results is the International Prostate Symptom Score (IPSS) (the current standard primary endpoint for BPH trials), and, based on the results of Study ARI40005, the Avodart sponsor seeks the additional indication "Avodart in combination with the alpha-blocker tamsulosin is indicated for the treatment of symptomatic BPH."

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Avodart (dutasteride) was approved for the "treatment of benign prostatic hyperplasia (BPH) in men with an enlarged prostate to improve symptoms" on November 20, 2001. On October 9, 2002, the drug was also approved for the additional indication of "reduction of the risk for acute urinary retention and the risk of BPH-related surgery" in the same patient population. Tamsulosin was approved "for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)" in 1995 in Europe and in 1997 in the United States.

A guidance meeting with the sponsor to discuss the protocol for ARI40005 was held on March 26, 2003. An additional teleconference to discuss the overall design and study endpoints was held on August 6, 2003. With regard to the two year data analysis:

1. The Division of Reproductive and Urologic Products (DRUP) recommended that a placebo group be added to the study. The sponsor did not believe that a placebo group was justified in a four year study in men with moderate/severe BPH. If the primary endpoint of the two year data from study ARI40005 were the IPSS,

DRUP agreed that a placebo control arm would not be required. The co-administration therapy would need to be superior to each monotherapy for the primary endpoint.

2. DRUP accepted an alpha level of 0.01 in the absence of a second confirmatory trial.

A pre-NDA meeting for the year two data from study ARI40005 was held on June 26, 2007.

3. CMC/Microbiology

Both dutasteride and tamsulosin are approved drugs. No new CMC or microbiology data were submitted. The CMC reviewer recommended approval.

4. Non-clinical Pharmacology/Toxicology

No new non-clinical data were submitted for either of these two approved drugs.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data were submitted. Previously submitted study ARI1011 showed that co-administration of dutasteride did not significantly affect the pharmacokinetics of tamsulosin. No formal drug interaction study of the effect of tamsulosin on the PK of dutasteride was conducted. The clinical pharmacology reviewer believes that "a direct pharmacokinetic assessment of dutasteride in the presence of tamsulosin co-administration is not needed for an adequate assessment of the safety and efficacy of the proposed combination use of dutasteride and tamsulosin for the following reasons:

a. A review of available data suggests that tamsulosin co-administration is unlikely to significantly affect the PK of dutasteride.
b. Dutasteride and tamsulosin were administered at their respective proposed doses in Phase 3 Study ARI40005 without significant increase in adverse events relative to each monotherapy.
c. Dutasteride appears to have a wide therapeutic range for safety. Dutasteride doses up to 5 mg once daily were given for 24 weeks in Phase 2 study ARIA2001 and no significant adverse events were identified."

Study ARI40005 used two different formulations of 0.4 mg tamsulosin, the U.S. product Flomax 0.4 mg and the European product Omnic 0.4 mg. A bioequivalence study (Trial ARI10021) demonstrated that these two formulations of tamsulosin are bioequivalent.

The clinical pharmacology reviewer believes that the "Clinical Pharmacology section for NDA 21-319 SE 014 is acceptable."

6. Clinical Microbiology

No new microbiology data were submitted for these two approved drug products.

7. Clinical/Statistical

The primary data to support efficacy for the co-administration of dutasteride and tamsulosin was generated from two year data obtained from one large, international, multicenter, randomized, double-blind, parallel group trial (ARI40005) in which 4844 subjects were randomized to one of three treatment groups: co-administration of dutasteride (0.5 mg once daily) and tamsulosin (0.4 mg once daily), dutasteride (0.5 mg once daily) alone, and tamsulosin (0.4 mg once daily) alone.

The primary endpoint was the change from baseline in the International Prostate Symptom Score (IPSS) at month 24.

Important inclusion criteria included:

- Men >50 years of age with a clinical diagnosis of BPH
- IPSS > or = to 12 at screening
- Q_{max} (maximum urinary flow rate) >5 and <15 cc/sec
- Prostate volume >30cc by transrectal ultrasonosgraphy
- Serum PSA > 1.5 ng/mL at screening

Important exclusion criteria included:

- Serum PSA > 10.0 ng/ml
- Post-void residual urine >250 cc
- Previous surgery or invasive procedures to treat BPH
- History of acute urinary retention within 3 months of screening

Of the 4844 randomized patients, 3822 (79%) completed two years of treatment. Similar completion rates (78-80%) were observed in the three treatment groups. Of the 1022 subjects who discontinued prematurely, 398 (39%) discontinued because of an adverse event, 240 (23%) withdrew consent, 89 (9%) were lost to follow-up, 68 (7%) were protocol violators, 134 (13%) experienced lack of efficacy, and 93 (9%) were “others.”

Efficacy: IPSS changes in the co-administration group were statistically superior to both monotherapies at Month 24 (primary endpoint) (Table 1).

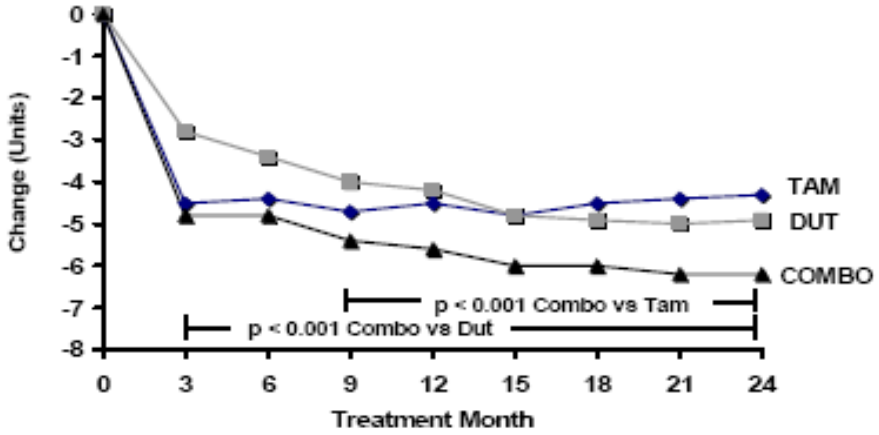
Table 1. Mean change from baseline IPSS at Month 24 (LOCF, ITT)

Time point	**Mean change from baseline (SE)**		
Month 24	Combination -6.2 (0.15)	Dutasteride -4.9 (0.15)	Tamsulosin -4.3 (0.15)
Time point	**Mean difference of combination and monotherapy (95% CI)**		
Month 24	Dutasteride -1.3 (-1.69, -0.86) p-value <0.001		Tamsulosin -1.8 (-2.23, -1.40) p-value <0.001

IPSS improvement in the co-administration group was statistically superior to both monotherapies starting at Month 9. IPSS improvement in the co-administration group was statistically superior to the tamsulosin group starting at Month 9 and superior to the dutasteride group starting at Month 3.

The changes from baseline IPSS at three month time points are shown in Figure 1.

Figure 1: Mean change from baseline IPSS over the 24-month treatment period (ITT, LOCF)



Source: Study report, Table 18, p. 58; Figure 1, p. 59

At month 24, the percentage of patients who experienced a >3 unit increase in IPSS was 72% for the combination group, 65% for the dutasteride alone group, and 62% for the tamsulosin alone group.

Secondary endpoints of interest:

1. Q_{max}:
   The increase from baseline Q_{max} was greater with combination therapy compared to each monotherapy from Month 6 to Month 24. At Month 24, the mean difference between co-administration and dutasteride was 0.51 cc/sec (p=0.003) and between co-administration and tamsulosin was 1.52 cc/sec (p<0.001).
2. Prostate volume:
   At month 24 the mean percent changes from baseline in prostate volume for the co-administration group was -26.9%, for dutasteride alone was -28.0%, and for

tamsulosin alone was 0.0%. This is the expected finding. 5ARI's are known to decrease prostate size while alpha-adrenergic antagonists do not.

Statistical Review:

The statistical reviewer concluded that "the combination therapy (dutasteride and tamsulosin) showed a statistically significant superiority ($p<0.01$) in the improvement of IPSS score when compared to dutasteride (0.5 mg) and tamsulosin (0.4) monotherapy. From a statistical perspective, data reported in this submission demonstrated efficacy of combination therapy in treating benign prostatic hyperplasia (BPH)."

In summary, from an efficacy standpoint, the Division agreed that the results from one large (approximately 4500 patients), multicenter, randomized, double-blind trial could support approval. A p-value adjustment to <0.01 was agreed upon because of the single trial. The sponsor believed that a placebo group was not appropriate for a 4 year study in patients with significant symptoms of BPH. Although the inclusion of a placebo control group was recommended, the Division agreed that a placebo control group would not be required in this trial of two drugs approved for the treatment of BPH if the IPSS were used as the primary endpoint and that the co-administration of the two drugs was superior to each monotherapy.

The co-administration group demonstrated a significantly higher improvement in IPSS at 24 months than did either monotherapy group. Although no placebo group was included in the trial, the changes in IPSS seen with dutasteride alone were consistent with those reported in the placebo controlled phase 3 studies performed in a similar population that led to approval of the dutasteride monotherapy. I agree with the medical officer's review (pages 33-35) that tamsulosin monotherapy also performed as expected in Trial ARI4005. Although a placebo group in this trial would have made the interpretation of the study more straightforward, I believe that the trial did provide substantial evidence that demonstrated that the co-administration of dutasteride and tamsulosin is superior to either monotherapy for the primary endpoint IPSS at Month 24.

8. Safety

Sources reviewed for safety assessment included 7578 subjects enrolled in four completed studies, post-marketing databases, and the 120-day Safety Update. The 7578 subjects enrolled in the four completed studies included 4844 in the pivotal study (ARI40005), 2385 in two supporting efficacy studies (ARI40013 and ARI40002), and 22 in one healthy volunteer drug-drug interaction study (ARIA1011). Overall, 3533 subjects were exposed to the combination of dutasteride 0.5 mg and tamsulosin 0.4 mg once daily. The Division concurred with the sponsor's proposal to not integrate the safety data from the clinical trials because of major differences in the design and treatment schedules among the studies.

Summary of safety for Trial ARI40005:

Trial ARI40005 did not contain a placebo control group. Adverse events occurring in the three treatment groups (dutasteride plus tamsulosin, dutasteride alone, and tamsulosin alone) were compared.

There were 61 deaths in this two year trial. The all cause death rate was 1% for each treatment arm (20/1610 for the drug combination group, 20/1623 for the dutasteride alone group, and 21/1611 for the tamsulosin alone group). Deaths occurring in supportive studies ARI40013 and ARI40002 were reviewed and no new safety findings were identified.

Over the 24 months of treatment, 12% of the entire group of study patients experienced a serious adverse event (SAE) (12% drug combination group, 12% dutasteride alone group, and 13% tamsulosin alone group). The most commonly reported SAE's were myocardial infarction and prostate cancer. Compared to each monotherapy, co-administration was not associated with a higher incidence of any specific SAE (Table 2).

Table 2. Number of subjects (%) with common (>5 subjects/group) SAE's.

Preferred Term	Combination N=1610 n (%)	Dutasteride N=1623 n (%)	Tamsulosin N=1611 n (%)
Any SAE	188 (12)	196 (12)	207 (13)
Prostate cancer	14 (<1)	3 (<1)	13 (<1)
Myocardial infarction	10 (<1)	12 (<1)	14 (<1)
Pneumonia	9 (<1)	4 (<1)	4 (<1)
Angina pectoris	8 (<1)	8 (<1)	7 (<1)
Atrial fibrillation	7 (<1)	4 (<1)	7 (<1)
Coronary artery disease	5 (<1)	7 (<1)	13 (<1)
Inguinal hernia	4 (<1)	8 (<1)	6 (<1)
Osteoarthritis	3 (<1)	6 (<1)	5 (<1)
Cerebrovascular accident	3 (<1)	6 (<1)	3 (<1)
Colon cancer	3 (<1)	5 (<1)	3 (<1)
Transient ischaemic attack	3 (<1)	5 (<1)	1 (<1)
Urinary retention	2 (<1)	2 (<1)	5 (<1)
Intervertebral disc protrusion	1 (<1)	5 (<1)	0

Source: Table S15
SAEs with onset on or after randomisation (or missing onset of treatment date).

Source: Study report, Table 44, p. 84

SAE's occurring in supportive studies ARI40013 and ARI40002 were reviewed and no new safety concerns were identified.

Overall, 9% of the entire group of patients discontinued due to adverse events (AE's). AE's believed by the investigator to be drug related which led to premature patient withdrawal occurred in 5% of the subjects in the co-administration group and 3% in each of the monotherapy groups. The higher withdrawal rate in the co-administration group was primarily attributable to more withdrawals from sexual and breast related AE's (erectile dysfunction, decreased libido, ejaculation failure, breast tenderness, breast enlargement, and nipple pain) (Table 3).

Table 3: Subjects with common AE's (≥ 5 subjects/group) leading to study withdrawal

Preferred Term	Combination N=1610 n (%)*	Dutasteride N=1623 n (%)*	Tamsulosin N=1611 n (%)*
Any AE withdrawal	164 (10)	127 (8)	148 (9)
AE's of combination group > AE's of BOTH monotherapies			
Erectile dysfunction	21 (1)	15	15
Libido decreased	11	7	4
Ejaculation failure	8	0	2
Retrograde ejaculation	5	2	3
Breast tenderness	6	3	0
Breast enlargement	6	2	2
Nipple pain	6	0	1
AE's of combination group no greater than AE's of BOTH monotherapies			
Prostate cancer	17 (1)	7	21 (1)
Myocardial infarction	2	6	9
Dizziness	7	3	6
Fatigue	3	7	2
Asthenia	1	4	1

* Percentage not provided if < 1%
Source: Study ARI40005, Summary of Clinical Safety, Module 2.7.4, Table 40

The most common AE's (>3%)/group) are shown in Table 4.

Table 4: Subjects with common AE's (≥ 3%/group) by Preferred Term

Preferred Term	Combination N=1610 n (%)	Dutasteride N=1623 n (%)	Tamsulosin N=1611 n (%)
Any AE	1048 (65)	1039 (64)	1011 (63)
Erectile dysfunction	132 (8)	118 (7)	72 (4)
Hypertension	81 (5)	92 (6)	90 (6)
Nasopharyngitis	80 (5)	91 (6)	102 (6)
Retrograde ejaculation	70 (4)	10 (<1)	18 (1)
Back pain	68 (4)	61 (4)	73 (5)
Libido decreased	60 (4)	52 (3)	28 (2)
Influenza	50 (3)	50 (3)	63 (4)
Dizziness	50 (3)	39 (2)	51 (3)
Upper respiratory tract infection	45 (3)	35 (2)	35 (2)
Arthralgia	45 (3)	36 (2)	47 (3)
Ejaculation failure	41 (3)	10 (<1)	14 (<1)
Headache	25 (2)	49 (3)	38 (2)

Source: Table S6
AEs with onset on or after randomisation (or missing onset of treatment date).
Source: Study report, Table 28, p. 71

AE's deemed by the investigator to be drug related are shown in Table 5.

Table 5: Subjects with common (≥ 1%) investigator determined drug-related AE's.

Preferred Term	Combination N=1610 n (%)	Dutasteride N=1623 n (%)	Tamsulosin N=1611 n (%)
Any Drug-Related AE	391 (24)	291 (18)	259 (16)
Erectile dysfunction	119 (7)	98 (6)	61 (4)
Retrograde ejaculation	67 (4)	10 (<1)	18 (1)
Libido decreased	55 (3)	45 (3)	28 (2)
Ejaculation failure	39 (2)	8 (<1)	13 (<1)
Semen volume decreased	29 (2)	5 (<1)	13 (<1)
Loss of libido	28 (2)	21 (1)	15 (<1)
Dizziness	26 (2)	12 (<1)	27 (2)
Breast enlargement	22 (1)	29 (2)	13 (<1)
Nipple pain	20 (1)	9 (<1)	5 (<1)
Breast tenderness	16 (<1)	17 (1)	5 (<1)

Source: Study ARI40005 Table S11
AEs with onset on or after randomization (or missing onset of treatment date).

Source: Study report, Table 37, p. 79

Safety related subgroup analyses:

Age: Younger subjects (<65 years of age) experienced a higher incidence of sexual AE's than older subjects. The incidence of SAE's was higher in subjects >65 years of age compared with those <65 years of age (combination: 13% vs. 10%; dutasteride: 15% vs. 8%; tamsulosin: 15% vs. 9%). These differences in SAE's appear to be primarily due to age-related co-morbidities (cardiovascular events and prostate cancer).

Race: The incidence of AE's was higher in non-white subjects in all 3 treatment groups 75-76% compared to White subjects (61-64%). The relatively small number of non-White subjects (12%) in the trial makes interpretation of this finding problematic.

Two AE's of special interest were analyzed by the sponsor: a) sexual and reproductive and b) cardiovascular.

A summary of subjects with sexual AE's, breast disorders, and prostate cancer is shown in Table 6.

Table 6: Summary of subjects with sexual AE's, breast disorders and prostate cancer

Composite AE Term	Combination N=1610 n (%)	Dutasteride N=1623 n (%)	Tamsulosin N=1611 n (%)
Ejaculation disorders	159 (9.9)	32 (2.0)	49 (3.0)
Impotence[a]	132 (8.2)	118 (7.3)	73 (4.5)
Altered (decreased) libido	100 (6.2)	83 (5.1)	51 (3.2)
Breast disorders	44 (2.7)	49 (3.0)	21 (1.3)
Breast tenderness	34 (2.1)	31 (1.9)	12 (0.7)
Breast enlargement[b]	23 (1.4)	29 (1.8)	13 (0.8)
Prostate cancer	21 (1.3)	11 (0.7)	26 (1.6)

Source: Study ARI40005 Table S22, Table S26, Table S30, Table S34, Table S38, Table S42, Table S46

a. Includes erectile dysfunction
b. Includes gynecomastia

Source: Summary of Clinical Safety, Table 46, p. 59

Compared to each monotherapy, combination therapy was associated with a 3 to 5-fold increase in the incidence of ejaculation disorders. This adverse event is not serious and can be adequately labeled.

There were no cases of breast cancer in the entire safety database. Prostate cancer was reported in 21 (1.3%), 11 (0.7%), and 26 (1.6%) of the combination group, dutasteride only group, and tamsulosin only group, respectively. These numbers were not statistically different.

Cardiovascular AE's are shown in Table 7.

Table 7: 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

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) 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 summary, from a safety perspective, no new significant concerns were identified following 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 for this NDA submission. Both dutasteride (approved in 2001) and tamsulosin (approved in 1997) are currently approved drugs for the treatment of BPH. The safety profiles of both drugs given as monotherapy are well characterized. The combination of a 5ARI and alpha-adrenergic blocking agent are currently commonly co-prescribed in the United States. No increase in significant adverse events was detected with the co-administration of these two drugs which act through different mechanisms.

10. Pediatrics

A consultation was requested from the Pediatric Review Committee (PeRC). PeRC agreed with granting a pediatric waiver for this sNDA because the condition being treated (BPH) is included in the list of adult diseases which are "automatic waivers" for pediatric studies.

11. Other Relevant Regulatory Issues

The following consultations were requested and considered:

a. Division of Drug Marketing, Advertising, and Communications (DDMAC):
   DDMAC's suggested labeling changes were implemented or considered (see medical officer review page 12).
b. Study Endpoints and Labeling Team (SEALD):
   [redacted]
   ii. SEALD's comments concerning the PLR formatting were incorporated into labeling.
c. Division of Scientific Investigations:
   The review team did not consider a DSI audit of study sites to be warranted for this sNDA. Dutasteride and tamsulsoin are not new molecular entities, are not the first drugs in their class, are not intended for a novel population, are not used for a new diagnostic category, and are not delivered by a new route of administration. In

addition, a routine investigation of a limited number of several hundred study sites would not be likely to impact the overall integrity of the data.

d. Office of Surveillance and Epidemiology (OSE):
   A consultation was not submitted because dutasteride and tamsulosin are both approved products and no new significant safety concerns were identified in this review. No postmarketing commitments are necessary.
e. Division of Medical Errors and Technical Support (DMETS):
   A consultation was not submitted because there are no trade name changes associated with this efficacy supplement.
f. Pregnancy Labeling Team:
   A consultation was not requested because neither dutasteride nor tamsulosin are indicated in women. Pregnancy risk categories remain unchanged for both products. Risks of dutasteride exposure to the male fetus remain unchanged and have been adequately addressed in the dutasteride label.
g. Financial disclosure: Adequate information was submitted in the NDA to demonstrate compliance with financial disclosure requirements.

12. Labeling

The sponsor's proposed label in PLR format was reviewed by clinical, pharmacology-toxicology, clinical pharmacology, chemistry, and statistical reviewers as well as by DDMAC, SEALD, and MHT. The edited label was initially returned to the sponsor on May 15, 2008. The final label was agreed upon by the Sponsor and the Division on June 5, 2008.

14. **Recommendations/ Risk Benefit Assessment**

The primary medical officer and the pharmacology-toxicology, clinical pharmacology, chemistry, and statistical reviewers all recommended that this efficacy supplement (NDA 21-319/SO14) be approved. I agree.

The efficacy data presented in the two year, large, multicenter, randomized, double-blind trial (ARI40005) demonstrated that the co-administration of dutasteride and tamsulosin was superior to either drug alone in reducing the symptoms of benign prostatic hyperplasia.

Both dutasteride and tamsulosin are currently approved drugs for the treatment of BPH. No significant new safety concerns with co-administering these two drugs were identified. Some sexual (erectile dysfunction, loss of libido, and disorders of ejaculation) and breast (nipple pain) adverse events were numerically higher in the combination drug group, but these events are uncommon, not serious, and can be adequately addressed in labeling.

Overall, the risk/benefit assessment favors approval of the co-administration of dutasteride and tamsulosin for the treatment of the symptoms of BPH in men with enlarged prostate glands.

No Post-marketing Risk Management Activities (including REMS) or Post-marketing studies are recommended. No specific comments need to be conveyed to the sponsor in the regulatory action letter.

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/s/

George Benson
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MEDICAL OFFICER