CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-319

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-319

GlaxoWellcome
Attention: Craig A. Metz
Director, Regulatory Affairs
Five Moore Drive
PO Box 13398
Research Triangle Park
NC 27709-3398

Dear Dr. Metz:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	dutasteride soft-gelatin capsules, 0.5 mg
Review Priority Classification:	Standard (S)
Date of Application:	December 21, 2000
Date of Receipt:	December 21, 2000
Our Reference Number:	NDA 21-319

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 20, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 20, 2001 and the secondary user fee goal date will be December 20, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the

application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102© of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-319

INFORMATION REQUEST LETTER

Glaxo SmithKline
Attention: Munir Abdullah, Ph.D.
Product Director, Regulatory Affairs
5 Moore Drive
PO Box 13398
Research Triangle Park, North Carolina 27709

Dear Dr. Abdullah:

Please refer to your December 21, 2000, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dutasteride soft gelatin capsules, 0.5 mg.

We also refer to your submission dated July 20, 2001.

We are reviewing the physician package insert section of your submission and have the following comments. Revisions have been incorporated directly into the enclosed package insert. Additions have been noted with double underlining, and deletions have been noted as ~~strikeouts~~.

Please submit your revised package insert as soon as possible so that we can continue the evaluation of your pending NDA submission.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Revised package insert

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-319

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Munir Abdullah, Ph.D.
P.O.Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. Abdullah:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dutasteride.

We are reviewing the toxicology section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. For B6C3F1/Tac mice, please submit historical tumor incidence data for 5 or 6 studies performed at approximately the same time and at the same laboratory as the dutasteride study.

2. Please submit the statistical dataset electronically as a desk copy for ease of review. See attached documents for guidance.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri F. Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachments:
Division of Biometrics II, Information Sheet for Submission of Carcinogenicity Data
Guidance for Industry: Providing Regulatory Submissions in Electronic Format — NDAs

Division of Biometrics II
Information Sheet for Submission of Carcinogenicity Data

The statistical reviewer responsible for this carcinogenicity study review requests that the sponsor recreate the tumor data in conformance to the electronic format specified in the Agency's guidance document of January 1999.

To streamline the reviewing process and improve the review quality, the Agency published *Guidance for Industry, Providing Regulatory Submissions in Electronic Format-NDAs* in January 1999. In Appendix 1 of this document the Agency details the data-format specifications for the pharmacology and toxicology datasets. The sponsor needs to familiarize itself with the data-format requirements in detail. We are only requesting the tumor dataset at this time (see page 61 of the guidance which is attached to this information sheet).

The above guidance document can be found at http://www.fda.gov/cder/guidance/2353fnl.pdf (or, one can go to the Guidances index page (http://www.fda.gov/cder/guidance/index.htm) then find the Electronic Submissions section, then access Regulatory Submissions in Electronic Format: New Drug Application (Issued 1/1999, Posted 1/27/1999). To assist the sponsor to correctly construct the tumor data, the Agency provides a downloadable example. Please visit *Example of an Electronic New Drug Application Submission* (posted 2/17/1999) at http://www.fda.gov/cder/guidance/NDA_Example.htm. The data for submission should have exactly the same format as the data in the example (named tumor.xpt), including designated variable names.

Please contact the Agency to provide a time line regarding providing the tumor data. The sponsor needs to carefully meet the data-format specifications in order to comply with the above guidance. Any data without 100% conformity will have to be returned for resubmission.

Full cooperation in providing data sets in the required format will facilitate a prompt review of the submission. In addition to a copy for the statistical reviewer, NDA submissions require an archival copy of all data sets for the Electronic Document Room - see Guidance for Industry: Providing Regulatory Submission in Electronic Format - General Considerations at http://www.fda.gov/cder/guidance/2867fnl.pdf for instructions.

NDA 21-319 **DISCIPLINE REVIEW LETTER**

Glaxo SmithKline
Attention: Munir Abdullah, Ph.D.
Product Director, Regulatory Affairs
5 Moore Drive
PO Box 13398
Research Triangle Park, North Carolina 27709

Dear Dr. Abdullah:

Please refer to your December 15, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dutasteride soft gelatin capsule, 0.5 mg.

Our review of the Clinical Pharmacology and Biopharmaceutics section of your submission is complete, and we have identified the following 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.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Evelyn R. Farinas, R.P.H., M.G.A., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research