CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-319

ADMINISTRATIVE DOCUMENTS

1.2. Patent Information

Item 13

Time Sensitive Patent Information

Pursuant to 21 C.F.R. § 314.53
For
Dutasteride Soft-Gelatin Capsules

NDA 21-319

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Active Ingredient:	**Dutasteride**
Dosage Form:	**Soft-Gelatin Capsule**
Strength:	**0.5 mg**

U.S. Patent 5,565,467

Expiration Date:	September 17, 1993
Type of Patent:	Drug Substance and Drug Product
Name of Patent Owner:	Glaxo Wellcome Inc.

The undersigned declares that U.S. Patent 5,565,467 covers dutaseride, the drug substance, and compositions containing the drug product, that are the subject of this application for which approval is being sought.

U.S. Patent 5,846,976

Expiration Date:	September 17, 2013
Type of Patent:	Method of Use
Name of Patent Owner:	Glaxo Wellcome Inc.

The undersigned declares that U.S. Patent 5,846,976 covers the method of use of dutaseride that is the subject of this application for which approval is being sought.

U.S. Patent 5,998,427

Expiration Date:	September 17, 2013
Type of Patent:	Drug Substance, Drug Product, and Method of Use
Name of Patent Owner:	Glaxo Wellcome Inc.

The undersigned declares that U.S. Patent 5,998,427 covers dutaseride, the drug substance, and compositions containing the drug product, that are the subject of this application for which approval is being sought and the method of use of dutaseride that is the subject of this application for which approval is being sought.

Please address all communications to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-7656

Respectfully submitted by:
Glaxo Wellcome Inc.

December 4, 2000
Date

Robert H. Brink
Robert H. Brink
Attorney or Applicant

EXCLUSIVITY SUMMARY for NDA # 21-319 SUPPL #

Trade Name _____ **Generic Name** dutasteride
Applicant Name GlaxoSmithKline HFD-580
Approval Date November 20, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_x__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /___/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_x__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

      YES /__x_/ NO

/___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_x__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_x__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /x___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Evelyn R. Farinas,
Regulatory Project Manager November 20, 2001

_____
Signature of Preparer Date
Title:

Daniel Shames, M.D.
Acting Director November 20, 2001
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

1.3. Marketing Exclusivity

NDA 21-319

GI198745 Tablets

Request for Marketing Exclusivity

Under Sections 505(c)(3)(D)(ii) and 505(j)(4)(D)(ii) of the Federal Food, Drug and Cosmetic Act, Glaxo Wellcome request five years of exclusivity from the date of approval of this new drug application of GI198745 Tablets for the treatment of Benign Prostatic Hyperplasia as a new chemical entity pursuant to 314.108(a) and 314.108(b)(2).

The active ingredient of the drug product for which approval is being sought under this application is GI198745 (5-alpha reductase inhibitor) also known as (5α, 17β)-N-{2, 5 bis(trifluoromethyl) phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide.

Applicant states that to the best of its knowledge and belief that the drug product which is the subject of the application contains no "active moiety" as defined under 21 CRF 314.108 that has been approved by the FDA under 505(b) of the Federal Food, Drug and Cosmetic Act; therefore, the drug product of the application falls within the definition of "new chemical entity" under 21 CRF 314.108.

Whereas the drug product for which approval is being sought under the application lies within the definition of a " new chemical entity" pursuant to the Agency's regulations promulgated October 3, 1994 in the Federal Register, Applicant respectfully submits that nothing in the present request be interpreted as it conceding to the validity of the Agency's definition of "new chemical entity".

Printable Pediatric Page

Welcome to the Pediatric Page Printed Page. To produce your pediatric page, simply print this page (this paragraph will not print). However, most versions of Internet Explorer will print a header on each page (i.e., the name of the web site, etc.) To eliminate these when printing the Pediatric Page, go to 'File', then 'Page Setup', and clear the 'Header' and 'Footer' Boxes. (Cut and paste to a document [or write down] the contents of these boxes first if you want to restore the headers and footers afterwards.)

PEDIATRIC PAGE

NDA Number:	021319	**Trade Name:**	DUTASTERIDE 0.5MG SOFT-GELATIN CAPSULES
Supplement Number:	000	**Generic Name:**	DUTASTERIDE
Stamp date:	12/21/00	**Action Date:**	12/21/00
Supplement Type:	N		
COMIS Indication:	TREATMENT OF SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA IN MEN WITH AN ENLARGED PROSTATE GLAND		

Indication #1: Benign Prostatic Hyperplasia - Date Entered: 11/19/01

Status: A full waiver was granted for this Indication.

Reason for This Waiver: Disease or condition does not exist in children

Comments:

This page was printed on 11/19/01

/S/ 11/19/01

Signature Date

NEW DRUG APPLICATION

NDA 21-319
Dutasteride Soft-Gelatin Capsules

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

11 Nov 2000

Charles E. Mueller
Head, North American Clinical Compliance
World Wide Compliance

Date

Division Director's Memorandum

FROM: Daniel A. Shames MD
Acting Director, DRUDP

TO: Florence Houn MD
Director, ODE III

REGARDING: Opinion and Rationale for Regulatory Action of **NDA 21-319**

Date submitted: December 21, 2000
Memo Completed: November 9, 2001

Sponsor: **GlaxoSmithKline**
Five Moore Drive
Research Triangle Park, North Carolina 27709

Drug: Generic: **Dutasteride**
Trade: Pending

Class: Type 1 and Type 2, 5-alpha reductase inhibitor

Route/Dosing: Oral, Once Daily

Dosage form: Soft-gelatin capsule

Strength: 0.5 mg

Proposed indication: Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate gland

Related INDs [redacted]

1.0 BACKGROUND

BPH is a common condition in aging men. Historically, symptomatic BPH has been treated primarily by surgery consisting either of transurethral or open surgical prostatectomy. Several "minimally invasive" techniques including microwave therapy and laser vaporization have been introduced. The frequency of surgery for BPH has markedly decreased in recent years primarily because of the development of pharmacologic therapy.

Pharmacologic research has resulted in approval of 2 major classes of drugs for treating the symptoms of BPH. The first drugs to be approved for this indication were alpha-adrenergic receptor blocking agents. These drugs are thought to improve symptoms of BPH by blocking alpha-adrenergic receptor mediated smooth muscle contraction in the prostatic stroma (and probably bladder neck) and thereby decreasing the magnitude of bladder outlet obstruction. The alpha-adrenergic blocking drugs terazosin, doxazosin, and tamsulosin are approved for this indication.

The second approach to the drug therapy of BPH consists of 5-alpha-reductase inhibition. Dihydrotestosterone (DHT) is thought to be the primary androgen responsible for facilitating hyperplastic growth of the prostate. Dihydrotestosterone is produced from testosterone by the action of the enzyme 5 alpha-reductase. Treatment with a 5 alpha-reductase inhibitor is thought to decrease the size of the prostate and thereby decrease the degree of prostatic obstruction. . Men who have congenital Type II 5 alpha-reductase deficiency have small prostate glands throughout life and do not develop benign prostatic hyperplasia (BPH). Although Type I 5-alpha-reductase is also present in the prostate gland, its role in this tissue is not clear. There are no known congenital deficiencies of the Type I enzyme. The 5-alpha-reductase (Type 2) inhibitor finasteride is currently approved for the treatment of symptomatic BPH in men with an enlarged prostate gland.

Dutasteride is a Type 1 and Type 2 5-alpha-reductase inhibitor. The proposed indication is the "treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate gland." The recommended dose is 0.5 mg orally daily.

2.0 NDA: DATA AND ANALYSIS

2.1 Conduct of Trials: In support of NDA 21319, the sponsor submitted three Phase 3 trials. Two were conducted entirely in the United States and the third was conducted in 19 countries. The design of all 3 studies was virtually identical. All three trials are 4-year studies. The first 2 years consist of randomized, double blind, placebo-controlled, parallel group studies followed by a 2-year open-label extension. The first year of the trials was designed to evaluate the efficacy and safety of dutasteride in the treatment of BPH. The second year portion of the trials was designed to determine the effect of dutasteride on the incidence of acute urinary retention and the need for prostate surgery.

This NDA submission contains mainly data from Year 1 of the pivotal studies dealing with the treatment of BPH. The sponsor plans to provide the results from Year 2 of the double-blind treatment phase and from the open-label phase (Years 3 and 4) in subsequent submissions.

In the three studies, 4324 patients were randomized (2158 patients to the placebo group and 2166 to dutasteride). Three thousand five hundred twenty-two (3522) patients (1750 placebo and 1772 dutasteride) completed the 12 month treatment period.

2.2 Efficacy: The primary efficacy endpoint in all Phase 3 trials was the change from baseline at 12 months in the American Urologic Association Symptom Index (AUASI). This validated questionnaire is currently used as a primary endpoint for all drug trials of

the treatment of BPH. Statistically significant improvement was observed in all three trials. Significant improvement in the two major secondary endpoints, maximum urinary flow rate (Qmax) and prostate volume, was also observed.

2.3 Safety: In the three major controlled studies, 2166 patients took dutasteride for a total of 1866 patient years of drug exposure. Two-year safety data is provided for 445 patients who completed the 2-year double blind phase of on the studies was submitted. The patient population in the clinical trials reflects the probable marketing exposure.

Reported significant adverse events in this NDA database are primarily those related to known side effects of 5-alpha-reductase inhibitors. There was only one serious adverse event that may have been related to dutasteride. This was a severe "allergic" rash that occurred after the patient had been on dutasteride for approximately one year. Although, data directly comparing the safety of dutasteride and finasteride is limited, the adverse events observed in the clinical trials of these two drugs appear similar.

In addition, there were two placebo-controlled studies done in phase 1/2 that yielded important information about patient exposure to doses higher than the proposed label dose (0.5mg once daily). In first study, 4 patients received a 40mg single dose and three groups of 4 patients received 1, 5 and 40mg for seven days without drug related adverse event. In the second study, 57 patients received 2.5mg and 60 patients received 5 mg of dutasteride daily for six months. There did not appear to be a signal for serious adverse events related to dutasteride.

2.4 Metabolism and Pharmacokinetics: After review of the NDA, and presentation of the review to the CPB management briefing (9/21/01), the OCPM team determined that there were five deficiencies "not deemed critical" for approval that should be addressed by the sponsor. It was determined that some of the deficiencies should be addressed as phase 4 commitments and some in the label. A discipline review letter was sent to the sponsor on 10/4/01 stating the deficiencies. On 10/15/01, Drs. Parekh and Malinowski spoke with their counterparts at GSK regarding methods to address the deficiencies.

Listed below are the five deficiencies:

1. Consider conducting a study to investigate the effect of hepatic impairment on the PK of dutasteride.
2. We remind you that the Division has not received the population PK analysis to verify certain drug-drug interaction claims. For example, data regarding increase in dutasteride exposure by 37 % to
   44 % with calcium channel antagonists should be submitted.
3. Submit a mass balance study and characterization of parent and metabolites profiles in serum, urine, and feces following oral administration.
4. Submit an *in vitro* metabolism study using therapeutically relevant dutasteride concentration to characterize the metabolic pathways.
5. Submit a drug interaction study with ketoconazole in humans.

The final dispensation of the five deficiencies is as follows:

Deficiencies 1 and 5 will be addressed in the label. **Deficiency 2** was resolved when the sponsor resubmitted a population PK report that that had the appropriate information required by the OCPB reviewer.

The sponsor agreed to address **deficiency 4** with a phase 4 in-vitro metabolism study. **Deficiency 3** was the most technically and scientifically difficult to address. The OCPB team and the sponsor agreed during the 10/15/01 tcon that a concept protocol to address mass balance (Deficiency 3) would be sent to the OCPB team within one month of the Action Letter.

More detailed information regarding the interaction between the sponsor and OCPB can be found in the 10/15/01 tcon minutes or the Memo from the OCPB team leader.

3.0 Issues of Concern

Concerns exist regarding potential adverse events in patients taking 5 alpha-reductase inhibitors:

3.1 Exposure of Pregnant Women: Exposure of a pregnant woman to dutasteride could result in inadequate development of the genitalia of a male fetus. Exposure could result from ingesting capsules, contact with broken gelcaps and subsequent absorption through the skin, or through contact with semen from a male taking dutasteride. This issue is adequately addressed in the Warnings section of the label. The primary medical reviewer and the pharmacology/toxicology reviewer believe that the administration of dutasteride does not require condom use when engaging in sexual intercourse with a woman of childbearing potential because the risk of fetal damage through this route is low. Similar reasoning was applied to the risk for women participating in oral sex during pregnancy. Therefore, condom use is not mentioned in the label.

3.2 PSA Levels: Serum PSA levels decreased by approximately 50% after 12 months of dutasteride therapy. Reduction in serum PSA in patients taking 5-alpha-reductase inhibitors and its impact on prostate cancer detection is well recognized and this issue is adequately addressed in the label.

3.3 Testosterone Levels: Since 5-alpha-reductase inhibitors block the conversion of T to DHT, serum T levels do increase. The increase in serum T is approximately 20%. The clinical significance f this is unknown. This information is in the label.

3.4 Semen Quality: Five alpha-reductase inhibitors could potentially adversely affect semen quality. In Trial ARIA1009, the semen changes were studied in 30 volunteers on dutasteride 0.5mg. A 25% reduction in mean ejaculate volume and total sperm per ejaculate was observed. Two dutasteride treated patients did experience decreases in their sperm count to less than 10% of baseline at the end of 52 weeks of drug exposure. Both patients showed recovery at the 26-week follow-up visit. The clinical significance of these observations is unknown. However, the issue of semen quality is discussed in the label.

3.5 Blood donations: Because the terminal half-life of dutasteride is five weeks at steady state and dutasteride has the potential to cause fetal harm, there is concern about patients

on dutasteride donating blood that could be transfused into pregnant women. Based on calculations regarding how long dutasteride will remain in the blood after discontinuation, the primary medical officer and pharmacology/toxicology reviewer believe that blood donations should not be made for approximately 6 months following discontinuation of the drug. This information has been placed in the label.

3.6 ADME Issues: Because of technical, scientific or business reasons there were some deficiencies regarding the clinical and preclincal information regarding pertaining to absorption, distribution, metabolism and excretion of dutasteride. The paucity of metabolic information impacted on several areas including predicting carcinogenicity. The CAC agreed that dutasteride would be safe to administer to humans with appropriate labeling. Other issues such as drug/drug interactions, renal and hepatic impairment that are impacted by ADME of dutasteride are dealt with in the label or phase 4 commitments.

4.0 RISK/BENEFIT EVALUATION

The large controlled safety database submitted in the NDA did not signal that any serious adverse drug reactions, except perhaps allergic reactions, would occur after dutasteride is marketed. Smaller studies with administration of dutasteride at ten times the recommended dose for six months also seemed reassuring. The adverse event profile of dutasteride appears similar to finasteride, the only other 5 alpha reductase inhibitor currently on the US market.

The benefit to patients with BPH of dutasteride is moderate and its efficacy appears to be very similar to finasteride. There are potential risks with this class of compounds, which have been discussed in section 3.0. In addition, there may be additional unknown risks with dutasteride because of the paucity of clinical and preclincal ADME information.

The sponsor, however has presented substantial evidence that indicates that dutasteride is both safe and effective for the proposed indication.

5.0 RISK MANAGEMENT ASSESSMENT

As previously mentioned, the risks identified with dutasteride and 5-alpha reductase inhibitors in general are handled by statements in the PPI and PI. In addition, more controlled safety data will be available to the Division as the major trials will continue up to four years and additional safety data will be submitted with efficacy supplements after the initial approval.

6.0 CONCLUSIONS AND REGULATORY RECOMMENDATIONS

I concur with the primary reviewer and medical team leader that dutasteride should be approved if agreements on the labeling and phase 4 commitments can be reached with the sponsor.

Daniel A. Shames MD
Acting Director
DRUDP/CDER/FDA

NDA 21-319

Supervisory Medical Officer's Memorandum

FROM:	**Mark S. Hirsch, M.D.** **Medical Team Leader, HFD-580**
TO:	**Flo Houn, M.D.** **Office Director, ODE-3**
THROUGH:	**Dan Shames, M.D.** **Acting Division Director, HFD-580**
DATE:	**November 9, 2001**
REGARDING:	**Recommendations for regulatory action - NDA 21-319**
SPONSOR:	Glaxo Wellcome Inc
DATE SUBMITTED:	December 21, 2000
CDER STAMP DATE:	December 21, 2000
DIV DOC ROOM DATE:	December 22, 2000
DRUG PRODUCT:	*Trade name*: DUAGEN™ *Established name*: dutasteride *Code name*: GI198745
DOSAGE: **ROUTE:** **DOSAGE REGIMEN:**	0.5 mg oral soft-gelatin capsule take one 0.5 mg soft-gelatin capsule by mouth daily
DRUG CLASS: **PROPOSED INDICATION:**	5-alpha reductase inhibitor "Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enalrged prostate gland."
RELATED INDs:	IND # [redacted]

Table of Contents

1. Materials used in conducting the review:

In arriving at my decision, I conducted a supervisory medical review of the following items:

From the original NDA:

1. Integrated Summaries of Efficacy (Volume 1.274) and Safety (Volume 1.276)
2. Narrative portions of final study reports for Studies ARIA3001 (Volume 1.160), ARIA3002 (Volume 1.185), and ARIB3003 (Volume 1.211).
3. Clinical data summary (Volume 1.1)
4. Proposed annotated physician and patient package inserts
5. Minutes of all previous FDA/sponsor interactions
6. 4-month Safety Update
7. Narrative portion of the final study report for ARIA2001 (1.242)

Draft review by the primary medical officer:

Dr. George Benson's primary medical review: containing individual reviews of "pivotal" studies ARIA3001, ARIA3002, and ARIB3003, an integrated summary of safety (ISS), a review of the 120-Day Safety Update (SU), and individual reviews of ARIA1009 ("semen study"), ARIB3004 ("urodynamic study"), and ARI10010 ("QT study").

Consultation reports:

1. Dr. Jennifer Fan's (OPDRA) Proprietary Name Review – dated September 6, 2001
2. Dr. MaryAnn Gordon's (Division of Cardio-Renal Drug Products, DCRDP) Consultation – dated July 30, 2001
3. Ele Ibarra-Pratt's (DSI) Evaluation of the Clinical Site Inspections – dated September 7, 2001

4. Barbara Chong's (DDMAC) Draft Review of Proposed Physician Package Insert – received on September 26, 2001
5. Karen Lechter's (DDMAC) Draft Review of Proposed Physician Package Insert – received on September 26, 2001

2. Executive summary:

2.1. Recommendation:

The purpose of this memorandum is to provide the Office Director with the supervisory medical officer's recommendation regarding this request for marketing approval.

In my opinion, dutasteride should be **approved** for marketing at this time.

This application should be approved because:

1. Clinical effectiveness, as defined by acceptable treatment parameters for symptomatic BPH in men with an enlarged prostate, was demonstrated in three multi-center, randomized, trials (including a total of 4324 patients).
2. The overall clinical safety database, as collected in adequate controlled and uncontrolled human trials, demonstrated an overall benign adverse event profile. Clinical safety information was collected in a large number of appropriate patients for one year (N=1772), a smaller number for 2 years (N=455), and a smaller number at ten-fold that dose for 6 months (N=55). In my opinion, this experience represents a robust human safety database.

Nevertheless, I agree with my collegues in clinical pharmacology that the sponsor should conduct **Phase 4 investigations** to more fully elucidate the metabolism of dutasteride. The details of that commitment are still being negotiated with the sponsor at the time of this review.

It is important for the reader to understand that the final metabolic pathways for dutasteride are not yet fully elucidated. The liver appears to be the focus for metabolism and cytochrome p450 3A4 is probably the enzyme most involved. However, not all the pathways responsible for metabolism have been identified. In addition, there is no information relevant to the use of the product in those patients with hepatic dysfunction or those with renal dysfunction. There is also a limited amount of data from focused drug-drug interaction studies, especially in patients chronically taking concomitant potent cytochrome P450 inhibitors. Finally, we can account for the full disposition of the drug in only a very few subjects.

Clinically, this lack of complete information is important because:

1. For those patients with baseline concomitant hepatic dysfunction it is unclear how the drug will be handled by the body and whether presumed (and undetermined) higher exposures in these patients will result in clinical adverse reactions.
2. A similar question exists for patients chronically taking potent inhibitors of the cytochrome P450 3A4 system.
3. During the post-marketing period, if a previously undetected drug-related adverse reaction becomes evident, the management of such an event may be difficult because:
    a) the drug has a long half-life, and
    b) there is a real potential for drug accumulation in currently unidentified bodily tissues.

Nevertheless, I do not believe that these clinical pharmacology issues should preclude overall approval. I believe that the product has been demonstrated to be safe and effective in robust human trials. I believe that labeling should be adequate to manage the risks in special

populations (e.g. hepatic, renal, and concomitant medications). Finally, I believe that a Phase 4 commitment to conduct additional investigations into drug metabolism is a reasonable approach to the issue of missing clinical pharmacology data in this case.

2.2. Clinically relevant issues derived from other disciplines' reviews

2.2.1. Non-clinical pharmacology/toxicology

In her final review, overall, the primary toxicology reviewer (Dr. McLeod) found the NDA to be "**approvable, with changes to the label**". Changes to the label were suggested by Dr. McLeod and these were conveyed to the sponsor. At the time of the review, these items were under negotiation but it appears that the sponsor is willing to accept Dr. McLeod's labeling suggestions.

Dr. McLeod's 8-page summary and evaluation includes several items of importance to the clinician. These include:

1. Dutasteride was tested chronically in rats and dogs at multiples of parent drug greater than 200 times the expected clinical exposure. However, as Dr. McLeod notes, "it was discovered relatively late in drug development that metabolism is extensive in humans and low in the animal species used for toxicity testing. Although human exposure of all known major metabolites have been shown to be present in rats given very high doses of parent drug, the **metabolites**, which constitute a major proportion of human exposure, have been *minimally* studied for carcinogenicity, genotoxicity, and reproductive effect."

   Dr McLeod poses some potential safety issues regarding this issue as follows (page 5 of her review):

   "The effects of low metabolic coverage in animal studies, especially when metabolites may constitute the majority of drug to which humans are exposed, is to limit the information about margins of safety which might be expected for endpoints which cannot be studied in human populations. These endpoints might include carcinogenicity, reproductive toxicity, and low level chronic toxicity that are occasionally discovered by using large multiples of human dose in animal studies. Therefore, labeling of dutasteride should not include references that the drug has been studied in animals at many multiples of the human dose without discussion of the chemical species actually tested in those studies."

   Reviewer's comments:

   1. *According to the draft CAC minutes, dated August 22, 2001, and signed by Dr. Joe DeGeorge, "The parent drug and major metabolites were all studied at human exposure levels or higher (in carcinogenicity studies)." Thus, the study of the metabolites was considered "acceptable" by the CAC. It is thus also acceptable to this reviewer.*
   2. *Dr. McLeod's labeling suggestions were conveyed to the sponsor, are currently being negotiated, and appear likely to be accepted in total.*
   3. *Dr. McLeod's concerns appear valid to me. She notes that some "endpoints cannot be studied in human populations". I believe that this issue is particularly true for "low level chronic toxicity occasionally discovered by using large multiples of human dose in animal studies". However, the sponsor has submitted a substantial human safety database at the to-be-marketed dose, and even some chronic use information at ten times that dose, both of which are supportive of safety. Since approval is ultimately based on these human results, I do not believe that Dr. McLeod's concerns should preclude approval*

2. Dr. McLeod notes "In addition, it is possible that up to **55% of the fate of this drug** in humans is still unknown".

   Reviewer's comment: For more discussion of this particular issue please refer to Section 2.2.2. Clinical pharmacology and biopharmaceutics.

3. Drug-related clinical signs of toxicity in rats and dogs were primarily neurotoxic and were only seen at very, very high blood levels. These signs reversed when blood levels fell below "critical" levels (following drug withdrawal), but **reversal of drug-related toxic effects** required "several weeks".

   Reviewer's comment: Evidence of drug-related toxicity was seen only at exposures well above expected human exposure. This fact appears in the label. However, it is relevant to note that reversal of toxic effects required several weeks. This is not surprising given the long half-life of the drug. This could become clinically relevant in the management of unexpected toxicities noted in the post-marketing period.

   Although the potential for unexpected toxicities always exists in the post-marketing period, the safety database for this product is adequate to assess toxicity in humans at doses up to 10 times the to-be-marketed dose. Even at that exposure, the overall safety profile is good. Thus, in my view, this potential problem should not preclude approval.

4. **Adrenal effects** were observed in dogs and mice at relatively high doses. In rats and mice, the highest apparent concentration of dutasteride-associated radiolabel was in the adrenal at all measured times.

   Reviewer's comment: There was no evidence of adrenal toxicity in human (including the results from an ATCH stimulation test in normal volunteers). Nevertheless, it is interesting to note that dutasteride was found in highest concentration in rodent adrenal. Given its long half-life, dutasteride could accumulate in human adrenal as well. This is unknown since no radio-labeled mass-balance study has been conducted by the sponsor. At this time, there is no evidence that even if such accumulation were to occur, that it would result in detrimental clinical effects.

5. **Effects on other organs**, including the thyroid, pituitary, female reproductive organs, mammary glands, spleen, bone marrow, lungs and liver, were also observed at high doses in dogs.

   Reviewer's comment: To the best of my knowledge, these effects were noted only at exposures well above those anticipated in humans.

6. **Canine Purkinje fiber model** did not reveal a direct effect on potassium channels, however, "confirmation in HERG-transfected oocytes was not done" and "major human metabolites were not tested".

   Reviewer's comment: Assessment of the QT interval was conducted in humans using an optimal study design and very high exposures. There was no effect on the QT interval.

7. **Effects on male fertility and reproductive organs** was observed at 0.05 mg/kg/day in rats. This dose produced exposures equivalent to approximately 0.04 to 0.11 times the steady-state

clinical blood levels in men. The pathological findings included decreased weights of the prostate, seminal vesicle, and epididymis.

Reviewer's comments:

1. *This finding is consistent with the therapeutic (pharmacodynamic) effect of dutasteride.*
2. *Special studies were conducted in humans to assess the effect of dutasteride on semen parameters. These revealed a drug-related reduction in semen volume of approximately 25%, with corresponding reduction in total sperm count per ejaculate. Despite this reduction, mean parameters remained within normal limits and there was no effect on sperm concentration, morphology or motility. At the time of this review, labeling negotiations were underway to describe these findings in the PI.*

8. Although dutasteride is not intended for use by women, it has been postulated that **pregnant women could be exposed** through various forms of contact. For example, exposure could occur through direct contact with handling capsules, through blood donation, or through contact with semen of a male partner.

Via semen of a male partner

In the human male, a maximum concentration of 14 ng/mL has been measured in semen.

Dr. McLeod writes in her summary that in order to estimate the risk to an unborn fetus of an exposed woman, certain assumptions were made:

a. First, that a woman is exposed daily to 5 mL of semen from a dutasteride-treated partner,
b. Second, that all of a 70 ng dose is absorbed and fully crosses the placenta, and
c. Third, that the maternal blood volume is about 4000 mL.

Given these conditions, Dr. McLeod postulated that the potential fetal dutasteride blood level would be 0.0175 ng/mL. This estimate does not take into account the high level of protein binding in the semen that is likely to reduce vaginal absorption nor does it comment upon the duration of such daily vaginal exposure.

Studies were conducted in rats, rabbits, and primates to estimate the potential risk of fetal exposure through seminal dutasteride. In one study using pregnant Rhesus monkeys, dutasteride was injected intravenously during 80 days of gestation.

Potential for feminization

For the pregnant Rhesus monkey study, Dr. McLeod writes, "No effect on anogenital distance (marking the feminizing effect of 5-alpha reductase inhibition) was observed at doses resulting in blood levels ranging from 4 to 16 times estimated blood levels of women exposed through a treated partner."(that is, blood levels of 0.07 ng/mL to 0.28 ng/mL compared to the postulated potential blood level of 0.0175 ng/mL)

Dr. McLeod believes that the steady-state blood level that would put a fetus "at-risk" for feminizing effects (e.g. lengthening of the anogenital distance) would have to be higher than 0.07 ng/mL (the no-effect level) and would most likely be higher than 2.0 ng/mL (the low-effect level).

The blood level of 2.0 ng/mL was derived from a study in rats, where "some evidence of feminization was observed at blood levels of 2.0 ng/mL (>100 times) along with a decrease in fetal body weights."

For rabbits, Dr. McLeod notes that "feminization was observed after blood levels of 5 to 15 ng/mL (>200 times) were maintained during gestation (no-no effect level was established)."

Finally, Dr. McLeod points out that "No information regarding metabolites in rabbits or monkeys is available."

Potential for effects on other organs
For the pregnant Rhesus monkey study, Dr. McLeod notes however that "effects on adrenal, testis, ovarian, and prostate weights were observed at those doses"(page 5). Specifically, she wrote, "Reduction of adrenal weights, reduction in prostate weights, and increases in ovarian and testis weights were observed at the high dose. at blood levels ranging from 4 to 16 times human levels."(page 55).

Thus, for an effect on fetal adrenal, prostate, testis and ovary weight, Dr. McLeod believes that the steady-state blood level that would put a fetus "at-risk" would have to be higher than 0.05 ng/mL (again, the no-effect level). For purposes of comparison, the potential fetal blood level was postulated to be 0.0175 ng/mL under the worst-case scenario.

I reviewed Dr. McLeod's findings in this particular trial. The table on page 53 of her review describes the necropsy findings in the five dose groups. I've re-compiled the most clinically relevant data herein:

Table 1: Necropsy evaluation in Pre-clinical Study no. P40366: Intravenous Embryo-Fetal Study in the Rhesus Monkey.

Corrected dose (ng/day)	**0**	**400**	**780**	**1325**	**2010**
Anogenital distance (mm)					
-Males	43	44	45	44	42
-Females	14	13	14	14	13
Adrenal weights (% of control)					
-Males	--	-10.7	-18.0	-18.9	-23.8
-Females	--	- 8.1	-25.0	-25.2	-19.2
Ovary weights (% of control)	--	136	-5.8	1.7	20.3
Testes weights (% of control)	--	8.9	-2.5	5.0	23.0
Sem ves weights (% of control)	--	2.4	15.8	-2.7	-8.7
Prostate weights (% of control)	--	-0.7	0.8	-3.5	-13.4

Based upon her concerns for the fetal adrenal, prostate, testes and ovary (especially the adrenal), Dr. McLeod asked Dr. Karl Lin of Biometrics to formally review these

particular results. In particular Dr. Lin was asked to focus on the fetal adrenal, prostate, testes and ovaries.

Dr. Lin concluded in his draft memo (dated 11/9/01) that "the group means of fetal adrenal weight of the five treatment groups are not statistically significant based on the global test in the analysis of variance. After adjusting for the effect of multiple testing, the results of the pairwise comparisons between the control group and each of the treated groups show that there is also no statistical difference in fetal adrenal weight between the pairs of groups compared."

However, Dr. Lin makes the following comments about the study:

1. The study was not adequately powered to detect statistical differences based on too small numbers of fetuses in the study.
2. "The test results show that the slope of the means of the fetal adrenal weight is statistically significant from zero. That is, there is a statistically negative trend in mean group weights of this organ."
3. "The group means are not statistically significant among the treatment groups for fetal prostate weight and testes weight"
4. "The slope of the group means is not statistically different from zero for the fetal prostate, testes, and ovaries weights".
5. "However, the group means of fetal ovaries weight are statistically significant among the treatment groups."

Thus based upon Dr. McLeod's and Dr. Lin's review of this data, a conclusion was drawn that a reduction in fetal adrenal and prostate weights, and increases in ovarian and testes weights was seen in the highest dose group. This dose resulted in blood levels ranging from 4 to 16 times estimated blood levels of women exposed through a treated partner. (That is, blood levels of 0.07 ng/mL to 0.28 ng/mL compared to the postulated potential blood level of 0.0175 ng/mL).

Despite this finding, Dr. McLeod still informs me that condom use is not considered necessary and that labeling is considered adequate to convey this remote risk.

Thus, overall, Dr. McLeod concludes that the risk of transmission of teratogenic concentration of dutasteride through semen is low. However, she makes no formal recommendation about the need (or lack of need) for condom use while taking dutasteride.

Reviewer's comment: Based on these results, I believe that the risk of feminization of the male fetus via seminal transmission of dutasteride is highly remote and would not require the use of a condom.

Based on Dr. Lin's review, I also believe that the risk of decreased fetal adrenal and prostate weight, and increased ovarian and testes weight via seminal transmission of dutasteride is also remote and would also not require use of a condom. I believe that the label adequately describes the findings of this trial.

Via handling of capsules

Dr. McLeod writes that "a woman exposed to dutasteride through transfusion or handling of broken tablets must absorb enough drug to produce steady-state blood levels greater than

0.05 ng/mL to be at risk for effects on fetal adrenals or reproductive organ weights, greater than 0.07 ng/mL (no-effect level with a low-effect level at about 2 ng/mL) to be at risk fior feminization of a male fetus, and greater than 74 ng/mL to be at risk for other reproductive effects."

She continues: "Some evidence of male fetus feminization might be expected if a woman were to absorb an average daily dose of 5% of a 0.5 mg tablet."

Reviewer's comments:

1. *Dutasteride is supplied as a soft-gelatin capsule, not a tablet.*
2. *According to Dr. McLeod's review, there was no evidence of fetal anogenital distance changes in the pregnant Rhesus monkey study at any dose.*
3. *According to Dr. McLeod's review, there is only a very remote risk of other fetal organ toxicity derived from the pregnant monkey study.*
4. *The scenario of a woman of child-bearing potential absorbing 5% of a 0.5 mg tablet daily (for an unspecified duration of time) may not be realistic.*
5. *Nevertheless, the label contains warnings that clearly address the risk of potential transdermal absorption of dutasteride and recommend caution for women handling dutasteride.*

Via blood donation

The average serum concentration of a man taking 0.5 mg dutasteride daily is approximately 40 ng/mL. A single blood transfusion (or "unit") contains 200 to 250 mL. When transfused, many recipients receive 2 units.

Dr. McLeod writes: "If a woman normally having 4 liters of blood is administered 0.5 liter of blood containing dutasteride, her initial (dutasteride) blood concentration would be about 5 ng/mL" As discussed above, such a blood level could represent a risk for male fetal feminization. Thus, Dr. McLeod advises: "Warnings against donation of blood from dutasteride treated patients should be in the drug label for the protection of pregnant women."

Reviewer's comment: After further discussion with the Office of Blood Application, CBER, I agree with Dr. McLeod and the Division proposed such a warning in the PI. This label change is currently under negotiation with the sponsor. At this time, it appears that the sponsor will accept such labeling, albeit in the Precautions section rather than the Warnings section.

9. Dr. McLeod writes that in the two-year carcinogenicity studies, "there was a significant increase in female **mouse hepatocellular adenomas** at the high dose of 250 mg/kg/day (290 times the clinical dose of parent drug. There was no neoplastic effect in male mice at 500 mg/kg/day (270 times the clinical exposure of parent drug." These findings were not noted in rats. Dr. Mcleod notes that this finding should be reported in the label

   Reviewer's comment: Dutasteride is not indicated in females. While I agree that this finding should be reported in the label, I do not believe that this is a clinical concern.

10. Dr. McLeod writes that in the two-year carcinogenicity studies, "there was a significant increase in **Leydig cell adenomas in male rats** at 53 mg/kg/day and in hyperplasia at 7.5 and 53 mg/kg/day (52 and 135 times the clinical exposure of parent drug).

    In assessing the clinical importance of this finding, Dr. McLeod poses the following issues:

a. A literature reference (Cook et al) states that while a non-genotoxic, 5-alpha-reductase inhibitor-induced increased in LH is probably "relevant" in humans, the no-observed-effect level for the induction of these tumors in rodents provides an adequate margin of safety for protection of human health.
b. In these rodent studies, the tumorigenic dose level was associated with a 167% increase in LH after 80 days of dosing. In man, LH was reported to rise by 19% after one year of treatment.
c. Such tumors were also noted in rodents treated with finasteride (Proscar) at LH levels that were only 2 to 3-fold above baseline.
d. It appears that humans are less sensitive than rodents to the "tumorigenic" effect of LH on the Leydig cell.

Reviewer's comment: Dr. McLeod believes that this finding should be included in the label and I agree.

11. Dr. McLeod refers to several issues she believes are important in the interpretation of the **carcinogencity studies**. Herein, I will try to delineate these:

a. "The metabolite mixture to which humans are actually exposed was minimally tested in rats, but not in mice".
b. "The multiples of parent drug in rat carcinogenicity studies were nearly 300 times the expected drug levels in humans, but analysis of known human metabolites in human and rat serum indicate that rats were not exposed to significantly more than the human dose of the known metabolites during the course of these lifetime studies."
c. "Similarly low percentages of some of the human metabolites were also present in mouse serum.
d. "The fate of possibly 55% of administered drug is not known."
e. "and, no judgement of the validity of the carcinogenicity testing with regard to this material can be made, except that profiles in animals appeared to be similar to humans by mass spectrometry."

12. In concluding her review, Dr. McLeod provides an "internal comment". This comment, which I believe is intended for the medical officer, describes several apparent **weaknesses in the pre-clinical reproductive toxicology studies**. Specifically, Dr. McLeod states:

"The reproductive effects of this drug have been minimally assessed in animals and humans due to:
-low concentrations of major human metabolites in rats,
-no knowledge of major human metabolites in rabbits and monkeys, and
-few pregnancies in the course of clinical trials."

Dr. McLeod warns in this internal comment that "Ultimately, any true risk for human reproductive effects will most likely be assessed through monitoring of human populations." But, "It should be considered that a pregnancy registry, if ever needed, might be difficult to establish since the patient taking the drug is not the mother of the child."

Reviewer's comments:

1. *The reviewer is aware that studies in rats used a dose that provided exposures of major metabolites approximately equal to human exposure. It is my understanding that this was considered adequate by the pharmacology/toxicology team leader and management.*
2. *The reviewer is aware of the difficulties inherent to a pregnancy registry for this drug. We have faced similar problems in analyzing these types of sporadically reported adverse events with finasteride (Proscar). During this review cycle for dutasteride, this particular issue was presented to representatives of OPDRA at a formal briefing. They are aware of the need for heightened sensitivity to these reports.*
3. *The fact that we have "no knowledge" of major human metabolites in the sera of monkeys appears to me to be a valid concern. If it is true that human metabolites were not studied in the pregnant Rhesus monkey study, the conclusions that can be drawn from that exploratory study are even more limited. Despite this lack of information, our pharmacologists do not suggest that the sponsor undertake additional testing in the monkey to search for such metabolites. The reason for their decision (as described by Dr. McLeod in a briefing to the review team on November 8th) is that:*

    a. *Some "linkage" was actually noted between the substances in rat sera and those in monkey sera. In short, all species eventually did show some evidence, albeit at low levels, of the same metabolites. These metabolites showed evidence of being similar to dutasteride in pharmacological activity.*
    b. *Virtually all conclusions from this "monkey study" should be considered "scientifically exploratory" anyway.*

    In assessing the need for additional pre-clinical studies (e.g. Phase 4 type investigations), I accept the opinion of my pharmacology collegues that these are not necessary.

2.2.2. Clinical pharmacology and biopharmaceutics

In summating his final draft review dated October 5, 2001, Dr. Al-Habet wrote:

> "Based on the information submitted this NDA was **found to be deficient** from clinical pharmacology and biopharmaceutics perspective. However, based on the information available on safety and efficacy, discussion with review team, and OCPB management, this NDA is **acceptable** provided that the sponsor addresses these deficiencies as Phase IV commitments. These deficiencies are listed below:"

Dr. Al-Habet then lists 4 deficiencies delineated herein:

Deficiency #1: "Approximately **55% of the administered dose is unaccounted for**. In addition, the metabolism and metabolic pathways were not adequately determined."

Reviewer's comment: There are actually two major issues in this one comment.

1. The first issue refers to 55% of the administered dose being "unaccounted for".

To place this issue into context, the reader should understand that in many new drug applications, the reviewers are provided the results of a "mass-balance" study. In the most typical "mass-balance" study, the drug-product is radio-labeled and administered to a subject. The excreta are then collected until the "balance" of the drug product has been re-captured. For this NDA, the sponsor did not conduct such a study. In explaining the reason for not conducting such a study, the sponsor argued that it was unethical and unsafe to expose subjects to many weeks of radioactivity. While the sponsor agreed that a single-dose radio-labeled study may have been ethically feasible, they argued that such a study would not provide relevant information.

Instead, the sponsor incorporated a different type of mass-balance study into an ongoing multiple-dose clinical trial (ARIA 1009). A small number of subjects (N=8) were enrolled into this "substudy" and in these patients, the flourine atom in the dutasteride molecule was "tracked" using NMR. Samples of excreta (feces, urine) were examined using flourine-NMR. The results of this revealed were "mixed", in that most of the dose could be "accounted for" in only a few subjects. The range of collected flourine was actually 5% (lowest amount collected) to 97% (greatest amount collected). In assessing the results of this study, Dr. Al-Habet concluded "approximately 55% of the administered dose was accounted for".

In order to mitigate this lack of information, Dr. Al-Habet recommended a Phase 4 commitment of a mass-balance study. This recommendation was posed to the sponsor who argued against carrying out a full mass-balance study on the basis of feasibility.

In regard to this issue, in her team leader's memo (dated November 6th), Dr. Parekh wrote: "It was agreed that a concept protocol would be proposed by the sponsor. This should be submitted within 1 month of the Action Letter date. Following the FDA review of this proposal, the feasibility and conduct of this study will be discussed with the sponsor."

It is notable that such a "concept protocol" for a mass-balance study was actually submitted by the sponsor and received by the Division on November 6th.

Reviewer's comment: I am in agreement with the handling of this issue.

2. The second issue refers to **"inadequate" determination of the metabolic pathways** for dutasteride. Dr. Al-Habet elaborates on this particular issue in his final 3 deficiencies, as follows:

> **(Deficiency #2)**: "The identification of the isoenzymes responsible for the metabolism of dutasteride have not been appropriately characterized. The available data from in vitro study (sic) show that CYP 3A4 is responsible for approximately 5% of the metabolism of the drug. No other isoenzymes were found or identified that can be responsible for the metabolized of dutasteride (sic). This may be due to the high concentration of dutasteride used in this study. However, based on in vivo data, the drug is extensively metabolized to approximately 11 metabolites (four major and 6 minor)."
>
> In regard to this issue, the sponsor has agreed to conduct a Phase 4 study to investigate in vitro metabolism using therapeutically relevant dutasteride concentrations to characterize

the metabolic pathways. A draft protocol for such a study was submitted by the sponsor and received by the Division on November 6th. Dr. Parekh would like the formal protocol submitted within 1 month after receipt of the Action Letter date. She would like the study completed within the next 3 months of that date. She would like the results of the study submitted to the Agency within 6 months of completing the study. In the meantime, we have carefully described all known information about metabolism in the package insert.

Reviewer's comment: I am in agreement with the handling of this issue.

(Deficiency #3): "Due to inadequate information on metabolism of the drug, it is difficult to predict any potential drug-drug interaction with dutasteride."

Based upon the limited information at this time, Dr. Al-Habet proposed that the most relevant study to undertake in order to understand potential drug-drug interaction would be a Phase 4 "drug interaction study with ketoconozole in humans." The sponsor argued against conducting such a study since the dutasteride has a long half-life and they believed that a single dose, drug interaction study with ketoconozole would not be therapeutically relevant.

In regard to this issue, the minutes of a teleconference between Dr. Parekh, Dr. Malinowski and the sponsor, state: "Rather than conducting a study that is not relevant, it was agreed that this concern related to drug interactions with chronic potent CYP 3A4 inhibitors would be addressed appropriately in the label".

In her memo, Dr. Parekh wrote: "In subsequent labeling discussions with the clinical team and OCPB, it was decided that information regarding lack of study in drug interaction potential should be included in the Clinical Pharmacology and Precautions sections (of the label)". The sponsor has agreed with this proposal and has carried out appropriate labeling changes.

Reviewer's comment: I am in agreement with the handling of this issue.

(Deficiency #4): "Since the drug is extensively metabolized and a study in hepatic impaired subjects has not been undertaken, it should be contraindicated in patients with hepatic impairment."

In regard to this deficiency, Dr. Al-Habet proposed that "the sponsor may consider conducting a study to investigate the effect of hepatic impairment on the PK of dutasteride." Again, the sponsor argued against conducting such a study, stating that no such study was done during dutasteride's development to date and none was intended.

In regard to this issue, the minutes of a teleconference between Dr. Parekh, Dr. Malinowski and the sponsor, state: "In absence of this study, it was agreed that this information could be addressed in the label and an additional study in hepatically impaired patients would not be a requirement and will be left to the sponsor's discretion."

In her memo, Dr. Parekh wrote: "In subsequent labeling discussions with the clinical team and OCPB, it was decided that information regarding lack of study in hepatic patients should be included in the Clinical Pharmacology and Precautions sections (of the

label)". The sponsor has agreed with this proposal and has carried out appropriate labeling changes.

Reviewer's comment: I am in agreement with the handling of this issue.

Finally, Dr. Al-Habet noted that "the Agency is still awaiting the population pK analysis to verify certain drug-drug interaction claims. For example, data regarding increase in dutasteride exposure by 37% to 44% with calcium channel anatagonists should be submitted."

Ultimately, it was realized that such information had been submitted with the original archival NDA, but had not been submitted in the clinical pharmacology reviewer's desk volumes. The sponsor sent in a replacement reviewer's copy. This was reviewed and appropriate information was included in the label.

Reviewer's comment: Thus, this issue is considered resolved pending final agreement on labeling.

2.2.3. Biometrics

Dr. Hoberman's reported that he "re-checked" the sponsor's analyses of the primary and secondary endpoints". He states that "the consistently reported **p-values in the range of .001 were confirmed**."

A minor issue related to the reporting of prostate volumes in the PI was noted. The sponsor has since modified that section appropriately to accommodate Dr. Hoberman's comment.

2.2.4. Chemistry, manufacturing, and controls

The chemistry team leader's review stated that "From chemistry, manufacturing, and controls point of view, as the primary reviewer recommends, this NDA may be **approved**."

Of note, 36-month of shelf life was "granted based on "real-time data". In addition, "all test methods and acceptance criteria (for *specifications*)" were considered "adequate after being appropriately tightened to reflect the manufacturing experience and stability data."

One chemistry issue that still remains somewhat unclear to this reviewer is the issue of the *tradename.*

The sponsor's proposals of "DUAGEN" and "ZYGARA" were found to be not acceptable by OPDRA based on potential for medication error. In the case of "Duagen", OPDRA's review revealed a potential for prescription "look-alike" to the oral contraceptive "Desogen". In the case of "Zygara", OPDRA found a potential for prescription "look-alike" to the antipsychotic "Zyprexa". Clinically, I agree with the rejection of both these tradenames.

In his team leader memo, Dr. Rhee writes, "The sponsor made a commitment that when they create a new tradename after this NDA is approved, it will be submitted to the Agency before it is used in the labeling including labels of container and cartons." This issue was discussed between Dr. Rhee and the sponsor in a tcon dated October 10, 2001 and was re-stated in writing in a fax from the sponsor to the Division dated October 17, 2001. The sponsor wrote, "We acknowledge that if NDA 21-319 is approved without a tradename, GSK will submit a tradename for Agency's review and approval either as a labeling supplement or as part of a supplemental NDA containing 2-year efficacy and safety data".

Reviewer's comment: This agreement seems reasonable to me.

3. *Summary comments pertaining to efficacy:*

3.1.Overview

Dutasteride blocks the conversion of testosterone to dihydrotestosterone; it acts as an inhibitor of 5-alpha-reductase. There are actually two isozyme forms of 5-alpha-reductase, Types I and II. Type II is found predominantly in the prostate and Type I in the liver, skin and brain. Finasteride (or Proscar®) is an approved Type II 5-alpha-reductase inhibitor, while dutasteride inhibits both subtypes. Proscar 5 mg daily is approved for the treatment of symptomatic BPH in men with an enlarged prostate gland.

Symptom relief with Proscar is known to be modest, both in terms of reduction in symptom score and in improvement in urinary flow rate. However, Proscar has also been demonstrated to reduce long-term negative clinical outcomes including the incidence of acute urinary retention (AUR) and the need for BPH-related surgical procedures. I believe that this linkage between modest symptom relief and long-term benefit serves to significantly enhance the benefit profile of this type of product. Symptom relief is considered to be more pronounced and more rapid with the alpha-receptor sympathetic antagonist type drugs (e.g Flomax ®, Cardura ®, Hytrin ®) but long-term urological outcomes have not yet been assessed with these types of drugs.

In embarking on this development, the sponsor proposed that the blockade of two 5-alpha-reductase isozymes might ultimately be shown to have clinical benefit over blocking a single isozyme in terms of improved suppression of DHT, increased prostate volume reduction and subsequent symptom relief and improvement in long-term outcomes. The NDA submitted at this time contains the results of three individual, robust, 2-year long, placebo-controlled, Phase 3 trials. This NDA focuses on the 1-year timepoint. Some safety information is available at 2-years exposure. Some information is available at 10 times the to-be-marketed dose. The sponsor plans to submit a major efficacy supplement in approximately 1 year, after the results of long-term follow-up become known. This supplement is intended to include data about incidence of AUR and BPH-related surgery.

3.2. Primary efficacy analysis:

In my opinion, the results of three adequate and well-controlled Phase 3 clinical trials demonstrate that dutasteride was shown to be effective in relieving symptoms and signs associated with benign prostatic hypertrophy (BPH) in men with an enlarged prostate gland. The clinical benefit, while numerically modest, is in line with similar benefit reported for finasteride, and could imply long-term benefit (e.g. avoidance of AUR and BPH-related surgery).

The primary medical officer's review presents the efficacy data in great detail. Herein, I will present a brief outline of the same data.

In selecting the dose for Phase 3, the sponsor used the results from the Phase 2 studies ARIA 1003 and ARIA 2001. In these studies, it was determined that 0.5 mg was the lowest maximally effective dose in terms of DHT suppression and reduction in prostate volume. Of note, the 0.01 mg dose appeared to be ineffective in terms of suppression of DHT and reducing prostate volume. The 5.0 mg dose appeared to have a similar efficacy to the 0.5 mg dose but was slightly less well-tolerated (increased incidence of diminished libido).

Three Phase 3 studies were undertaken to confirm the effect of dutasteride 0.5 mg relative to placebo on treating symptomatic BPH in men with an enlarged prostate. These were entitled

ARIA 3001, ARIA3002, and ARIB3003. These were virtually identical, large, multi-center, randomized, placebo-controlled studies. The former two were conducted entirely in the U.S. and the later in 19 countries. Each was designed as a 4-year trial with a 2-year placebo-controlled period and a 2-year open-label extension. The results presented in this NDA reflect only the first year's efficacy experience. The two-year results are intended to support and efficacy supplement. Of note, each of these studies was designed to assess primary efficacy after a full 1-year placebo-controlled treatment period.

The primary efficacy endpoint for all three trials was the change from baseline at 12 months in the American Urological Association Symptom Index (AUA-SI). This is a validated questionnaire that is considered acceptable as a primary endpoint in trials of this sort. It is scored on a 0-30 basis, where 30 is the worst possible symptoms and zero is the best. The symptom score is obtained monthly. The change-from-baseline results are compared between active and placebo groups.

In one study (ARIA 3002), a statistically significant difference between groups was noted by Month 3 and maintained through Month 12. In the other two studies, significant differences were noted at Month 12.

When the studies are pooled at Month 12, the clinical effect becomes more evident. The mean change-from-baseline in the drug group (N=2119) was –3.3 units versus –1.2 units for the placebo group (N=2122). The sponsor has originally powered each study to detect a mean difference between groups of 1.5 units. This numeric difference was noted in ARIA 3002, but was slightly less in both ARIA 3001 and ARIB3003. Nevertheless, the 95% confidence interval sorrounding the point estimate for mean difference included 1.5 units in both ARIA 3001 and ARIB 3003.

In my opinion, these results reveal strong evidence of a drug effect on improvement of voiding symptoms. This effect, in my opinion, is clinically meaningful on its own. While modest benefit was enjoyed across the entire population, some patients enjoyed more substantial benefit than others. In addition, this modest mean benefit across the entire group may actually translate into substantial long-term clinical benefit in terms of reducing AUR and BPH-related surgery.

Below, in table 2, these results are depicted in tabular format:

Table 2. AUA-SI Change-from-Baseline

	ARIA3001 *Placebo*	Dutasteride	**ARIA3002** *Placebo*	Dutasteride	**ARIB3003** *Placebo*	Dutasteride
Month 1	*N=706*	N=703	*N=664*	N=677	*N=723*	N=737
Mean	*-1.4*	-1.3	*-1.2*	-1.2	*-1.4*	-1.5
Mean difference		0.1		0.0		-0.1
p-value		0.81		0.98		0.78
Month 3	*N=709*	N=705	*N=670*	N=663	*N=738*	N=750
Mean	*-2.1*	-2.3	*-1.8*	-2.4	*-2.8*	-2.7
Mean difference		-0.2		-0.6		0.0
p-value		0.39		**0.032**		0.90
Month 6	*N=709*	N=705	*N=671*	N=664	*N=741*	N=750
Mean	*-2.4*	-2.9	*-1.9*	-2.7	*-2.8*	-3.4
Mean difference		-0.5		-0.8		-0.6
p-value		0.12		0.008		0.038
Month 12	*N=709*	N=705	*N=671*	N=664	*N=742*	N=750
Mean	*-2.0*	-3.0	*-1.3*	-2.8	*-2.9*	-4.1
Mean difference		-1.1		-1.5		-1.2
p-value		<0.001		<0.001		<0.001

The secondary efficacy endpoints for all three trials were prostate volume (PV) and maximum urinary flow rate (Qmax). The sponsor analyzed these endpoints in a "heirarchical" fashion, with AUA-SI first, prostate volume second, and maximum flow rate, third.

Significant reductions from baseline in mean prostate volume were noted in each study in the dutasteride group at the earliest measured points. These reductions increased at each measurement. The reductions in the placebo group were negligible. When these results were compared between treatment groups, the differences were statistically significant at the earliest measured timepoint in each study. At Month 12, for the pooled studies, the mean percent decrease in prostate volume was –24.6% for dutasteride versus –3.4% for placebo. That mean difference (in the pooled studies) equaled –21.2% (range across the three studies of –20.9% to –21.5%).

The reader should understand that reductions in prostate volume alone do not necessarily imply reduction in symptoms. Thus, when analyzing this "pharmacodynamic" endpoint (similar to changes in serum DHT), one should ask: "Does this reduction in prostate volume imply clinical benefit." In my opinion, clinical benefit lags behind prostate shrinkage by several months and ultimately, prostate shrinkage tends to be more impressive than actual relief of symptoms.

Maximum urinary flow rate increased from baseline in both the treatment group and the placebo group in all three studies. The differences in change-from-baseline improvement were statistically significant at Month 1 in ARIA 3001 and at Month 3 in the other two studies. At Month 12, for all three trials pooled, the mean increase in Qmax was +1.6 mL/sec for dutasteride and +0.7 mL/sec for placebo. This mean difference equaled +0.9 mL/sec with a range across the three studies of +0.7 to +1.1 mL/sec.

When assessing these data for clinical significance, the reader should be aware that patients were not randomized if their baseline Qmax was >15 mL/sec. In actuality, the mean baseline value in the pooled studies was 10 mL/sec. Thus, in my opinion, a very small mean change (e.g. +1.6 mL/sec) represents a modest but potentially clinically meaningful improvement. Of course, some of the better responders will enjoy a substantially better improvement in flow than the mean value. I conclude that this improvement in maximum flow is of modest clinical benefit. However, it has been repeated in three large Phase 3 trials and it is consistent with historical finasteride data. Again this improvement may actual portend a clinically meaningful benefit in terms of reduction in AUR and need for BPH-related surgeries.

3.2. Benefit over available therapies (efficacy):
In my opinion, no evidence has been presented to substantiate a clinical benefit of dutasteride over the existing product (finasteride) in terms of efficacy.

It must be acknowledged that there is very little head-to-head data to analyze, and that cross-NDA comparison is fraught with bias. However, when the results of numerous finasteride publications are assessed it becomes clear that these dutasteride results are in "the same ballpark" with the historical finasteride data in terms of effects on symptom relief, urinary flow improvement, and prostate shrinkage.

It remains to be seen if the long-term outcomes (e.g. AUR and BPH-related surgery) will be affected by dutasteride and how that effect will compare to historical finasteride data.

4. Summary comments pertaining to safety:
4.1 Overview
4.1.1. Potential teratogencity
As previously stated, dutasteride is a 5-alpha-reductase inhibitor. As such, its pharmacological effect is to reduce the blood levels of DHT. In that regard, it induces regression of the prostate and seminal vesicles. This becomes an issue in a discussion of potential teratogencity. Previously in this review, the issue of potential harm to a fetus has been discussed. The various routes by which this could occur have been analyzed (blood transfusion, semen, and transdermal). Methods of risk prevention, including informative labeling, have been discussed in previous sections.

4.1.2. Safety implications of clinical pharmacology issues
Further, dutasteride has a terminal elimination half-life of approximately 5 weeks. This implies a long "wash-out" in the event of the need to stop the drug for an adverse reaction. It also implies accumulation in the bodily organs, currently unspecified. The lack of information in the hepatically-impaired population and in those taking chronic potent inhibitors of cytochrome P450 3A4 is an issue to consider when discussing potential toxicity of high-level dutasteride exposure. These issues have also been discussed in previous sections of this memo.

4.1.3. Safety issues notable in the class
Finasteride, the only approved 5-alpha-reductase inhibitor, has been marketed for many years and overall has been associated with a fairly benign adverse event profile. Reports of substantive controlled pre-marketing clinical investigations as well as extensive post-marketing experience reveals a safety profile notable only for effects on libido, erectile function, breast irritation/benign growth, and ejaculate volume. The reviewer acknowledges that the adverse event profile of dutasteride may still be different than that of finasteride.

4.1.4. Safety database in the NDA

Safety data for this NDA was collected from a total of 5305 patients enrolled in 19 completed studies in the U.S. and 18 other countries. There were 4324 patients in the Phase 3 trials, including 2166 who received dutasteride 0.5 mg daily.

Approximately 1726 patients received dutasteride for at least 1 year and 455 patients for at least 2 years. Overall, the sponsor claims that there has been 1866 patient-years of exposure to dutasteride. Safety data is available on 57 patients who received 5.0 mg daily for 6 months

The vast majority of exposure was in the appropriate patient population (e.g. mean age 66.5 years with a range of 50-94). Focused studies were conducted in humans to assess the potential effects of dutasteride on semen quality, on the QT interval, on bone mineral density, on plasma lipids, on adrenal function.

Reviewer's comment: Overall, this is considered a robust human safety database.

4.2. Overall adverse reactions

Overall, the adverse reactions noted in this application were consistent with alfuzosin's known and expected pharmacological action as a 5-alpha-reductase inhibitor. These were generally mild to moderate in severity and transient. As previously discussed, this type of compound has been associated with such adverse events as erectile dysfunction, diminished libido, ejaculatory disturbance, gynecomastia and breast tenderness.

Overall, 64% of patients reported any single adverse event in the dutasteride group versus 63% in the placebo group. Of these, investigator-assessed "drug-related" adverse events were reported by 13% and 12%, respectively (dutasteride/placebo). Of all patients, 6% in both groups discontinued due to adverse events. Finally, 9% of patients reported serious adverse events (SAEs) in the drug group versus 8% in the placebo group.

The overall adverse reactions reported by greater than ≥2% of patients in any treatment group, as tabulated for the pooled three, double-blind, placebo-controlled, 1-year treatment period, pivotal studies (ARIA 3001, ARIA 3002, and ARIB3003) is shown in Table 3. Table 3 describes all adverse events without assessment of causality.

Table 3. Frequency of Adverse Events Reported by ≥2% of Patients in Double-Blind Portion of Pivotal Trials.

	Placebo (N=2158)	Dutasteride 0.5 mg (N=2166)
Diarrhea	71 (3%)	57 (2%)
Ear, nose and throat infection	136 (6%)	166 (6%)
Viral ear, nose and throat infect	122 (5%)	115 (4%)
Impotence	78 (4%)	149 (7%)
Altered libido	49 (2%)	90 (4%)
Ejaculation disorder	20 (<1%)	59 (2%)
Musculoskeletal pain	178 (7%)	148 (5%)
Arthralgia & rheumatism	49 (2%)	45 (2%)
Arthritis	41 (2%)	25 (1%)
Viral respiratory infection	108 (4%)	98 (4%)
Bronchitis	54 (2%)	54 (2%)
Cough	53 (2%)	46 (2%)
Headache	69 (3%)	62 (3%)
Dizziness	50 (2%)	41 (2%)

Sleep disorders	35 (2%)	18 (<1%)
Malaise & fatigue	66 (3%)	43 (2%)
Hypertension	65 (3%)	67 (3%)
Coronary artery disorder	26 (1%)	26 (1%)
Urinary infection	62 (3%)	53 (2%)
Dysuria	28 (1%)	39 (2%)
Disorders of lipid metabolism	47 (2%)	53 (2%)

In my opinion, Table 3 is notable for the low incidences of all adverse events across the board.

The clinical safety review of dutasteride focused specifically on adverse events of "special interest", particularly those related to sexual function and other endocrinologic-based events.

Table 4 shows the number and percentage of patients reporting "adverse events of special interest" during the pivotal trials.

Table 4. Adverse Events of Special Interest in Patients Taking 5-alpha Reductase Inhibitors

	Placebo (N=2158)	Dutasteride (N=2166)
Decreased libido	49 (2%)	88 (4%)
Impotence	76 (4%)	141(7%)
Ejaculation disorder	18 (<1%)	53 (2%)
Sexual function disorder	2 (<1%)	7 (<1%)
Gynecomastia	11 (<1%)	32 (1%)
Prostate cancer	12 (<1%)	11 (<1%)

Again, in my opinion, these adverse events were generally mild to moderate and transient. Overall, the drug was well-tolerated. Of note, in those patients older than 65 years of age, diminished libido and "sexual function disorders" was reported in similar frequency between drug and placebo groups. The sponsor attributes this to lower overall baseline function in this age group compared with the group of men younger than 65 years.

None of these overall "common" adverse events should preclude approval.

4.3. Deaths, serious adverse events, and other medically significant adverse events

Overall, there was no significant cardiovascular, hepatic, renal or hematologic toxicity identified in this broad database.

4.3.1 Deaths

In the pivotal efficacy trials, eight patients in the placebo group (<1%) and 12 patients (<1%) in the dutasteride groups died. In the judgement of the investigators, none of these deaths were considered drug-related.

In the eight patients in the placebo group, 4 died of cancer (bladder, rectum, lung, and lung metastases), one died of DIC, one died of a stroke, and two died of cardiac disorders (cardiac arrest and acute MI).

In the 12 patients in the dutasteride group, 4 died of cancer (angiosarcoma, leukemia, lung, and bladder), one died of "natural causes", one died of "worsened COPD", two died of strokes, and 4 died of cardiac disorders ("atherosclerotic CAD", MI x2, and cardiac arrest).

Although four patients died of cardiac disorders in the drug group versus 2 in the placebo group, the sponsor believes that there was no real difference between the groups in this regard. I agree with this conclusion.

4.3.2. Non-fatal serious adverse events (SAEs)
As noted by Dr. Benson, serious adverse events were reported by 171 (8%) in the placebo group and by 197 (9%) in the dutasteride group. Almost all these were considered by the investigator to not be related to study drug.

Four serious adverse events in four patients were considered by the investigator to be related to study drug. Three of these events were in placebo-treated patients.

The single dutasteride-treated patient experienced a severe "allergic" rash approximately one year after starting study medication. This patient was hospitalized and all concomitant medication was stopped. The event resolved 11 days after onset.

4.4. Abnormal laboratory data
There were no obvious clinically significant changes in routine hematology, chemistry, or urinalysis values.

There was a minor difference in incidence of "normal-to-abnormal" changes in serum ALT between dutasteride and placebo groups (5% versus 3%, respectively). There was a minor difference in incidence of "normal-to-abnormal" changes in serum alkaline phosphatase between dutasteride and placebo groups (3% versus 1%, respectively). The sponsor does not believe that this represents a drug-related effect on the liver and I agree.

Of note, dutasteride significantly impacts the serum PSA. Within 3-6 months of starting dutasteride, a new baseline for PSA screening is necessary. This baseline, like finasteride, is approximately 50% of the starting PSA. This issue is acknowledged in the label.

Of note, dutasteride is associated with an increase in serum testosterone (T) from baseline. The median increase in serum total T appears to be approximately 19%, but remains within normal limits. Only 11 dutasteride patients had serum total T values exceeding the upper limit of normal (>10,000 pg/mL), and all of these were only mildly above normal. Most of these patients had relatively high starting serum T levels. The sponsor did not consider these findings clinically meaningful. I agree. Nevertheless, this issue is again acknowledged in the label.

4.5. Safety information from other trials
4.5.1. QT interval
The effect of dutasteride on the QT interval was carefully assessed in a special protocol. The design of the protocol called for an accelerated dosing schedule to attain very high blood levels quickly.

The results of this study were reviewed by Dr. MaryAnn Gordon of the Cardio-Renal Division. Dr. Gordon found that "There was no effect of dutasteride 0.5 mg or 5 mg on the uncorrected QT interval." Dr. Gordon believed that there was no need to correct for heart rate since dutasteride had no effect on heart rate.

Dr. Gordon concluded that: "The range of serum concentration was from approximately 20 ng/ml to approximately 900 ng/ml. This finding, however, does not rule out an effect of dutasteride on repolarization at higher concentrations." Given that the steady-state blood level at the 0.5 mg

daily dose is about 40 ng/mL, I believe there is an adequate safety margin in most realistic settings.

4.5.2. Semen quality

Trial ARIA 1009 was conducted specifically to assess the impact of dutasteride on semen parameters. Although the number of volunteers was low, there did not appear to be a significant drug effect on sperm concentration, motility or morphology. However, there was a notable decrease in mean ejaculate volume (approximately 25%) with a corresponding decrease in total sperm per ejaculate. Nevertheless, even these mean parameters remained within normal limits.

There were two subjects in whom sperm count dropped to approximately 10% of baseline by Week 52 of the trial. After discontinuation of dutasteride, semen parameters resolved in both men by Recovery Week 26.

These findings are described fully in the package insert.

4.5.3. Exposure to high dose (ARIA 2001)

In this Phase 2 dose-ranging trial, 300-350 patients were randomized to daily therapy with placebo, dutasteride 0.01 mg, 0.05 mg, 0.5 mg, 2.5 mg, or 5.0 mg, or finasteride 5 mg daily. This was conducted in 33 centers in the U.S. and Canada. Treatment duration was 24 weeks. Safety, efficacy and pharmacokinetics were measured.

In this head-to-head study, it is interesting to note that symptoms score improvement and "rate of response" was highest in the finasteride group. The greatest reduction in prostate volume was in the 2.5 mg dutasteride group. No statistically significant improvement in maximum urinary flow rate over the effect of placebo was noted in any group.

In terms of safety, dutasteride was well-tolerated at all dose levels. Incidences of commonly reported AEs such as decreased libido, impotence, malaise and fatigue, musculoskeletal pain, headache, ear, nose and throat infections, and dizziness appeared similar across the groups with only a moderate increase in the incidence of decreased libido in the 5.0 mg group (N=57) over the others. No true dose-response relationship for adverse events was determined even for the adverse events of "special interest". There were no significant changes in baseline gynecomastia or vital signs in any group and no significant changes in ECG in the higher-dose groups.

Twenty-nine subjects were discontinued due to adverse events. These were fairly evenly distributed among the groups (3-5 patients in each group). Most of these were not considered drug-related by the investigator.

Twenty-nine subjects reported serious adverse events (SAEs). These were fairly evenly distributed amongst the groups. None were considered drug-related by the investigator.

There were two deaths. One patient in the 0.01 mg group died of cardiopulmonary arrest and one patient in the 0.05 mg group died of MI. Neither was considered to be drug-related.

> *Reviewer's comment: The results of this trial support the safety of chronic use of ten times the recommended dose of dutasteride.*

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 21, 2001

FROM: Florence Houn MD MPH

SUBJECT: Office Director Memo

TO: NDA 21-319 Dutasteride 0.5mg capsules (GlaxoSmithKline)

This memo documents my concurrence to approve dutasteride, a selective inhibitor of both type 1 and type 2 isoforms of steroid 5-alpha reductase, indicated for the treatment of symptomatic benign prostatic hypertrophy at 0.5 mg orally daily. The Division of Reproductive and Urologic Drug Products (DRUDP) has recommended approval with phase 4 commitment to study the in vitro metabolism of the drug product. The decision to allow approval given the absence of this knowledge is based on the clinical studies of about 2,000 men exposed to drug, including data of patients on ten times the approved dose that showed no clinical safety concerns and no effects on QTc, producing no safety signal concerning metabolism. Efficacy has been demonstrated in three clinical trials using accepted American Urologic Association Symptom Index endpoints. The issues of the drug's teratogenicity and effects on PSA and testosterone and semen quality have been dealt in labeling. The other remaining policy issue is the drug's 5 week half-life and implications for such a long drug presence.

The main issues surrounding the approval of this drug are summarize nicely by the acting division director's memo, the medical reviewer's note, pharmtox reviews, and biopharm reviews: teratogenicity, impact on PSA screening for prostate cancer, lowering of testosterone levels, adverse effect on semen quality, ADME issues. I agree with the resolution of these issues in labeling and phase 4 study.

In brief, this drug product can feminize a human male fetus should a pregnant woman be exposed to the drug. There is labeling to alert physicians and consumers to this fact. DRUDP has coordinated with CBER to ensure that once marketed, blood collection centers know to exclude patients on the drug from blood donation for concern the recipient of a donor on dutasteride could be a pregnant woman. This information is also in the labeling. The Division has also considered risk of birth defect via drug being delivered in the prostatic fluid during sex, oral sex, and transdermally (such as when women handle the drug product). The risk was viewed as remote in all but the latter situation given estimates of levels of drug conveyed. The labeling addresses transdermal absorption.

The terminal elimination half-life is about 5 weeks. This long half-live accentuated problems with respect to teratogenic potential. It has other implications as discussed at the end of this memo.

The metabolism of the drug has not been adequately defined. However, it is extensively metabolized. Labeling states that caution should be used in the administration of dutasteride in patients with liver disease. Effects on potent CYP 3A4 inhibitors have not been studied. There is, however, no effect on QTc. The clinical implication of higher levels of drug and/or long exposure time at this time appear to be minimal given the data from 57 patients at 2.5 mg and 60 patients at 5mg of dutasteride daily for six months. Effects on lowering of testosterone are unknown; PSA effects are labeled to alert the public that accuracy of screening for prostate cancer using PSA may be affected. The single patient who developed a severe allergic rash and resolved after 11 days and being hospitalized raises the possibility that the long half-life of the drug may mean longer resolution times for associated adverse events. I've asked that the overdose section reflect that clinical management of overdoses may need to accommodate the long half-life of the drug.

The drug's 5 week half-life raises the issue of what advantages and disadvantages this drug characteristic offers. On face value, minimizing unnecessary exposure to drugs is desirable. Can a drug with such a long half-life be taken in a manner other than daily and still sustain an effect (i.e, daily until steady state, then every few days or weekly)? These types of regimens are probably unappealing to marketers because they fall out of the norm of how one treats a chronic disease, which as a tradition has been daily. I discussed the issue of using this pharmacokinetic property in the future to drive dosing regimens with the division. One area to advance drug safety is to explore non-daily dosing that may, in turn, minimize side effects or adverse events. The long half-life of dutasteride did raise a feeling in the review staff of why would one want this type of drug exposure and what are the implications for patients who must or wish to terminate the medication. Finasteride, the drug's competitor, does not have this dilemma. In part, there is no good answer to why would a 5 week half-life be a desirable drug characteristic for a BPH drug that is taken daily. Phase 1-2 dose studies did not explore non-daily dosing. Finally, the labeling tells patients that if you wish to engage in certain activities, you must accommodate to the drug's very long half-life. Unfortunately, the drug is a teratogen and accommodation with respect to delaying blood transfusions must be made. If postmarketing reveals adverse events that are implicated to this long half-life, more discussion and action may be required. All the above issues were discussed with the acting division director and the medical team leader.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

Food and Drug Administration
Center for Drug Evaluation and Research
Division of CardioRenal Drug Products
Consultation

Date: July 30, 2001

To: Susan Allen, MD
Division Director, HFD-580

From: Maryann Gordon, MD
Medical Reviewer, HFD-110

Through: Norman Stockbridge, MD, PhD
Medical Team Leader, HFD-110

Raymond Lipicky, MD
Division Director, HFD-110

Subject: Dutasteride (GI198745, NDA#21,319) for benign prostatic hypertrophy
Review of abbreviated study report for protocol ARI10019

Conclusion

The sponsor reported the results of a double blind, placebo controlled, randomized, 28-day study with healthy male volunteers that evaluated the effect of 2 doses of dutasteride on cardiac repolarization. I reviewed the protocol during a previous consult.

Overall, this study showed no effect of dutasteride 0.5 mg or 5 mg on the uncorrected QT interval. (Since the ventricular rate was unaffected by the drug, no correction factor is necessary.) The range of serum concentration was from ~20 ng/ml to ~900ng/ml. This finding, however, does not rule out an effect of dutasteride on repolarization at higher concentrations. Therefore, the reviewing division must determine if other drugs or diseases interfere with the dutasteride's metabolism.

Introduction

Dutasteride, an inhibitor of 5(alpha)-reductase enzymes type 1 and 2 which convert testosterone into 5(alpha)-dihydrotestosterone, is being developed for the treatment of benign prostatic hyperplasia and androgenetic alopecia. It is similar to the approved agent finasteride (Propecia and Proscar).

Multiple doses up to 40 mg of GI198745 have been tolerated. Preliminary findings in humans suggested that the drug could have the potential to affect cardiac repolarization. The data being reviewed in this document is from a study that was specifically designed to investigate this effect.

Preclinical data including effects on cardiac ion channels are not available.

Protocol: # ARI10019: A double blind, placebo controlled, randomized parallel group study to investigate the changes in the corrected QT interval following repeated oral doses of dutasteride in healthy male volunteers.

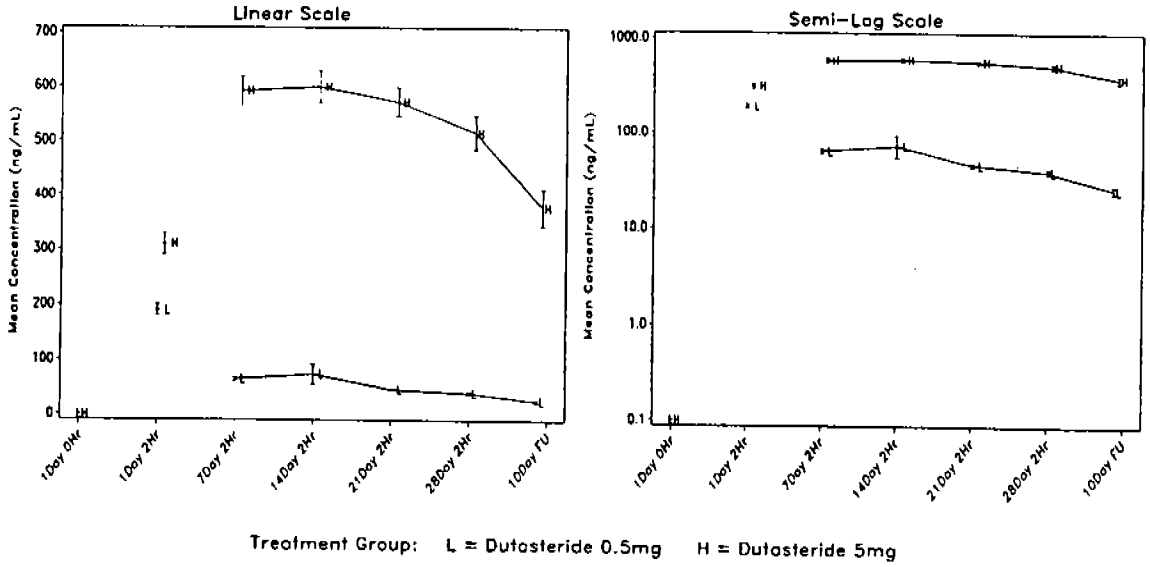
Objective: the purpose of the study was to determine whether there is evidence to suggest that dutasteride prolongs cardiac repolarization.

Study treatment arms and study duration: there were 3 treatment arms consisting of oral daily dose of placebo, oral daily doses 0.5 mg[1] dutasteride (with 1 day loading dose of 25 mg), and oral daily doses of 5 mg dutasteride (with 7 day loading dose of 40 mg). There was a 10 day follow up after the last dose of study drug.

The linear and log plots of serum concentration over time are shown below.

Population: Intent-to-Treat

Figure 4
Comparative Linear and Semi-logarithmic Plots of the Serum Concentration Over Time



Treatment Group: L = Dutasteride 0.5mg H = Dutasteride 5mg

Study subjects: 97 healthy male subjects (with screening QTc interval ≤ 450 msec) were randomized. Demographics are shown below.

[1] The sponsor considers this dose to be the lowest effective dose.

	Placebo (n=34)	Dutasteride 0.5mg (n=31)	Dutasteride 5mg (n=32)
Age (yrs)			
mean	37.4	31.6	39.5
SD	11.1	9.4	12.6
Min : max	20 : 59	19 : 52	18 : 60
Race			
White	12 (35%)	9 (29%)	9 (28%)
Black	2 (6%)	4 (13%)	0
Hispanic	20 (59%)	18 (58%)	23 (72%)
BMI (kg/m^2)			
Mean	25.74	25.01	25.64
SD	2.54	2.48	2.72
Min : max	20.8 : 28.8	19.7 : 28.7	19.7 : 28.9

Source data: Table 4

Study completions

Of the 97 subjects enrolled, 91 completed the study. The 6 subjects who dropped out included 1 placebo (other), 4 dutasteride 0.5 mg (2 for adverse event and 2 for protocol violation) and 1 dutasteride 5 mg (protocol violation).

ECG recordings: 12-lead ECGs were recorded for 12 hours after dosing on Days -1, 1, and 28 at predose (3 readings at least 5 minutes apart) and at 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. EGGs were also obtained at days 7, 14, and 21 days after start of dosing as well as during follow up.

Heart rate

Compared to placebo, neither dose of dutasteride (LO or HI) had an effect on ventricular rate.

Protocol: ARI10019
Population: Intent-to-Treat

Table 20
Summary of Results of Analysis of Covariance of Weighted Mean Ventricular Rate, PR Intervals and QRS Duration with Baseline Covariate

Parameter	Day	Comparison	Dutasteride (Test) LSmean	Placebo (Reference) LSmean	Treatment Difference (Test-Ref)	90% CI for Difference in LSmean
Vent. Rate (beats/min)	1	LO-Placebo[1]	65.46	66.77	-1.31	(-2.53, -0.09)
		HI-Placebo[2]	66.20	66.77	-0.57	(-1.78, 0.65)
	28	LO-Placebo[1]	66.53	65.18	1.35	(-0.77, 3.48)
		HI-Placebo[2]	64.63	65.18	-0.55	(-2.58, 1.49)

Primary study endpoint: weighted mean[2] QT. QT corrected for heart rate (Bazett's correction and Fridericia's correction) was also calculated by the sponsor so figures showing the results are included in

[2] See appendix 1 for definition of weighted mean.

the appendices 2 and 3 for completeness.

The 12 hour profiles of QT intervals obtained on day –1 (baseline) and day 28 (endpoint) are shown below.

QT interval ± SD (msec): mean change from baseline at day 28

Hour after dose	Placebo N=33	Dut 0.5 mg N=32	Dut 5 mg N=31
0	1.4 ± 13.4	0.5 ± 14.1	2.0 ± 18.6
1	-1.5 ± 15.3	-5.5 ±15.4	-1.8 ± 19.5
2	-0.1 ± 13.6	-0.8 ± 19.3	-3.9 ±17.0
3	-1.7 ± 12.0	-2.4 ± 19.0	-0.5 ± 20.5
4	0.8 ± 16.2	0.5 ± 19.3	2.5 ± 14.7
6	-0.7 ± 12.9	-2.9 ± 16.1	-0.5 ± 16.6
8	-1.1 ± 17.1	-4.6 ± 16.2	-0.1 ± 16.5
10	-2.8 ± 17.6	-0.4 ± 19.2	-0.7 ± 16.9
12	-9.1 ± 16.7	-10.9 ±16.8	-6.6 ± 16.0

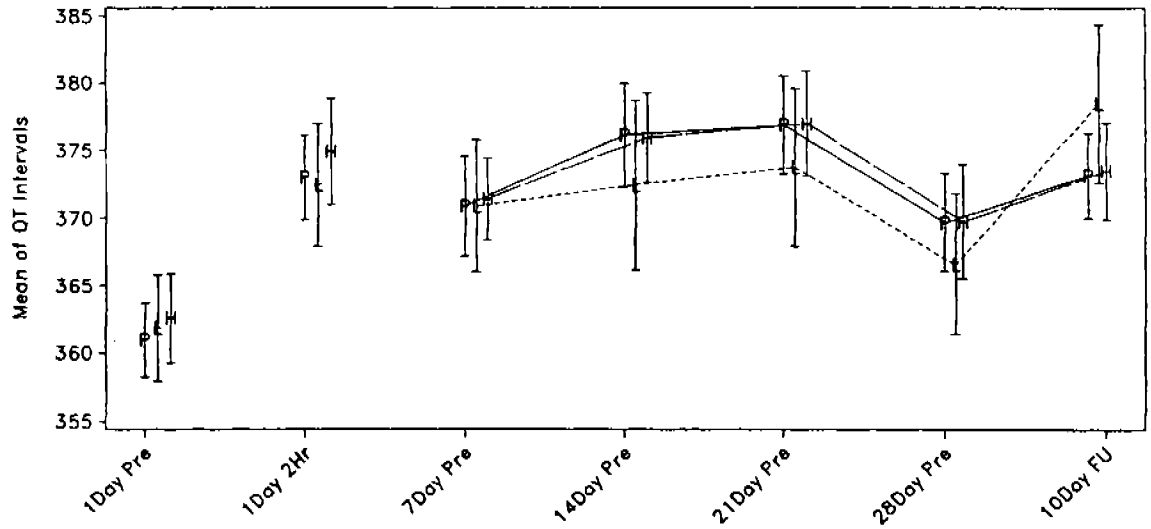
Table 8

The mean changes from baseline are similar for all 3 treatment groups at all time points.

Mean QT interval measured at trough (pre dose) for every clinic visit is shown in the figure below.

Protocol: ARI10019
Population: Intent-to-Treat

Figure 3
Mean of QT Intervals Over Time



Treatment Group: P = Placebo L = Dutasteride 0.5mg H = Dutasteride 5mg

Compared to placebo, neither dose of dutasteride had an effect on QT (see appendices 2 and 3 for results

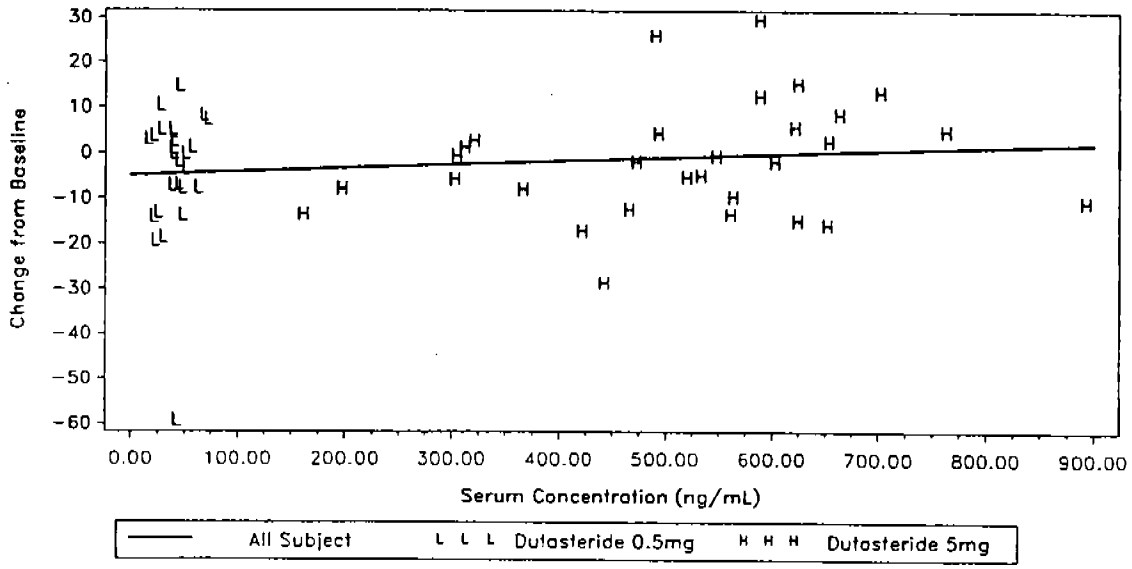
of QTc and QTf).

Effect versus serum concentration

Changes from baseline for the QT interval at serum concentrations ranging from about 25 ng/ml to about 900 ng/ml are shown below.

Protocol: ARI10019
Population: Intent-to-Treat

Figure 19.1
Change from Baseline in Weighted Mean of QT Intervals v.s Serum Concentration on Day 28 by Treatment



Secondary endpoint: number and percent of subjects with change in QT from baseline of <30 msec, 30 to 60msec, and >60msec. The results for pre dose, day 28, are shown below by treatment group.

Protocol: ARI10019
Population: Intent-to-Treat

Table 15
Summary of QT Intervals by Category : Change from Baseline at Day 28

	Category Change (msec)	Placebo (N = 34)	Dutasteride 0.5 (N = 31)	Dutasteride 5 (N = 32)
Pre-dose	n	33	30	31
	< 0	13 (39%)	13 (43%)	16 (52%)
	0 - 30	20 (61%)	17 (57%)	13 (42%)
	30 - 60	0	0	2 (6%)

The finding that 6% of patients in the dutasteride 5 mg is not consistent with the other results in this study and probably is only normal variation.

5. DATA ANALYSIS METHODS

5.4.8. Derived Data

Percent compliance were calculated for treatment Day 8 through Day 28 by the following formula:

%compliance = Total number of pills that are actually taken, as recorded on the CRF, divided by the total number of days (i.e. 21 days), and multiplying by 100.

See Section 6.5.6 for details.

When calculating number of days relative to treatment start date, the date that study treatment started were counted as Day 1. Days on study were calculated as following:

Days on Study = (Visit Date - Study Treatment Start Date) + 1

(Visit Date $\geq$ Study Treatment Start Date).

The following derived data were calculated:

QT interval corrected by Fridericia's formula:

QTcF = QT/cube root(RR)

QT interval corrected by Bazett's square root formula:

QTcB = QT/sqrt(RR)

In all analysis described in this document, predose QT intervals (corrected or origin) were the average of the 3 predose ECGs taken at least 5 minutes apart, and were referred as the measurement at 0 hour. The weighted mean of the serial measurements (including QT, QTcB, QTcF, etc) were area under the curve divided by the total time interval and were calculated for each subject as follows:

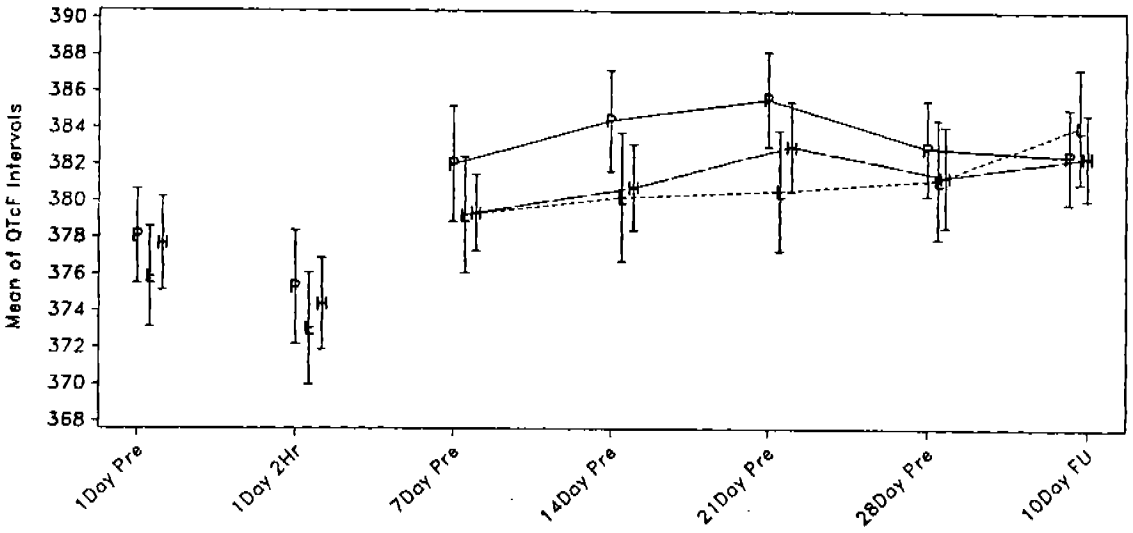
$$\text{Weighted mean}_1 = [t_1*M_0/2+(t_1+t_2)*M_1/2+(t_2+t_3)*M_2/2+(t_3+t_4)*M_3/2+(t_4+t_6)*M_4/2$$
$$+(t_5+t_8)*M_6/2+(t_8+t_{10})*M_8/2+(t_{10}+t_{12})*M_{10}/2+t_{12}*M_{12}/2]/\ t_n.$$

Where t_n was the actual time between scheduled #-1 and # hours measurements and M_8 was the measurement at scheduled # hour post dose and $t_n = t_1+t_2+t_3+t_4+t_5+t_8+t_{10}+t_{12}$.

Appendix 2

Protocol: ARI10019
Population: Intent-to-Treat

Figure 1
Mean of QTcF Intervals Over Time



Treatment Group: P=Placebo L = Dutasteride 0.5mg H = Dutasteride 5mg

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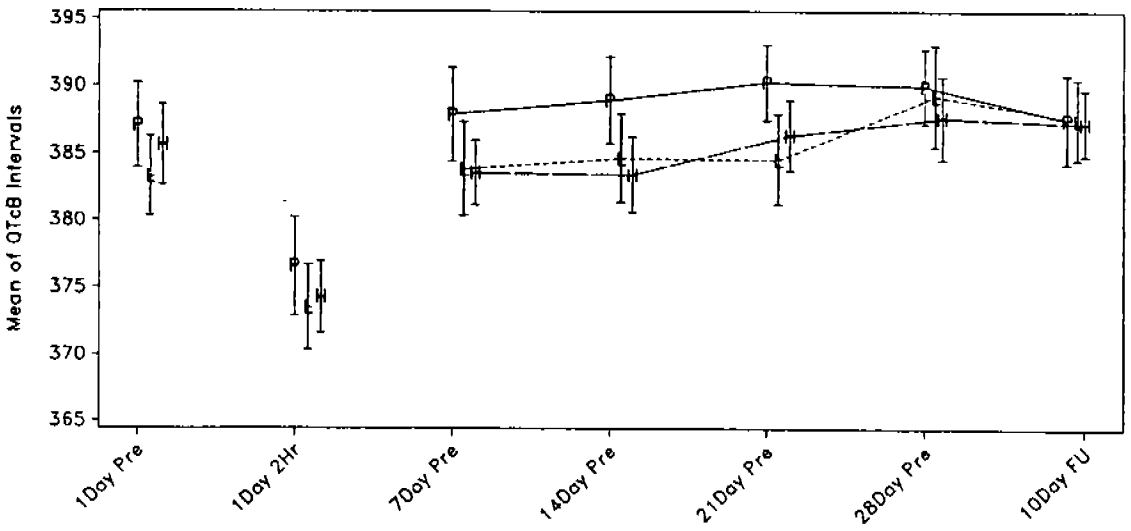
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Appendix 3

Protocol: ARI10019
Population: Intent-to-Treat

Figure 2
Mean of QTcB Intervals Over Time



Treatment Group: P = Placebo L = Dutasteride 0.5mg H = Dutasteride 5mg

APPEARS THIS WAY

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: February 8, 2001 **Time:** 3:00-3:30 PM, EDT **Location:** Parklawn; 17B-43

NDA 21-319 **Drug:** dutasteride **Indication:** Benign Prostatic Hyperplasia (BPH)

Sponsor: GlaxoWellcome

Type of Meeting: Clarification

Meeting Co-Chairs: Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

External Lead: Munir Abdullah, Ph.D., Product Director, Regulatory Affairs

Meeting Recorder: Evelyn R. Farinas, RPh, M.G.A., Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

FDA Attendees:
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Jean Salemme, Ph.D. – Chemist, DNDC II, @ DRUDP (HFD-580)
Ronald Kavanagh, B.S. Pharm, Pharm.D., Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. - Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Munir Abdullah, Ph.D. - Product Director, Regulatory Affairs, GlaxoWellcome
Bekki Komas – Assistant Director, Regualatory Affairs, GlaxoWellcome
Ralph Caricofe – CMC Team Leader, GlaxoWellcome, GlaxoWellcome
Steve Meyerhoffer, Ph.D. – Research Investigator II, GlaxoWellcome
Len Galante, Ph.D. – Department Head, Analytical Sciences, GlaxoWellcome
Linda Haberer, Ph.D. – Clinical Pharmacokineticist IV, GlaxoWellcome

Meeting Objective: To request additional information and clarification for NDA review.

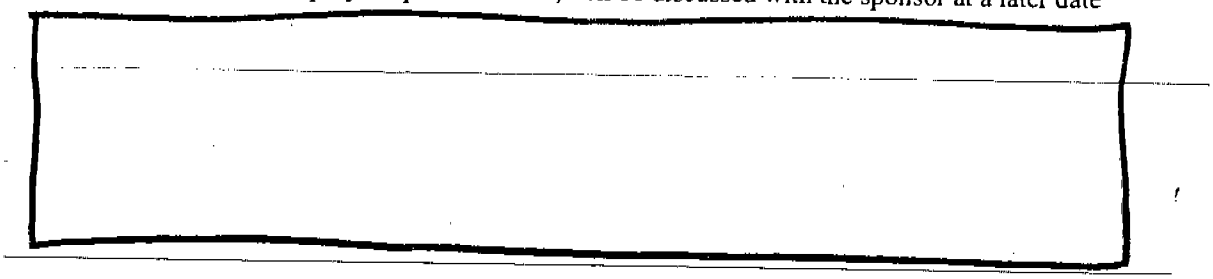
Background: On December 21, 2000, the sponsor submitted the new NDA 21-319 for dutasteride soft gelatin capsules. The proposed indication is the treatment of symptomatic BPH in men with an enlarged prostate gland. Dutasteride is a selective inhibitor of Type 1 and Type 2 5-alpha-reductase, an enzyme that converts testosterone to 5-alpha-dyhydrotestosterone. A preliminary review of the December 21, 2000 submission indicated that further clarification from the sponsor was needed prior to the filing date.

Discussion:

Clinical Pharmacology and Biopharmaceutics:

- specific and more detailed information should be supplied regarding the formulations used in the clinical trials
- a summary table indicating which assay validation pertains to each study should be provided
- dissolution profiles along with raw data should be submitted; the submitted averages regarding link and cross-linked gelatin are not sufficient
- all Biopharmaceutical issues should be included under Item 6 (ex. PK/PD data, semen study, etc.), and not scattered through different sections in the NDA
- if possible, electronic data sets (EDS) for population PK and PK/PD studies should be submitted for ease of review; in lieu of EDS, the data could be submitted in Word format
- the sponsor confirmed that the to-be-marketed formulation is the same as the clinical formulation
- it was confirmed that there were no hepatic nor renal impairment studies conducted

Chemistry, Manufacturing and Controls:

- the formulation codes should be identified by the sponsor
- dissolution profiles from bio batch or clinical batch should be provided
- individual data points at each time measured should be supplied
- additional issues, such as polymorphism studies, will be discussed with the sponsor at a later date
- 

Decisions made:

- all Biopharmaceutics information will be included under Item 6 of the NDA submission in a follow-up submission
- additional clarification and comments will be provided to the sponsor

Action Items:

- DRUDP will send Biopharmaceutic questions and requests for clarification to the sponsor *(facsimile sent on February 9, 2001; see Addendum)*
- available hepatic and renal impairment studies will be sent by the sponsor when requested by the Biopharmaceutics reviewer
- 
- minutes of this teleconference will be faxed to sponsor within 30 days

Minutes Preparer

Concurrence, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Teleconference Minutes

Date: May 8, 2001 **Time:** 10:30-11:15 AM, EDT **Location:** Parklawn; 17B-43

NDA 21-319 **Drug:** dutasteride **Indication:** Benign Prostatic Hyperplasia

Sponsor: GlaxoSmithKline

Type of Meeting: Clarification

Meeting Chair: Laurie McLeod, Ph.D., Pharmacologist, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: Munir Abdullah, Ph.D., Product Director, Regulatory Affairs

Meeting Recorder: Evelyn R. Farinas, RPh, M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Laurie McLeod, Ph.D. - Pharmacologist, DRUDP (HFD-580)
Sayed Al-Habet, Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Munir Abdullah, Ph.D. – Product Director, U.S. Regulatory Affairs
Lynda Haberer, Ph.D. – Clinical Pharmacology
Russ Yeager –Drug Metabolism and Pharmacokinetics
Dipak Patel – Drug Metabolism and Pharmacokinetics
Jackie Greene – Safety Assessment, Toxicology

Meeting Objective: To obtain clarification regarding the time of submission for additional preclinical and biopharmaceutics data.

Background: During the December 5, 2000, pre-NDA meeting, the sponsor indicated that quantification of the metabolite was anticipated by the first quarter of 2001, and that mutagenicity testing would be conducted by the middle of 2001. In the April 20, 2001 correspondence, the sponsor submitted a 120-day Safety Update Report. This submission also included an update of the non-clinical and clinical studies that were ongoing at the time of the NDA submission. The "Points-to-Consider (PTC) for Reviewers" section lists information or data that are outstanding and subject of ongoing studies. However, quantification of human, rat, and mouse serum dutasteride metabolites, needed for evaluation of carcinogenicity data, was not included.

Discussion:

- the sponsor stated the following:
  - metabolite data were not included in the April 20, 2001 submission because the assay could not be validated
  - there were "technical challenges" to synthesizing the metabolite
  - expect to submit results on the dutasteride metabolite quantification in June
  - expect to submit final results of a definitive metabolite exposure study in rats in August
  - it was difficult to establish the metabolic pathway, to generate large yields of metabolite, and to provide quantitative information
  - preliminary QT prolongation data was included in the April 20, 2001 submission
- DRUDP requested that the sponsor submit preliminary data in July to estimate the percentage of the metabolites in human serum so that the adequacy of toxicology studies could be reviewed in a timely manner
  - the main concern is to demonstrate that major human dutasteride metabolites are present in species used in the carcinogenicity studies (and other toxicology studies) in sufficient quantities to assure that metabolite toxicity has been adequately tested
  - there is also a concern about the pharmacology of the major dutasteride metabolites, and of the ratios of these metabolites to parent drug in human serum
  - additional protein-binding data are not required since the maximally tolerated dose of dutasteride was reached in carcinogenicity studies

Decisions made:

- results from blood samples from the carcinogenicity studies quantitating dutasteride metabolites will be submitted in June 2001
- preliminary data estimating the percentage of metabolites in humans, the preliminary results of a 90-day rat study (quantitating metabolites) and the preliminary results of the metabolite Ames test will follow in July 2001
- final results of a definitive metabolite exposure study in rats will be submitted in August 2001

Action Items:

- the sponsor will submit results of metabolite data from the blood samples from the carcinogenicity studies quantitating dutasteride metabolites in June 2001, preliminary data estimating the percentage of metabolites in human serum, preliminary results of a 90-day rat study and of an Ames test in July 2001, and final results of metabolite exposure study in rats in August 2001
- minutes will be sent to the sponsor in 30 days

Minutes Preparer **Concurrence, Chair**

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.