CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-319

CHEMISTRY REVIEW(S)

NDA 21-319
Dutasteride Capsules, 0.5 mg

CHEMISTRY DIVISION DIRECTOR REVIEW

Dutasteride Soft Gelatin Capsules 0.5 mg is new molecular entity which is an inhibitor of steroid α reductase, inhibiting conversion of testosterone to 5α dihydrotestosterone, and is indicated for treatment of BPH.

Drug Substance
Dutasteride is an aza steroid which is synthesized in 5 steps from 3-oxo-4androstene-17β-carboxylic acid. The drug substance is manufactured by GlaxoSmithKline at their Montrose Scotland facility, which was found to be acceptable from a Compliance perspective. The specification was found to be acceptable, including impurities which were tightened upon Division request. A retest date of 36 months was assigned. Structural proof was definitively confirmed with a single crystal X-ray.

Drug Product
Dutasteride is formulated with mono and di-glycerides of caprylic and capric acid, and BHT in soft gelatin capsules. The gelatin is from US source(s), which is stated in the labeling. Encapsulation is done by RP Scherer, Bleinheim, France, which was found to be acceptable from a Compliance perspective.

The specification was found to be acceptable following requests to tighten limits. A two tier dissolution method is approved – tier 1 without pepsin and tier 2 with pepsin. Some degree of gelatin cross linking was evident upon aging.

Product is packaged in blisters and [redacted] bottles. Stability was demonstrated with 4 batches, and an expiry of 36 months is granted based upon real-time data.

Note that there is no tradename – the proposed names Duagen and Zygara were rejected by OPDRA. Insert and container labeling is acceptable.

Recommendation
Approval.

Eric P Duffy, PhD
Director, DNDC II/ONDC

Summary of Chemistry Review of NDA 21-319
(No Tradename)

A. Drug Substances:

Dutasteride is a **new molecular entity**, which is a **5-alpha reductase** inhibitor. It inhibits conversion of testosterone to dihydrotestosterone, thereby alleviating growth of prostate gland. It has seven **chiral** centers and exists as a **single morphic** and **anhydrous** form. It is manufactured in **5-step synthesis**, and its structure has been characterized and confirmed with elemental analysis, mass spectrometry, infrared spectroscopy, proton and carbon-13 NMR spectrometry, and single crystal x-ray crystallography.

The manufacturer, **Glaxo Wellcome Operations, UK**, is **in compliance with cGMP**.

Its **quality** is controlled by specifications such as description, identification, content, related impurities ([redacted] total impurities, residual solvents, water content, and specific optical rotation. Acceptance criteria for impurities are tightened to reflect the manufacturing capability and stability data, and now all **test methods** and **acceptance criteria** are considered to be **adequate**.

Based on available stability data, **36-month of retest period** was proposed and deemed acceptable.

B. Drug Product:

The drug product is **soft-gelatin capsule** containing dutasteride (0.5mg), mono-di-glycerides of caprylic/capric acid (349.5mg), and butylated hydroxytoluene (0.035mg).

The drug product is manufactured by **RP Scherer ([redacted]) in compliance with cGMP**, and the supplier of raw materials for the soft gelatin capsules indicated that they are **in compliance with the Guidance for Industry** on **BSE.**

All other **excipients** conform to **USP/NF**.

The quality of capsules are controlled by **specifications** including description, identification [redacted], content, content uniformity, drug related impurities, and dissolution (Q [redacted] at 45 min). All **test methods** and **acceptance criteria** are considered to be **adequate** after being appropriately tightened to reflect the manufacturing experience and stability data.

The capsules are packaged in **90 cc and 120cc** [redacted] **bottles** with child resistant closure, which has an [redacted] Also used are **blister packs** composed [redacted]

They are all considered to be **adequate** to protect the capsules during the shelf-life.

The sponsor proposed **36-month of shelf-life** based on the available real time data, and **it is granted.**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-319

CHEMISTRY REVIEW(S)

The proposed tradenames, both **Duagen and Zygara**, were **not accepted** by OPDRA. 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. All other **labeling information**, after being appropriately revised, is deemed **satisfactory.**

C. Conclusion and Recommendation:

From chemistry, manufacturing, and controls point of view, as the primary reviewer recommends, this NDA may be **approved.**

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

APPEARS THIS WAY
ON ORIGINAL

Second Addendum to NDA 21-319 chemistry review #3

Regarding Changes in Labels

16-November-2001

The OPDRA Reviewer states in the OPDRA Consultation Response dated 6-Sept-2001 that the use of the proprietary names "Duagen" or "Zygara is not recommended. Additionally, in this Response, the reviewer provides comments regarding changes that should be made on the labels for the container and carton.

The OPDRA comments regarding changes to container and carton labeling were faxed to the sponsor on 8-Nov-2001 and at this time the sponsor agreed to incorporate these changes. In a Fax dated 16-November the sponsor provided the Agency with copies of the labels to be used on the bottle label x 100, hospital unit dose carton x 70, professional sample carton x 7, and on the hospital unit dose blister package and professional blister package. The labels show the changes suggested by OPDRA have been made.

Chemistry Reviewer:
J. Salemme, Ph.D.

R/D:
Chemistry Team Leader
M-J. Rhee, Ph.D.

ADDENDUM TO
NDA 21-319
CHEMISTRY REVIEW #3

Date: 17-October-2001 Reviewer: J. Salemme, Ph.D., HFD-580

A telephone conference was held between Dr. Moo-Jhong Rhee of DRUDP and the sponsor on 10-October-2001 to discuss how the sponsor would notify the Agency post-approval about a tradename for Dutasteride.

In a Fax to the Agency dated 17-October-2001 the sponsor states: "We acknowledge that if NDA 21-319 is approved without a trade name, GSK will submit a trade name 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."

Evaluation: This is acceptable. All CMC issues have now been addressed and resolved.

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
HFD-580
Review of Chemistry, Manufacturing and Controls

NDA #: 21-319
CHEMISTRY REVIEW #: 3

REVIEW DATE: 9-October-2001

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
Amendment	9-October-2001	received by FAX 9-Oct-2001

NAME & ADDRESS OF SPONSOR:
Glaxo Wellcome
Five Moore Drive
Research Triangle Park, NC 27709

DRUG PRODUCT NAME:	Tradename, Not Decided
USAN:	Dustasteride
PHARMACOLOGICAL CATEGORY:	5-alpha reductase inhibitor
DOSAGE FORM:	Soft-Gelatin Capsule
STRENGTH:	0.5 mg
ROUTE OF ADMINISTRATION:	Oral

SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS: [redacted]

COMMENTS:
- The Amendment of 9-October-2001 describes the change to the regulatory method for the quantitation of dutasteride in the drug product.
- This review provides the final tests, acceptance criteria, and specifications for the drug substance and for the drug product.

CONCLUSIONS & RECOMMENDATIONS
From a CMC perspective, this NDA can be approved.

Orig. NDA #21-319
HFD-580/Division File
HFD-580/Farinas
HFD-580/Rhee/Salemme
HFD-820/Duffy
HFD-800/Ho
R/D Init by: MJ Rhee

J. Salemme, Ph.D., Review Chemist

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
HFD-580
Review of Chemistry, Manufacturing and Controls

NDA #: 21-319
CHEMISTRY REVIEW #: 2 **REVIEW DATE:** 27-Sept-2001

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
Amendment (Responses to Deficiency Letter)	7-Sept-2001	10-Sept-2001

NAME & ADDRESS OF SPONSOR:
Glaxo Wellcome
Five Moore Drive
Research Triangle Park, NC 27709

DRUG PRODUCT NAME:	Tradename, Not Decided
USAN:	Dustasteride
PHARMACOLOGICAL CATEGORY:	5-alpha reductase inhibitor
DOSAGE FORM:	Soft-Gelatin Capsule
STRENGTH:	0.5 mg
ROUTE OF ADMINISTRATION:	Oral

SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS: [redacted]

COMMENTS:

- This review addresses the sponsor responses to the Deficiency Letter. Their response to Deficiency #7 required further t-cons, and further action, as discussed in the review.
- The final recommendation, Acceptable, from the Office of Compliance regarding the inspections of the manufacturing sites was reported in EES on September 24, 2001. The EES report is copied into this report.
- The acceptance criterion of Q = [redacted] in 45 minutes is in place for both release and stability samples. Due to the cross-linking of the gelatin in the capsules that occurs over time, the aged samples require more time to rupture than samples at release. The acceptance criterion is necessary so that samples pass the dissolution test during shelf-life. The Biopharmaceutics Review by Dr. S. Al-Habet, Draft Review September 2001, states the dissolution methods and the acceptance criterion of Q = [redacted] in 45 minutes are acceptable. From a CMC perspective while the acceptance criterion is not expected to be discriminative in the analysis of release samples, the acceptance criterion is expected to be discriminative in the analysis of aged samples thereby allowing a change in dissolution behavior that would result from a future manufacturing change to be detected. As such, the criterion of Q = [redacted] in 45 minutes is deemed acceptable.

- A Tradename has not yet been approved.

CONCLUSIONS & RECOMMENDATIONS

The sponsor has agreed to provide a modified method for the analysis of dutasteride in the drug product. Their submission is expected to be received by 3-October-2001. With the modified method, from a CMC perspective, this NDA can be approved.

Orig. NDA #21-319
HFD-580/Division File
HFD-580/Farinas
HFD-580/Rhee/Salemme
HFD-820/Duffy
HFD-800/Ho
R/D Init by: MJ Rhee

J. Salemme, Ph.D., Review Chemist

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA #: 21-319
CHEMISTRY REVIEW #: 1

DATE REVIEWED: 10-Jul-2001

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	22-Dec-2000	21-OCT 2001	9-Jan-2001
Amendment	1-Mar-2001	2-Mar-2001	
Amendment	15-May-2001	16-May-2001	
Amendment	27-Jun-2001	28-Jun-01	

NAME & ADDRESS OF SPONSOR:
Glaxo Wellcome
Five Moore Drive
Research Triangle Park, NC 27709

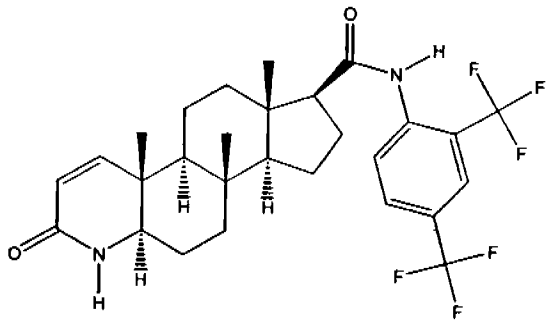
DRUG PRODUCT NAME: DUAGEN or ZYGARA are proposed

USAN: Dustasteride
Code Name/#: GI198745
Chem.Type/Ther.Class: Enzyme inhibitor

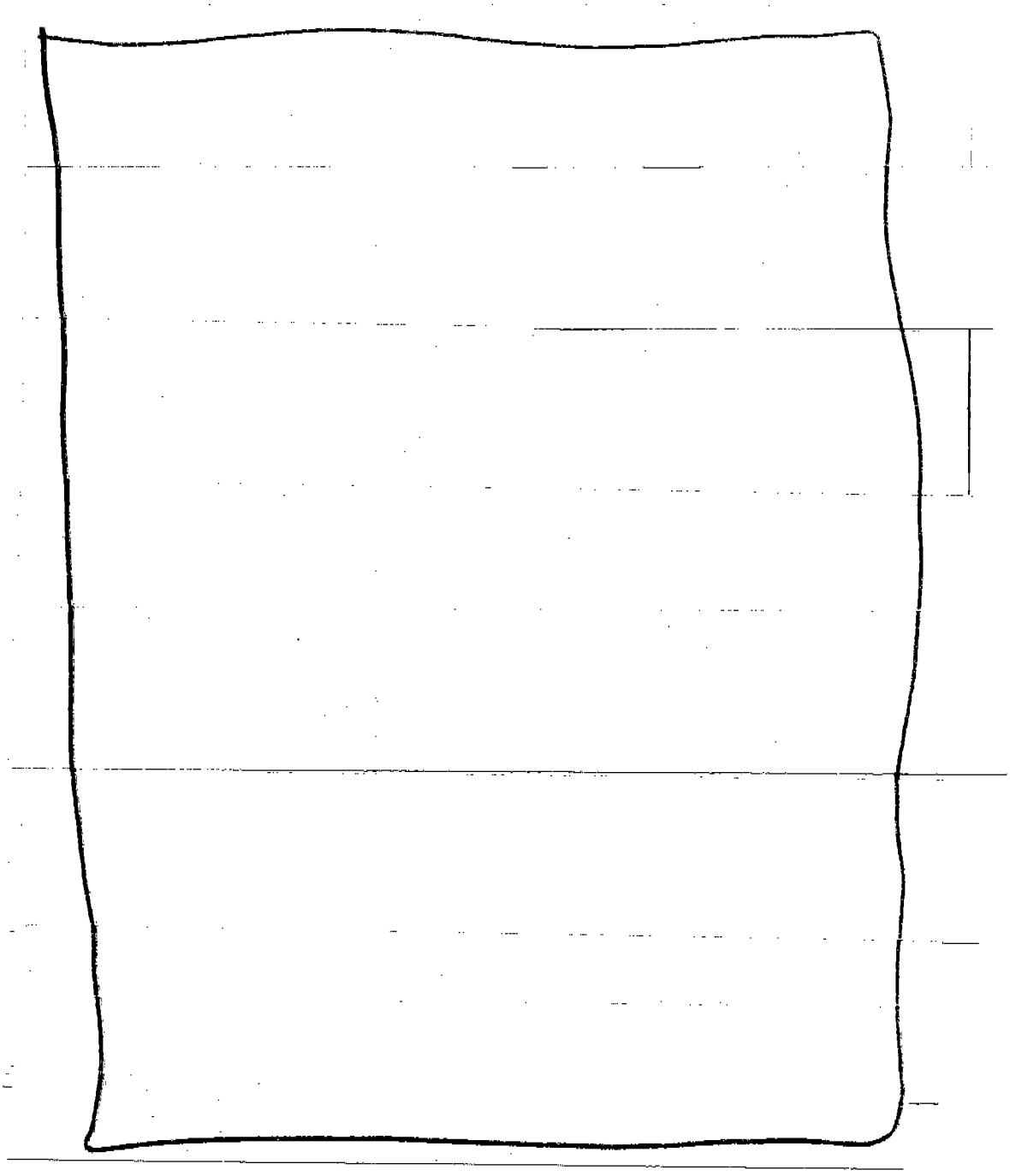
PHARMACOLOGICAL CATEGORY/INDICATION: 5-alpha reductase inhibitor for treatment of BPH (Benign Prostatic Hyperplasia)

DOSAGE FORM: Soft-Gelatin Capsule
STRENGTH: 0.5 mg
ROUTE OF ADMINISTRATION: Oral
SPECIAL PRODUCTS: _x_ Yes [gelatin capsules as mfd in DMF 14643]
SPOTS form submitted _x_ Yes

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(5-alpha-, 17-beta-)-N-[2,5-bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1-ene-17-carboxamide
$C_{27}H_{30}F_6N_2O_2$
Molecular Weight: 528.5



SUPPORTING DOCUMENTS



RELATED DOCUMENTS:

CONSULTS:

- A consult was sent to Microbiology in March 2001 to determine if the lack of tests and acceptance criteria for Microbial Testing is acceptable. The Microbiologist review of 8-August-2001 indicates the lack of

tests for microbial testing is acceptable.

- A consult was requested through EER in January 2001 for the inspection of drug substance and drug product manufacturing and testing sites. The sites have been inspected. The final recommendation from Office of Compliance has not yet been reported as of September 24, 2001.
- A consult to OPDRA for the Tradename review of the names DUAGEN or ZYGARA was requested in July 2001. In the response of 7-Sept-2001, OPDRA did not recommend the use of either name.

PATENT INFORMATION:

Patent 5,99,427 granted to Sponsor for Dutasteride Drug Substance and Drug Product, expiration 17-Sept-2013.

COMMENTS:

Dutasteride is a new molecular entity. As a 5-alpha reductase inhibitor, it inhibits the conversion of testosterone to dihydroxytestosterone, thereby inhibiting the growth of the prostate gland. Its indication will be for the treatment of BPH, benign prostatic hyperplasia. The drug is dissolved in [redacted] which is contained in soft gelatin capsules. The gelatin in the capsules has been found to cross-link over time making the gelatin more resistant to rupture. This cross-linking, however, does not affect the dissolution of the drug product.

The information request letter was sent to the sponsor on 27-August-2001. A request for a new tradename was conveyed to the sponsor on 14-September-2001.

- The Amendment of 2-March-2001 provided clinical pharmacology information and a better description of formulations used in studies.
- The Amendment 15-June-2001 was a request to change some of the container materials. See the Container/Closure Section of the Drug Product Review for a discussion.
- The Amendment of 28-June-2001 provided the 24-mo and 36-mo stability data for drug substance and drug product.

CONCLUSIONS & RECOMMENDATIONS

This NDA is approvable pending:

- Satisfactory responses from the sponsor to the deficiencies outlined in the draft deficiency letter.
- Satisfactory inspection reports for the manufacturing sites

Orig. NDA #21-319
HFD-580/Division File
HFD-580/Farinas
HFD-580/Rhee/Salemme
HFD-820/Duffy
HFD-800/Ho
R/D Init by: MJ Rhee_____

_____
J. Salemme, Ph.D., Review Chemist

Evaluation: Satisfactory.

25-SEP-2001

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21319/000
Stamp: 21-DEC-2000 Regulatory Due: 21-OCT-2001
Applicant: GLAXO WELLCOME
5 MOORE DR
RESEARCH TRIANGLE PARK, NC 27

Priority: S
Action Goal:
Brand Name: DUTASTERIDE 0.5MG SOFT-GELATIN CAPSULES
Established Name:
Generic Name: DUTASTERIDE
Dosage Form: CAP (CAPSULE)
Strength: 0.5 MG

Org Code: 580
District Goal: 22-AUG-2001

FDA Contacts: J. SALEMME (HFD-580) 301-827-7270 , Review Chemist

Overall Recommendation:

ACCEPTABLE on 25-SEP-2001 by M. GARCIA (HFD-322) 301-594-0095

Establishment: 1033964
GLAXO INC
1011 NORTH ARENDELL AVE
ZEBULON, NC 27597

DMF No:
AADA No:

Profile: CTL
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-FEB-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

OAI Status: NONE

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Establishment: 9610421
GLAXO WELLCOME LTD
DL128DT
BARNARD CASTLE, , UK

DMF No:
AADA No:

Profile: CTL
Last Milestone: OC RECOMMENDATION
Milestone Date: 02-FEB-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

OAI Status: NONE

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment: 9610414
GLAXO WELLCOME OPERATIONS L
DA1 5AH
DARTFORD, KENT, UK

DMF No:
AADA No:

Profile: CTL
Last Milestone: OC RECOMMENDATION
Milestone Date: 05-FEB-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

OAI Status: NONE

Responsibilities: FINISHED DOSAGE STABILITY TESTER

25-SEP-2001

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **9610419**
GLAXOCHEM LTD
COBDEN STREET
MONTROSE ANGUS, , UK DD108EA

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: **9615710**
RP SCHERER SA
67930
BEINHEIM, , FR

DMF No: [redacted]
AADA No:

Profile: **CSG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **25-SEP-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**