MAY 7 1981

NDA 85-865

Carter-Glogau Laboratories, Inc.
Attention: Samuel M. Fainberg, Ph.D.
5160 West Bethany Home Road
Glendale, AZ 85301

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testosterone Enanthate and Estradiol Valerate Injection, 90/4 mg. per ml.

Reference is also made to your amendments dated March 16, 1981 (2) and April 23, 1981.

We have completed the review of this abbreviated new drug application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

Any significant change in the conditions outlined in this abbreviated new drug application requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.8 of the new drug regulations.

This Administration should be advised of any change in the marketing status of this drug.

The requirement for adequate data to assure the biologic availability is being deferred at the present time. However, our action in approving this application is based upon an understanding that if this requirement is reinstated you will perform the appropriate procedures.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate advertising or promotional campaigns. Please submit both copies and a completed form FD-2253, together with a copy of the Final Printed Labeling, to the Division of Drug Advertising (HFD-170). A copy of form FD-2253 is enclosed for your convenience.

We call your attention to regulation 21 CFR 310.300 (b)(3) [or 451.60(b)(3) if Form 6] which requires that material for any subsequent advertising or promotional campaigns, at the time of their initial use, be submitted to our Division of Drug Advertising (HFD-170) with a completed form FD-2253.

The enclosures summarize the conditions relating to the approval of this application.

Sincerely yours,

Marvin Seife 5/7/81

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

Enclosures:
Conditions of Approval of a New Drug Application
Records & Reports Requirements

cc:
LOS-DO
HFD-313
HFD-616
MSeife/JLMeyer/MA Jarski MaJarski 5/6/81
R/D init JLMeyer/MSeife/5/5/81
pb/5/6/81 JMeyer 5/6/81
approved
2372E

NDA 85-865

APR 14 1981

Carter-Glogau Laboratories, Inc.
Attention: Jack K. Dale, Ph.D.
5160 West Bethany Home Road
Glendale, AZ 85301

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testosterone Enantnate and Estradiol Valerate Injection, 90/4 mg. per ml.

Reference is also made to your amendments dated December 17, 1979, May 22, 1980, July 24, 1980 and March 2, 1981.

We have completed the review of this abbreviated new drug application. However, before we are able to reach a final conclusion the following additional information is necessary:

1. Upoate specifications and tests for each components in accord with currently official compendia.

2. Provide an updated list of all manufacturers of each active ingredient and their U.S. representative.

3 .In your manufacturing procedure:
a) submit the referenced S.O.P.s or cross reference other documents that contain this information.

b) Provide information on the temperature to which the sesame oil is heated.

4. Container/closure: Submit information on the compatability of the container/closure system with the drug formula or cross reference other documents which contain such information.

5. Submit the specifications for and test methods used for each test performed on the drug product, i.e. in-process; release; stability, together with validating data for the method. If compendial procedures are used they should be in accord with currently official compendia.

lists benzyl alcohol and pages 3 and 4 are reversed).

6. Expand on your comments concerning the applicability of the USP preservative effectiveness test with oily base products containing chlorobutanol as a preservative, including any applicable data/information. We also request that you include your commitment to monitor the stability of the product and withdraw substandard lots from the market.

Please let us have your response.

Sincerely yours,

4/14/81

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
LOS-DO
HFD-616
JLMeyer/MAJarski
R/D init JLMeyer/MSeife/4/13/81
pb/4/13/81
rev w/f 2003E

JLMeyer 4/13/81

4/13/81

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 85-865

DATE APPROVAL LETTER ISSUED: MAY 7 1981

TO: Press Relations Staff (HFI-40)

FROM: [X] Bureau of Drugs [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION: [ ] ORIGINAL NDA [ ] SUPPLEMENT TO NDA [X] ABBREVIATED ORIGINAL NDA [ ] SUPPLEMENT TO ANDA

CATEGORY: [X] HUMAN [ ] VETERINARY

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG

Testosterone Enanthate and Estradiol Valerate

DOSAGE FORM: Oleagenous Injection

HOW DISPENSED: [X] Rx [ ] OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s). If amount is declared on label.)

Testosterone Enanthate	90 mg. per ml.
Estradiol Valerate	4 mg. per ml.

NAME OF APPLICANT (Include City and State)

Carter-Glogau Laboratories, Inc.
Glendale, AZ 85301

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

androgen/estrogen

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: Mary Ann Jarski MA Jarski DATE: 5/6/81

FORM APPROVED BY

NAME: Jack L. Meyer JL Meyer DATE: 5/6/81

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
HFD-530	85-865

3. NAME AND ADDRESS OF APPLICANT *(City and State)*

Carter Glogau Laboratories, Inc.
Glendale, AZ 85301

4. AF NUMBER

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)

6. NAME OF DRUG	7. NONPROPRIETARY NAME
	Testosterone Enanthate & Estradiol Valerate

8. SUPPLEMENT(S) PROVIDES FOR:

9. AMENDMENTS AND OTHER *(Reports, etc.)* **DATES**

3-16-81 (2)
4-23-81

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
Androgen/estrogen	☒ Rx ☐ OTC	see chemist's review completed 4-10-81

13. DOSAGE FORM (S)	14. POTENCY *(Iso)*
oleagenous injection	90/4 mg. per ml.

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS

CURRENT ☐ YES ☐ NO

REVIEWED ☐ YES ☐ NO

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

approval

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Mary Ann Jarski	MA Jarski 5/6/81	

DISTRIBUTION ☐ ORIGINAL JACKET ☒ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

CHEMIST'S REVIEW, Page 2

Enter evaluation or comments for each item. If necessary, continue on 8" x 10½" paper. Key continuation to item by number. Enter "NC" if no change or "NA" if not applicable.

NDA NUMBER 85-865

20. COMPONENTS AND COMPOSITION (6, 7)

see attached

21. FACILITIES AND PERSONNEL (8a,b)

–

22. SYNTHESIS (8c)

see attached and chemist's review completed 4-10-81

23. RAW MATERIAL CONTROLS (8d,e)

a. NEW DRUG SUBSTANCE

see attached

b. OTHER INGREDIENTS

—

24. OTHER FIRM(S) (8f)

25. MANUFACTURING AND PROCESSING (8g,h,j,k)

see attached and chemist's review completed 4-10-81

26. CONTAINER (8i)

see chemist's review completed 4-10-81

27. PACKAGING AND LABELING (8l,m)

–

28. LABORATORY CONTROLS (In-Process and Finished Dosage Form) (8n)

see attached and chemist's review completed 4-10-81

29. STABILITY (8p)

see attached and chemist's review completed 4-10-81

30. CONTROL NUMBERS (8c)

–

31. SAMPLES AND RESULTS (9)

a. VALIDATION supplied by the firm - see attached b. MARKET PACKAGE

32. LABELING (4)

see chemist's review completed 4-10-81

33. ESTABLISHMENT INSPECTION

satisfactory - see attached HFD -322 memo of 4-15-81

34. RECALLS

85-865

COMPONENTS

Testosterone Enanthate

Estradiol Valerate

Sesame Oil

Chlorobutanol (anhydrous)

COMPOSITION

	mg. per ml.
Testosterone Enanthate	90
Estradiol Valerate	4.0
Chlorobutanol Anhydrous	0.5%
Sesame Oil	q.s.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date APRIL 15, 1981

From Manufacturing Review Branch, HFD-322
Division of Drug Manufacturing

Subject APPROVABLE ANDAs 85-300, 85-865 TESTOSTERONE ENANTHATE AND ESTRADIOL VALERATE INJ

To Director
Division of GENERIC DRUG MONOGRAPHS (HFD 530)
Drug Products
Attn: MARY ANN JALSKI

APPLICANT: CARTER GLEGAN LABS INC, GLENDALE AZ

PRODUCT TESTING:

MANUFACTURING: CARTER GLEGAN LABS INC, GLENDALE AZ

We have evaluated the operations of THE ABOVE as they relate to compliance with Current Good Manufacturing Practice Regulations (21 CFR 211) with the exception of expiration dating (211.137) and stability testing (211.166) for the referenced application(s). Since you evaluate the applicants' submission of stability data and proposed expiration date, you should make the determination that the stability testing is adequate to support the proposed expiration date. If you desire, you can include appropriate references to (211.137) and (211.166) as deviations directly into your non-approvable letter if you conclude the stability testing is inadequate. Otherwise, we conclude there is no reason to withhold approval of the subject application(s) insofar as CGMP compliance of this/these firm(s) is concerned for the type of operations as specified in this/these pending application(s).

Our evaluation is based in part on Establishment Inspection and Quality Assurance Profile information.

Seymour Fishman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date .May 4, 1981

From Mary Ann Jarski - Chemist HFD-530

Subject The USP Antimicrobial Preservative Effectiveness Test for oil based products.

To Jack L. Meyer - Supervisory Chemist - HFD-530

In connection with 85-865 and 85-860 Testosterone Enanthate and Estradiol Valerate Injections, Carter-Glogau Laboratories, Inc. has submitted a set of correspondance with the USP that indicates that the Preservative Effectiveness test is not suitable for oil or petrolatum based products.

I suggest that this matter be taken up with the various Divisions of NDE and the USP to see if a satisfactory test can be arrived at.

Mary Ann Jarski

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

April 16, 1981

(EXHIBIT VI) 25

Aubrey S. Outschoorn, L.M.S., Ph.D.
The United States Pharmacopeia
12601 Twinbrook Parkway
Pockville, Maryland 20852

Dear Dr. Outschoorn:

Thank you very much for your letter of April 13, 1981 indicating that the USP Antimicrobial Preservative Effectiveness Test is not suitable for oil based products.

I have taken the liberty of sending a copy of your letter to Dr. Seife at the FDA Generic Drug Branch since I believe this acknowledgement by USP may enable FDA to waive their recent requests that this test be conducted initially and annually or otherwise on various unapproved/approved NDA OILY INJECTION products*.

Enclosed is a copy of a letter just sent to FDA which points out that such products may pass, but again, sometimes will fail. This is a very expensive and time-consuming test.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Jack K. Dale, Ph.D.
Vice-President, Quality Control

JKD/ta

*NDA NO./CARTER-GLOGAU OIL BASE PRODUCTS
list attached-page 2

THE UNITED STATES PHARMACOPEIA
THE NATIONAL FORMULARY
12601 TWINBROOK PARKWAY, ROCKVILLE, MARYLAND 20852
(301) 881-0666

F. S. OUTSCHOORN LIC. MED. SURG., PH.D.
Senior Scientist, Drug Standards Division

RECEIVED
APR 16 1981

April 13, 1981

27

Jack K. Dale, Ph.D.
Vice President, Quality Control
Carter-Glogau Laboratories, Inc.
5160 West Bethany Home Road
Glendale, Arizona 85301

Dear Dr. Dale,

This responds to your letter dated March 19, 1981, further to our correspondence in July 1979, about the use of the Antimicrobial Preservatives -- Effectiveness Test in relation to oil/water vehicles.

Since our correspondence in 1979, we did not receive any information which might have been useful to you. It has been recognized for some time, that the effectiveness test is not suitable for oil or petrolatum based products. Various workers have tried to develop modifications of the USP test that would accommodate petrolatum based products, however we are not aware of any studies which included oil vehicle injectables. One suggestion for modification was to use surfactants, but nothing seems to have developed from this. Your earlier solution to agitate the test throughout the test period was not considered appropriate. For instance, how often should the samples be agitated, e.g. daily, twice a day, or more often. The method of inoculation described for the test was not intended to simulate what might happen in practice. What it was hoped to demonstrate was that if the product became contaminated, by whatever means, then the preservative system would be effective.

I am sorry, therefore, not to be able to give you a current status report. We are also not in the position to suggest procedures which might be used for NDAs, since the tests in the USP are intended to be final product referee tests. I think the best we can do at present, is to suggest that you try to develop a suitable procedure for your purpose, yourself. You might also seek the advice of experts who have practical experience of these tests. If you wish, at a later stage, you may submit any developed procedure to us, and we will have them reviewed for possible incorporation of any useful points in our compendial standards. This does not mean that we will be in a position to advise regarding the suitability or otherwise of any such procedure for manufacturing purposes.

Published by The United States Pharmacopeial Convention, Inc. The United States Pharmacopeia and the National Formulary are the legally recognized compendia of standards for drugs and include assays and tests for the determination of strength, quality, and purity.

78

Your interest in this area of our compendial standards is greatly appreciated.

Sincerely yours,

Aubrey S. Outschoorn, L.M.S., Ph.D.

ASO:jp

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-8304

April 10, 1981

29

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
Department of Health, Education and Welfare
Public Health Service
Rood and Drug administration
Rockville, MD 20857

SUBJECT: TESTOSTERONE ENANTHATE AND ESTRADIOL VALERATE INJECTION 90/4
PRESERVATIVE EFFECTIVENESS TEST

Dear Dr. Seife:

The results obtained using the USP XX p 873 Antimicriobial Agent Effectiveness Test on the above product made with oily vehicle will depend on the concentration and type of preservative used, the transfer of preservatives from oily product to water phase slurry of microrganism and amount of agitation or shaking used initially, during storage and/or when the sampling transfers are done.

Please note first that the USP XX does not specify any remixing be done when testing the vials after storage for 1, 2, 3 and 4 weeks! Thus if aliquot samples for seeding are carefully removed after these times in a manner so as not to disturb any living microganism which have settled to the bottom, apparently acceptable USP levels may result!* (Note here that the product passes the USP test if less than 0.1% of the microganisms added are found and/or if molds and yeasts do not show an increase in numbers when aliquots are removed and added to media for counting) Of course the product may also pass if the preservative can diffuse across the oil/water boundary in sufficient concentration to do it's intended antibacterial function.

Naturally if the test containers are deliberately shaken (or even accidentally disturbed in sampling) some emulsification of water/microganisms will occur and may give false high or erratic readings if the organisms were not adequately exposed to preservatives while on the bottom!

In applying this test our lab has tried to get a representative sampling by shaking when sampling - however this can produce sampling errors if shaking is insufficient and non-homogeneous mixtures result.

*Consider oil normally floats on water. When microganism are introduced as an aqueous slurry these will slowly settle to the bottom and stick on the glass of the container in a very thin layer - almost impossible to see even with magnification! They are thus principally exposed to preservative during initial mixing and settling but then only to the extent to which the preservative can pass into the aqueous droplets or separated layer phase.

Dr. Fainberg brought to FDA attention the preliminary report that this Chlorobutanol/Sesame Oil product was sometimes erratic when tested by the USP Preservative Effectiveness test (it partially failed after 3 months at RT) although it passed initially. It was important to point out that such a problem may exist in applying this USP test to oily injections because FDA is currently requesting such data for several other similar NDA oily injection products. He felt that since our products are identical in formulation to the reference products, the FDA or USP Laboratory may already have developed a more consistant acceptable test procedure modification which we could use. Incidentally we believe the reason this second test was partially unsuccessful was not because the preservative level had changed significantly (Chlorbutanol was 108.2% initial vs 104.6% at 3 mo.) but because the mixing of oily product with test organisms was different and was insufficient. Please note - the shaker used at for the first test was not available at the time of the second test so identical test conditions were certainly not used. Please note again that no recommendation is made in the USP with regard to mixing parameters (temperature, time or degree of mixing, etc). This is apparently because the test is designed for aqueous products which mix almost instantaneously exposing each spore and micro-organism to the full level of preservative present. Since the vehicle of the product is Sesame Oil a uniform exposure of each water wetted spore/micro-organism to the preservative in the oily product would not occur as it does in aqueous products. Oil and water do not mix readily.

In the case of these oil products very extensive shaking or sonification would be needed for practical homogeneity and even then equivalent exposure might never occur as the water wetted spores would likely clump erratically as various size aqueous droplets in the oil hence would be exposed only to the preservative level which could diffuse over the oil/water boundary. Since chlorobutanol is more soluble in oil than in water it would be expected to stay principally in the oil - unless this could be corrected with proper validated procedures considering required total shaking time, temperature et al. Also most importantly USP test innoculation of the product is at a level which it would not be reasonable to expect could be encountered in medical practice (e.g. 100,000 to 1,000,000 microganism per ml of product! This test presents an artifical situation not encountered in practical use. It should further be noted that the A Niger test procedure which gives the most problem in reproducability adds 0.05% Polysorbate 80 to the sterile saline TS used to harvest the culture. This surface active wetting agent may be expected to absorb on the organisms and interfere with the action of the preservative since Polysorbate 80 is recommended to inactivate many preservatives!

Still further any spores must change to the vegetative growth form before they can be attacked successfully by a preservative! Normal growth of microganisms certainly does not occur in oil like it does in water!

For these reasons we believe our label direction to "Use the product within 30 days after first withdrawal" should limit any clinically introduced problem organism to an acceptable limit - and of course our products are sterile as supplied!

In conclusion we believe the USP Preservative Effectiveness test requires further development or modification before it is applied to oily products. A study of the actual test results recently submitted to you will show the erratic results when aliquots are taken out at weekly intervals and counted.

The attached correspondence with USP indicates our continuing interest in a meaningful validated preservative effectiveness test for oily injectables.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Jack K. Dale, Ph.D.
Vice President/Quality Control

JKD/ht

enc

CARTER-GLOGAU LABORATORIES, INC.
5160 WEST BETHANY HOME ROAD•GLENDALE, ARIZONA 85301•TELEPHONE (602) 939-7565•TELEX 66-6304

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March 19, 1981

Aubrey S. Outschoorn, L.M.S., Ph.D.
Senior Scientist, Drug Standards Division
The United States Pharmacopeia
The National Formulary
12601 Twinbrook Parkway
Rockville, Maryland 20852

Dear Dr. Outschoorn:

This is a follow-up to your letter of July 26, 1979 pertaining to certain aspects of oily injection testing by the Antimicrobial Preservatives - Effectiveness Test in the USP.

We have not received any reports from USP (or anyone) of the development of Preservative Effectiveness tests for oil based products, however it appears the USP test results are erratic for these as might be expected.

Could you please send a current status report or suggested alternate procedure? We need this for several NDA's.

Sincerely,

CARTER-GLOGAU LABORATORIES, INC.

Jack K. Dale, Ph.D.
Vice President/Quality Control

ht

THE UNITED STATES PHARMACOPEIA
THE NATIONAL FORMULARY
12601 TWINBROOK PARKWAY, ROCKVILLE, MARYLAND 20852
(301) 881-0666

AUBREY S. OUTSCHOORN, LIC. MED. SURG., PH.D.
Senior Scientist, Drug Standards Division

3 3

July 26, 1979

Jack K. Dale, Ph.D.
Vice President
Quality Control/Regulatory Affairs
Chromalloy Pharmaceuticals, Inc.
5160 West Bethany Home Road
Glendale, Arizona 85301

Dear Dr. Dale:

This responds to your letter dated June 19, 1979 addressed to our Dr. Heller, about certain aspects of the Antimicrobial Preservatives - Effectiveness Test in the USP.

The experiences you mention and your suggestions are very interesting and merit our fullest consideration. We have, therefore, referred your submissions to our advisers, and will keep you informed of developments.

Your interest in this area of our compendial standards is sincerely appreciated.

Sincerely,

Aubrey S. Outschoorn, L.M.S., Ph.D.

ASO/slb

cc: W. M. Heller
L. T. Grady

Published by The United States Pharmacopeial Convention, Inc. The United States Pharmacopeia and the National Formulary are the legally recognized compendia of standards for drugs and include assays and tests for the determination of strength, quality, and purity.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

34

June 19, 1979

William M. Heller, Ph.D.
Executive Director and Secretary
The United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, Maryland 20852

Dear Dr. Heller:

On several occasions FDA has requested "multiple entry data" for injectables. A request to FDA under Freedom of Information for a protocol to use turned up nothing. I asked Bernard T. Loftus and Joel Davis, Washington, FDA participants in the recent June 28-29, 1979 Los Angeles GMP Seminar, what FDA meant when they requested this test be run on a product but they did not know! Can you suggest a suitable protocol?

We have had test several oily vehicle injection products by the official USP "Preservative Effectiveness Test" but since the bacteria/molds are introduced into the vial as concentrated aqueous suspensions in media these settle to the bottom of the vial and do not always come into adequate contact with the preservative dissolved in the oil. Thus the tests are sometimes unsatisfactory. (This might be expected since oil and water to not mix and oil floats on water)

A repeat of the tests where agitation during the period of the test permitted proper contact of bacteria and preservative showed the preservative in the product was indeed effective against all 5 organisms specified by the USP. We believe agitation should be specified by the USP in the testing of oily injections and have so informed FDA and PDA. It is obvious that introduction of bacteria into a product during use would most likely be as a dry spore riding on a dust particle or other airborn particulate introduced from the top of a stopper, non-sterile room air, syringe/needle, etc, etc. Thus the current official USP test does not simulate practical reality.

Sincerely,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

Jack K. Dale

Jack K. Dale, Ph.D., Vice President
Quality Control/Regulatory Affairs

JKD/ht

GENERAL OFFICES:
60 WEST BETHANY HOME ROAD • GLENDALE, ARIZONA 85301
TELEPHONE (602) 939-7565 • TELEX 66-8304 (M-C LABS)

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFD-530

2. NDA NUMBER: 85-865

3. NAME AND ADDRESS OF APPLICANT *(City and State)*:
Carter Glogau Laboratories, Inc.
Glendale, AZ 85301

4. AF NUMBER:

5. SUPPLEMENT (S)
NUMBER(S) | DATE(S)

6. NAME OF DRUG:

7. NONPROPRIETARY NAME:
Testosterone Enanthate/
Estradiol Valerate

8. SUPPLEMENT(S) PROVIDES FOR:

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES:
see attached

10. PHARMACOLOGICAL CATEGORY:
estrogen/androgen

11. HOW DISPENSED:
☒ Rx ☐ OTC

12. RELATED IND/NDA/DMF(S):
see attached

13. DOSAGE FORM (S):
oleagenous injection

14. POTENCY *(Ies)*:
90/4 mg./ml.

15. CHEMICAL NAME AND STRUCTURE:

16. RECORDS AND REPORTS
CURRENT
☐ YES ☐ NO
REVIEWED
☐ YES ☐ NO

17. COMMENTS:

18. CONCLUSIONS AND RECOMMENDATIONS:
rev w/f

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Mary Ann Jarski	MAJarski 4/13/81	4-10-81

DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

CHEMIST'S REVIEW, Page 2

Enter evaluation or comments for each item. If necessary, continue on 8" x 10½" paper. Key continuation to item by number. Enter "NC" if no change or "NA" if not applicable.

NDA NUMBER 85-865

20. COMPONENTS AND COMPOSITION (6, 7)

see attached

21. FACILITIES AND PERSONNEL (8a,b)

-

22. SYNTHESIS (8c)

see attached

23. RAW MATERIAL CONTROLS (8d,e)

a. NEW DRUG SUBSTANCE

see attached

b. OTHER INGREDIENTS

24. OTHER FIRM(s) (8f)

- see chem review for 85-860

25. MANUFACTURING AND PROCESSING (8g,h,i,k)

see attached

26. CONTAINER (8j)

see attached

27. PACKAGING AND LABELING (8l,m)

-

28. LABORATORY CONTROLS (In-Process and Finished Dosage Form) (8n)

see attached and also see chem review for 85-860

29. STABILITY (8p)

see attached

30. CONTROL NUMBERS (8c)

-

31. SAMPLES AND RESULTS (9)

a. VALIDATION . to be supplied by the firm b. MARKET PACKAGE

32. LABELING (4)

satisfactory.

33. ESTABLISHMENT INSPECTION

requested 4-10-81

34. RECALLS

REVIEW OF RESUBMISSION, FPL

DATE COMPLETED: 3-12-79

ANDA #: 85-965

CO. NAME: Chromalloy Pharm., Inc.
Glendale, AZ 85301

NAME OF DRUG: Testosterone Enanthate 90 mg.
Estradiol Valerate 4 mg.

DATE OF SUBMISSION: 2-1-79

TYPE OF SUBMISSION: Resubmission - reply to FDA letters 10-14-77 and 1-4-78

CLINICAL EVALUATION:

1. Review of Studies:

Pertinent data is to be reviewed by the chemist.
Bio requirement - required

2. Review of Labeling:

Container labels: Satisfactory MOR 12-12-77

Package insert: Satisfactory
date: 11-78
PPI for estrogens: Aug 77

*Require PPI for androgens

CONCLUSION: Labeling is satisfactory except for PPI for androgens.

RECOM MENDATIONS: The firm is to be so notified.

CC:dup
VVK/wlh/3-13-79

V.V. Karusaitis, M.D.

CHEMIST's REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT	Statement Date:	NDA NUMBER: 85-865

NAME AND ADDRESS OF APPLICANT

Carter-Glogau Labs., Inc.
Glendale, AZ 85301

ORIGINAL
AMENDMENT
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE XXX
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

CHANGE IN CORPORATE NAME AND OWNERSHIP

DATE(s) of SUBMISSIO
9-4-79

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
androgen/estrogen	testosterone enanthate/ estradiol valerate	RX XXXXX OTC ____
DOSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/DMF
injection	90/4 mg/ml.	
STERILIZATION	SAMPLES	

LABELING

labeling as per letter of 8-3-79 and under new corporate name

BIOLOGIC AVAILABILITY

deferred

ESTABLISHMENT INSPECTION

requested

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

additional information

PACKAGING

additional information

STABILITY

Protocol:

Exp. Date: additional information

REMARKS AND CONCLUSION:

rev w/f

MAJarski

MAJarski 10/12/79

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 7/30/75
FROM: (thru J.L. Meyer)		OFFICE HFD-530
TO: Mary Ann Jarski Mr. David H. Bryant, Office of Compliance		DIVISION HFD-322

SUBJECT: Inspection Request

SUMMARY

In conncetion with ANDA 86-417, 86-418, 86-420

for: Testosterone Aqueous Suspension 25, 50 and 100/ mg. per ml.

Applicant: 86-865 Testosterone Enanthate/Estradiol Valerate 90/4 mg./ml Oleagenous xxx solution
86-266 Testosterone Enanthate/Estradiol Valerate 180/8 mg./ml.

Chromalloy Pharmaceuticals, Inc.
Carter-Glogau Laboratories Division
Glendale, AZ 85301

AF -

REQUESTED:

[ ] 1. Evaluation of compliance with CGMP for:

[ ] a. The applicant

[ ] b. Others

[ ] 2. Recommendation for approval/disapproval of the application/ communication/supplement, based on your evaluation of compliance with CGMP

Testing laboratory

REMARKS:

SIGNATURE

DOCUMENT NUMBER

NDA 85-865

AUG - 3 1979

Chromalloy Pharmaceuticals, Inc.
Carter-Glogau Laboratories Division
Attention: Samule M. Fainberg, Ph.D.
5160 West Bethany Home Road
Glendale, AZ 85301

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testosterone Enanthate/Estradiol Valerate, 90/4 mg./ml.

Reference is also made to your amendments dated February 1, 1979, and February 8, 1979.

We have completed the review of this abbreviated new drug application. However, before we are able to reach a final conclusion the following additional information is necessary:

1. Labeling is satisfactory except that a PPI for androgens is necessary. Specify

2. Your exact manufacturing sources for testosterone enanthate and estradiol valerate. Synthesis is required from each manufacturing source either by information submitted to the application or authorization to refer to a Drug Master File.

3. Please advise whether additives are included in the sesame oil. We request your supplier's descriptive material.

4. For the final dosage form:

   Submit test procedures, described in sufficient detail so that they may be duplicated in our laboratories. If have been developed for assay of the active ingredient and identification of degradation products, these are requested for validation. All procedures mentioned in your application, including methods and adapted compendial methods are to be submitted. To expedite review include a revised specification sheet. reference all applicable methodology and attach the description of the method.

5. Provide full information on containers and closures and tests run to assure compatability of the container-closure with the drug dosage form. We recommend that you check light sensitivity (see stability) and we request information as to whether vials are packaged with outer cartons.

6. With respect to stability:

   a) the normal protocol should include
   physical observation for appearance
   specific assay for each active ingredient
   specific assay for the preservative
   degradation products
   periodic evaluation for container-closure compatability

   b) Challenge studies as follows:

      1. Temperature cycling:
      Subject 3 vials of drug dosage to temperature cycling of 24 hours @4 C and 24 hours @45 C. Do full compliment of tests, as above. Compare with results of noncycled vials of the same batch tested in the same way.

      2. Light stability:

      Expose 6 vials to 75 and 500 ft. candles of light for a week. for half of the samples remove labels and directly expose vials to light source. For the other half retain labels and place in cartons. Observations as per stability protocol.

   c) All reports must include container closure system.

   d) Expiration dates should be established for (1) the manufactured product and (2) product after the first withdrawal from the multidose vial. Data is requested to substantiate these. Also, labeling should indicate 'Use within----(a time frame) after the first withdrawal. Your comment is requested.

Samples will be sent for validation after the question of methods (#4) is resolved.

Please let us have your response promptly.

cc
LOS-DO
HFD-614
JMeyer/MJarski
R/D init JMeyer/MSeife/8/2/79
pb/8/2/79
r ev w/f

8/2/79

Sincerely yours,

8/3/79

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

CHEMIST's REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT	Statement Date: 9-8-72(7-661	NDA NUMBER: 85-865

NAME AND ADDRESS OF APPLICANT
Chromalloy Pharmaceuticals Inc.
Carter-Glogau Laboratories Division
Glendale, AZ 85301

ORIGINAL XXX
AMENDMENT
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT
Manufacturing and labeling revisions

DATE(s) of SUBMISSIO
2-1-79
2-8-79

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
Estrogen/Androgen combination	testosterone enanthate/estradiol valerate	RX XXXX OTC ____
DOSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/DMF
Olegenous Injection (sesame Oil)	Testosterone Enanthate 90 Estradiol Valerate 4.0	
STERILIZATION	SAMPLES	
requested	submitted	

LABELING
See M.O.R. 3-12-79

BIOLOGIC AVAILABILITY
deferred

ESTABLISHMENT INSPECTION

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
additional information

PACKAGING
additional information

STABILITY
Protocol: modify protocol do challenge studies

Exp. Date: No judgement

REMARKS AND CONCLUSION: rev w/f M Jarski

Mx Jack 8/21/79

REVIEW OF RESUBMISSION

DATE COMPLETED: 1-11-80

ANDA #: 85-865

CO. NAME: Carter-Glogau Labs., Inc.
Glendale, AZ 85301

NAME OF DRUG: Testosterone Enanthate/Estradiol Valerate Injection
90/4

DATE OF SUBMISSION: 12-17-79

TYPE OF SUBMISSION: ANDA RESUBMISSION: FPL

CLINICAL EVALUATION:

1. Review of Studies:

   Pertinent data is to be reviewed by the chemist.
   Bio requirement - not required
   *New labels indicate formal change of name and corporate structure.

2. Review of Labeling:

   Container labels: Satisfactory
   Testosterone Enanthate 90 mg.
   Estradiol Valerate 4 mg. vials of 10 ml.

   Insert labeling: Not submitted

CONCLUSION: Container labels are satisfactory (FPL).

RECOMMENDATIONS: The firm is to be so notified.

V.V. Karusaitis, M.D.

cc:dup
VVK/wh/1-28-80

NDA 85-865

Carter-Glogau Laboratories, Inc.
Attention: Samuel M. Fainberg, Ph.D.
5160 West Bethany Home Road
Glendale, AZ 85301

Gentlemen:

We acknowledge receipt on October 4, 1979, of your communication dated September 20, 1979, regarding your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testosterone Enanthate/Estradiol Valerate Injection, 90/4 90/4 mg/ml.

Your communication:

(1) advised of a change in name and ownership

from: Carter-Glogau Laboratories Division
Chromalloy Pharmaceuticals, Inc.
A subsidiary of Chromalloy American Corporation

to: Carter-Glogau Laboratories, Inc.
A subsidiary of Revoo D.S. Inc.

(2) included an amended FD form 356H.

(3) indicated facilities and personnel at the Glendale, Arizone location remain the same

(4) committed to submit revised labeling.

We have reviewed the material submitted and acknowledge the change in name and ownership. However, before we are able to reach a final conclusion the following is necessary:

1. Information requested in our letter of August 3, 1979.

2. Final printed labeling under the new name.

Please let us have your response.

cc:
HFD-614
LOs-do
JMeyer/MJarski
r/d/ init. JMeyer/MSeife 10-9-79
f/t/wlh/10-10-79
rev w/f

10/12/79 10/12/79

Sincerely yours,

10/15/79

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

REVIEW OF ANDA

DATE COMPLETED: 7-1-80

ANDA #: 85-865

CO. NAME: Carter-Glogau Labs.
Glendale, AZ 85301

NAME OF DRUG: Testosterone Enanthate 90 mg/Estradiol Valerate 4 mg.

DATE OF SUBMISSION: 5-22-80

TYPE OF SUBMISSION: ANDA Resubmission- PPI
Reply to FDA 8-3-79 (9 months later) (draft)

CLINICAL EVALUATION:

1. Review of Studies:

Pertinent data is to be reviewed by the chemist.
Bio requirement - not required.

2. Review of Labeling:

Container labels: Satisfactory
Testosterone Enanthate 90 mg. vials of 10 ml. (multi-dose)
Estradiol Valerate 4 mg.

Insert labeling: Satisfactory
Estrogen PPI: Nov. 77

CONCLUSION: (Estrogen PPI) Insert labeling is satisfactory. Container labels are satisfactory.

RECOMMENDATIONS: The firm is to be so notified.

V.V. Karusaitis, M.D.

cc:dup
VVK/wh/7-14-80

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

February 1, 1979

Marvin Seife, M. D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
Department of Health, Education,
and Welfare
Food and Drug Administration
Public Health Service
Rockville, MD 20857

SUBJECT: TESTOSTERONE ENANTHATE/ESTRADIOL VALERATE 90/4
NDA 85-865

Dear Dr. Seife:

Reference is made to your letters of October 14, 1977 and January 4, 1978 for Testosterone Enanthate/ Estradiol Valerate 90/4.

We are supplying the following information, as requested.

LABELING:

1. Revised package inserts are attached, as requested.

Other information required by 314. (f) of the regulation:

1. Master Formula Card which specify Chlorobutanol as the preservative are enclosed.

2. Attached, as requested is the Manufacturer's Certificate of Analysis.

3. "Blank Page" was submitted in error.

4. Assurance of the identity, strength, quality and purity of the final dosage form are shown on the attached product specification sheets.

   Chlorobutanol is used in our product as a preservative.

GENERAL OFFICES:
5160 WEST BETHANY HOME ROAD • GLENDALE, ARIZONA 85301
TELEPHONE (602) 939-7565 • TELEX 66-8304 (M-C LABS)

5. Product stability in the container/closure system are attached. These bear out the suitability for use of Type I glass vial with stopper when protected from light.

   Also attached is the Master file Referral Letter from for the proposed stopper.

6. Available stability data are also enclosed, including some data at challenge conditions done at 0, 500, 1000 and 2000 hours at 37°C and multiple entry tests at 1, 10, 20 and 30 days.

   USP Preservative Effectiveness, assay for free Estradiol (a possible degradation product) after room temperature and 37°C storage are also enclosed.

Based on the above information and data collected on several older experimental formulas and data previously submitted separately for our NDAs on single entity injections of Testosterone Enanthate or Estradiol Valerate (Q.V.) we conclude this relatively inert oil-based product will be stable for 4 years at room temperature when protected from light. We propose based on available stability information a provisional expiration dating of two (2) years.

Based on multiple entry data, product appearance, i.e., we have observed no significant change in multiple dose vials within 30 days after first use.

Samples as requested are being submitted under separate cover.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC

Samuel M. Fainberg, Ph. D.
Director
Technical and Regulatory Affairs

/edc
encls:

5/14/81

Sterile 10 ml NDC 0381-0360-10 Multi-dose

TESTOSTERONE ENANTHATE - ESTRADIOL VALERATE INJECTION 90/4

Each ml contains Testosterone Enanthate 90 mg Estradiol Valerate 4 mg Chlorobutanol (Chloral derivative) 0.5% as preservative in Sesame Oil q.s. STORE AT ROOM TEMPERATURE (59° - 86°F). Use within 30 days after first withdrawal. **PROTECT FROM LIGHT** Keep vial in carton until used.

USUAL ADULT DOSE: Intramuscular. See package insert.

CAUTION: Federal law prohibits dispensing without prescription.

580/0360-10

CARTER-GLOCAU LABORATORIES, INC
Glendale, Arizona 85301 U.S.A.

MAY 7 1981

Sterile 10 ml NDC 0381-0360-10 Multi-dose

TESTOSTERONE ENANTHATE - ESTRADIOL VALERATE INJECTION 90/4

Each ml contains Testosterone Enanthate 90 mg Estradiol Valerate 4 mg Chlorobutanol (Chloral derivative) 0.5% as preservative in Sesame Oil q.s. STORE AT ROOM TEMPERATURE (59° - 86°F). Use within 30 days after first withdrawal. **PROTECT FROM LIGHT** Keep vial in carton until used.

USUAL ADULT DOSE: Intramuscular. See package insert.

CAUTION: Federal law prohibits dispensing without prescription.

580/0360-10

CARTER-GLOCAU LABORATORIES, INC.
Glendale, Arizona 85301 U.S.A.

MAY 7 1981

TESTOSTERONE ENANTHATE AND ESTRADIOL VALERATE INJECTION

90 mg./4 mg. per ml.
IN SESAME OIL

WARNING

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4]

The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] it therefore appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestagens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[1,5] This risk has been estimated as not greater than 4 per 1000 exposures.[1] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis.[6,12] It is not known whether this condition is a precursor of vaginal malignancy. Although similar data are not available with the use of other estrogens, it is reasonable to presume they would induce similar changes.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[13-15] One case control study[16] estimated a 4.7 fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The estimated rate of these abnormalities in the population from which the cases were obtained was 0.2 abnormalities per 1000 live births in the years 1968-1973. It is not known how many of the 0.2 abnormalities per thousand live births arose in women who were taking sex hormones; therefore 0.2 per 1000 is to some degree an overestimate of the spontaneous rate of these abnormalities. These data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000.

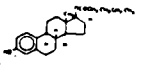
In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestagens are effective for these uses.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: A sterile solution of Testosterone Enanthate (Long Acting Androgen) and Estradiol Valerate (Long Acting Estrogen) for intramuscular injection. The Testosterone Enanthate component occurs as a white or creamy white, crystalline powder, is odorless or has a faint odor characteristic of heptanoic acid. It is insoluble in water, very soluble in ether; soluble in vegetable oils. It has the structural formula:

$C_{26}H_{40}O_3$
Androst-4-en-3-one, 17-[(1-oxoheptyl)oxy]-, (17β)-.
Testosterone heptanoate

Estradiol Valerate occurs as a white, crystalline powder, is usually odorless but may have a faint, fatty odor. Practically insoluble in water; soluble in castor oil, in methanol, in benzyl benzoate, and in dioxane; sparingly soluble in sesame oil and in peanut oil. It has the structural formula:



$C_{23}H_{32}O_3$
Estra-1,3,5(10)-triene-3,17-diol(17β)-, 17-pentanoate
Estradiol 17-valerate

Available as: Sterile Testosterone Enanthate-Estradiol Valerate Injection.

Each ml. contains: Testosterone Enanthate 90 mg., Estradiol Valerate 4 mg., Chlorobutanol (Chloral derivative) 0.5% as preservative in Sesame Oil q.s.

CATEGORY: ESTROGEN — ANDROGEN

ACTIONS: Testosterone Enanthate and Estradiol Valerate produce androgenic and estrogenic effects similar to the naturally produced hormones.

CLINICAL PHARMACOLOGY: Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. They promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts; indirectly, they contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Decline of estrogenic activity at the end of the menstrual cycle can bring on menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the preovulatory or nonovulatory cycle, estrogen is the primary determinant in the onset of menstruation. Estrogens also affect the release of pituitary gonadotropins.

The pharmacologic effects of conjugated estrogens are similar to those of endogenous estrogens. They are soluble in water and may be absorbed from mucosal surfaces after local administration.

In responsive tissues (female genital organs, breasts, hypothalamus, pituitary) estrogens enter the cell and are transported into the nucleus. As a result of estrogen action, specific RNA and DNA syntheses occur. Metabolism and inactivation occur primarily in the liver. Some estrogens are excreted into the bile; however they are reabsorbed from the intestine and returned to the liver through the portal venous system. Water-soluble estrogen conjugates are strongly acidic and are ionized in body fluids, which favor excretion through the kidneys since tubular reabsorption is minimal.

Androgenic hormones are secreted principally by the testis and, to a lesser extent, by the adrenal cortex and ovary. Testosterone, the most potent androgen, is the principal secretion product of the cells of Leydig, which are located in the interstitial spaces of the testis. Leydig cell function is controlled by the anterior pituitary through the gonad[illegible] interstitial cell-stimulating (ICSH) hormone. Testosterone, which circulates in a concentration of 280 to 1,400 ng./100 ml. in males, is reduced in most tissues to the highly potent 5α-dihydrotestosterone, which probably is the active intracellular androgen.

Under normal conditions, the adrenal cortex and ovary secrete very little testosterone, instead, they secrete less potent androgens, such as Δ-androstenedione and dehydroepiandrosterone, which are metabolized in the liver and kidney to testosterone. The circulating testosterone in normal women (25 to 125 ng./100 ml.) is derived primarily from the metabolism of these less potent androgens. When certain pathologic conditions of the adrenal cortex or ovary exist, such as hyperplasia, adenoma, or carcinoma, production of these androgens (including testosterone) may be markedly increased.

INDICATIONS: Moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions).

TESTOSTERONE ENANTHATE AND ESTRADIOL VALERATE INJECTION HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions:

1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
2. Known or suspected estrogen-dependent neoplasia.
3. Known or suspected pregnancy (See Boxed Warning).
4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders.
6. A past history of thrombophlebitis or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: 1. Induction of malignant neoplasms. Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina and liver. There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning).

At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[7,8] although a recent long-term followup of a single physician's practice has raised this possibility.[7a] Because of the animal data, there is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms.

2. Gall bladder disease. A recent study has reported a 2 to 3-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens,[18] similar to the 2-fold increase previously noted in users of oral contraceptives.[19] In the case of oral contraceptives the increased risk appeared after two years of use.[24]

3. Effects similar to those caused by estrogen-progestagen oral contraceptives. There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement are more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[20-22]

a. Thromboembolic disease. It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic diseases, including thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[24-27] Cases of retinal thrombosis, mesenteric thrombosis and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug.[32,33] An increased risk of post-surgery thromboembolic complications has also been reported in users of oral contraceptives.[34,35] If feasible, estrogen should be discontinued at least 4 weeks before, and not resumed until at least 4 weeks after, surgery of the type associated with an increased risk of thromboembolism.

While an increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogens has not been found,[18,36] this does not rule out the possibility that such an increase may be present or that subgroups of women who have underlying risk factors or who are receiving relatively large doses of estrogens may have increased risk. Therefore estrogens should not be used in persons with active thrombophlebitis or thromboembolic disorders, and they should not be used (except in treatment of malignancy) in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease and only for those in whom estrogens are clearly needed.

Large doses of estrogen (5 mg. conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men[37] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.

b. Hepatic adenoma. Benign hepatic adenomas appear to be associated with the use of oral contraceptives.[38-40] Although benign, and rare, these may rupture and cause death through intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestagen preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives.[39] The relationship of this malignancy to these drugs is not known at this time.

c. Elevated blood pressure. Increased blood pressure is not uncommon in women using oral contraceptives. There is now evidence that this occurs with use of estrogens in the menopause[41] and blood pressure should be monitored with estrogen use, especially if high doses are used.

d. Glucose tolerance. A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogen.

4. Hypercalcemia. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

APPROV
MAY 7 19

PRECAUTIONS: A. General Precautions.

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pre-treatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed.

2. Fluid retention — Because estrogens may cause some degree of fluid retention, conditions might be influenced by this factor such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

3. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.

4. Oral contraceptives appear to be associated with an increased incidence of mental depression. Although it is not clear whether this is due to the estrogenic or progestagenic component of the contraceptive, patients with a history of depression should be carefully observed.

5. Preexisting uterine leiomyomata may increase in size while using estrogen.

6. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

7. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.

8. Estrogens may be poorly metabolized in patients with impaired liver function and they should be administered with caution in such patients.

9. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.

11. Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

B. Information for the Patient. See text of Patient Package Insert which is attached below.

C. Pregnancy Category X. See Contraindications and Boxed Warning.

D. Nursing Mothers. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

Female patients should be watched carefully for symptoms or signs of virilization such as hoarseness or deepening of the voice, oily skin, acne hirsutism, enlarged clitoris, stimulation of libido, and menstrual irregularities. Androgen may cause masculinization of a female. Some of these changes, such as voice changes, may be irreversible even after drug is stopped. Cholestatic hepatitis with jaundice and altered liver function tests, such as increased BSP retention and rises in SGOT levels, have been reported after Testosterone. These changes appear to be related to dosage of the drug. Therefore, in the presence of any changes in liver function tests, drug should be discontinued.

Prolonged dosage of androgen may result in sodium and fluid retention. This may present a problem, especially in patients with compromised cardiac reverse or renal disease.

Hypersensitivity and gynecomastia may occur rarely. PBI may be decreased in patients taking androgens. Hypercalcemia may occur. If this occurs, the drug should be discontinued.

Virilizing effects are minimal but some patients may exhibit some effect from androgen activity. If these conditions occur dosage should be reduced. This product should be used with caution in patients with cardiac or renal disease epilepsy or asthma because of fluid retention that may aggravate the underlying disorders. Such patients should be carefully evaluated before and during treatment with the androgen-estrogen combination.

ADVERSE REACTIONS: (See Warnings regarding induction of neoplasia adverse effects on the fetus, increased incidence of gall bladder disease, and adverse effects similar to those of oral contraceptives, including thromboembolism.) The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives:

1. Genitourinary system.
Breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis; change in cervical eversion and in degree of cervical secretion; cystitis-like syndrome.
2. Breasts
Tenderness, enlargement, secretion.
3. Gastrointestinal
Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice.
4. Skin
Chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.
5. Eyes
Steepening of corneal curvature; intolerance to contact lenses.
6. CNS
Headache, migraine, dizziness; mental depression; chorea.
7. Miscellaneous
Increase or decrease in weight; reduced carbohydrate tolerance, aggravation of porphyria; edema, changes in libido.

ACUTE OVERDOSAGE: Numerous reports of ingestion of large doses of estrogen-containing oral contraceptives by young children indicate that serious ill effects do not occur. Overdosage of estrogen may cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION: For intramuscular administration.

1. Given cyclically for short term use only.
For treatment of moderate to severe vasomotor symptoms associated with the menopause.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g. 3 weeks on and 1 week off).

Attempts to discontinue or taper medication should be made at 3 to 6 month intervals.

The usual dosage range is 1 ml. to 2 ml. every 3 to 4 weeks.

A dry needle and syringe should be used. Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

Storage: Should be stored at room temperature. Storage at low temperatures may result in the separation of some crystalline material which redissolves readily on warming.

HOW SUPPLIED: Multiple dose vials of 10 ml.

CAUTION: Federal law prohibits dispensing without a prescription.

Literature Revised: November 1978

Product No. 0360-10

REFERENCES: 1. Ziel, H. K. and W. D. Finkle, "Increased Risk of Endometrial Carcinoma Among Users of Conjugated Estrogens," *New England Journal of Medicine*, 293:1167—1170, 1975.

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OCT 28 1977

NDA 85-239 NDA 85-703
NDA 85-620 NDA 85-704
NDA 85-666 NDA 85-885
NDA 85-673

Carter-Wallace Laboratories Division
Chromalloy Pharmaceuticals, Inc.
Attention: Samuel H. Feinberg, Ph.D.
5160 West Bethany Home Road
Glendale, AZ 85301

RE: Estrogen Containing Preparations - Requirement for Labeling Directed to the Patient.

Gentlemen:

In accord with the FEDERAL REGISTER notice of July 22, 1977, each estrogen drug product restricted to prescription distribution, shall be dispensed to patients with labeling in lay language containing information concerning effectiveness, contraindications, warnings, precautions and adverse reactions.

Excerpted sections of this notice are enclosed, and the extended effective date of the ruling was October 18, 1977.

Please submit the required Patient Package Insert.

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc: LOS-DD
Dup HFD-614
VVKarusaitis/JMeyer/HJarski
r/d/ init. JMeyer/HSeife 10-28-77
f/t/wlb/10-28-77
ACK

Enclosure:
F.R. July 22, 1977

Testosterone Enanthate { 180 mg./ml. } 10 ml. multiple
Estradiol Valerate { 8 mg./ml. } dose vials

November 28, 1977

Memorandum of In-House Meeting

Present: Dr. M. Selfe, HFD-530
Dr. V. V. Karusaitis, HFD-530
Dr. E. M. Ortiz
Dr. St. Raymond
Dr. Bennett
Dr. Berliner
Dr. Kertesz
Mr. Billian
Mr. Smith

Purpose: To determine the advisability and acceptability of a 10 ml. multiple dose vial containing 180 mg./ml. of Testosterone Enanthate and 8 mg./ml. of Estradiol Valerate.

Dr. Karusaitis opened the discussion with a brief statement as to the purpose of the meeting.

The Indications for this proposed product ~~was~~ were for postpartum breast engorgement and suppression of lactation. HFD-530 felt that the reference product, Squibbs Deladumone OB - 180/8 mg./ml., was sufficient and acceptable and that the proposed 10 ml. multiple dose vial was not. The danger of contamination and infection were the primary reasons for objection.

It appeared to be decided that the proposed 10 ml. multiple dose vial would be permitted.

F. Kirby Smith, Jr.
F. Kirby Smith, Jr., C.S.O.

cc:
Orig. ANDA
HFD-530/MSelfe
HFD-530/VVKarusaitis
HFD-130/(2)
HFD-130/FKSmith/11-28-77/ls/12-2-77

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Director HFD-130
Div. of Metabolism & Endocrine Drug Products

DATE: October 31, 1977

FROM : V.V. Karusaitis, M.D./Marvin Seife, M.D.
HFD-530

SUBJECT: Acceptability of 10 ml. Multiple Dose Vial Containing:

Testosterone Enanthate	180 mg.
Estradiol Valerate	8 mg.

Reference product is Deladuomone OB (Squibb) 2 ml. vial specifically used for a singular indication. See enclosures (2).

HFD-530's Proposed Stand: 2 ml. Vial - acceptable
10 ml. vial - unnecessary and unacceptable

Question: Does HFD-130 agree?

V.V. Karusaitis, M.D.

Marvin Seife, M.D.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Marvin Seife, M.D.
(HFD-530)

DATE: June 6, 1977

FROM : V.V. Karusaitis, M.D.

SUBJECT: Deviations from Reference Product:

Reference Product			Proposed Product
Deladumone[R] NDA			Generic Label
Testosterone Enanthate	90 mg.	INJ	. . . . .
Estradiol Valerate	4 mg.		
How Supplied: 5 ml. vials, 1 ml. vials			10 ml. multiple dose
			Chlorobutanol 0.5%
Testosterone Enanthate	180 mg.	INJ	
Estradiol Valerate	8 mg.		
HOW SUPPLIED: 2 ml. vial			10 ml. multiple dose
			Benzyl Alcohol 2%

Contents

Each ML

90 mg. Testosterone Enanthate
4 mg. Estradiol Valerate

0.5% Chlorobotanol . . . . . Preservative . . Benzyl Alcohol 2%

Sesame Oil Vehicle . . . . . Sesame Oil

**Unacceptable: 10 ml. vials (Multiple Dose) 180 mg.
8 mg.

Reference product is a 2 ml. vial specifically used for a singular indication: Prevention of Postpartum Breast Engorgement. Rationale for 2 ml vial: Large potency in small amount for injection
1 cc

RECOMMENDATION: Separate submissions for potencies.

V.V. Karusaitis, M.D.

Conversation with Dr. V.V. Karusaitis on 10-6-77

Squibb has two androgen/estrogen products Deladumone 90/4 mg./ml and Deladumone OB 180/8 mg./ml. Each product has a specific use and there are separate package inserts and specific packaging for each. Dr. Karusaitis noted this in his memorandum of 6-6-77

However, generaic manufacturers are proposing to manufacture the 90/4 mg./ml. and the 180/8 mg./ml. in 10 ml. multiple dose vials as interchangeable dosage forms for both uses and provide single package inserts.

At a meeting with Mr. Knapp, Dr. Karusaitis said it was decided that the Division of Metabolism and Endocrine Drug Products would be consulted as to the applicability of these generic products.

JAN 4

NDA 85-865

Carter-Glogau Laboratories Division
Chromalloy Pharmaceuticals, Inc.
Attention: Ronald M. Carter
5160 W. Bethany Home Road
Glendale, AZ 85301

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testosterone Enanthate + Estradiol Valerate Injection 90 + 4 mg./ml.

Reference is also made to (1) your communication dated October 31, 1977, enclosing a Patient Package Insert, and (2) our letter of October 14, 1977 requesting additional information.

We have reviewed the Patient Package Insert and note that unapproved estrogen products are included in the HOW SUPPLIED section. Therefore, before we are able to reach a final conclusion approval is necessary for all listed products.

Other information required by 314.1 (f) of the Regulations:

1. The information requested in our referenced letter.

2. Like information for multiple dose vials. For multiple dose vials also propose an expiration term for the vial after initial use. i.e. "Use within..." and submit data in support of it.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 1/4/78

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

cc:
LOS-DO
HFD-614
VVKarusaitis/JMeyer/MJarski 1/3/78
R/D init JMeyer/MSeife/1/3/78
ps/1/3/78
rev w/f

JMeyer cr 1/3/78

REVIEW OF AMENDMENT RESUBMISSION F.P.L.

DATE COMPLETED: 12-9-77

ANDA #: 85-865

CO. NAME & ADDRESS:
Chromalloy Pharmaceuticals, Inc.
Glendale, AZ 85301

F.R. DATE: 7-22-77

NAME OF DRUG: Testosterone Enanthate 90 mg/ml
Estradiol Valerate 4 mg inj.

DATE OF SUBMISSION: 10-31-77

TYPE OF SUBMISSION: Resubmission (Reply to FDA letter Oct. 28, 1977)

CLINICAL EVALUATION:

1. Review of studies:
Pertinent data is to be reviewed by the chemist
Bioavailability requirement: Not required

2. Review of labeling:

a. Container labels: Satisfactory
PPI

b. Insert labeling: Satisfactory
Except for "How Supplied" section: Many products are named which are not approved either through ANDA or NDA process

PPI

CONCLUSION: Labeling is satisfactory except for "How Supplied" Section

RECOMMENDATIONS: The firm is to be so notified

V.V. Karusaitis, M.D.

cc:
Dup
VVK/mlb/12-12-77

ABBREVIATED NEW DRUG APPLICATION
OR SUPPLEMENT

85-865
AF Number

Name and address of Applicant (City and State)

Carter-Glogau Laboratories Division
Chromalloy Pharmaceuticals, Inc.
Glendale, AZ 85301

Original
Amendment
Supplement xxxxx
Resubmission
Correspondance
Report
Other

Purpose of Amendment/Supplement

patient package insert

Date(s) of Submission(s)
10-31-77

Pharmacological Category	Name of Drug	
androgen estrogen	testosterone enanthate + estradiol valerate	
Dosage Form(s)	Potency(ies)	How Dispensed
injection	90 + 4 mg./ml.	R_x xxxx OTC
Sterilization	Samples	Related IND/NDA/DMF
requested	reqested	

Labeling
see medical officer's review of 12-9-77

Biologic Availability

not required

Establishment Inspection

requested

Components, Composition, Manufacturing and Controls

per issuing letter

Packaging
requested

Stability
Protocol requested

Expiration Date

Remarks and Conclusion

rev w/fr ~~majarski~~

REVIEWER

DATE

RW/F ORIGINAL

CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

October 31, 1977

NDA ORIG AMENDMENT

FPL

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
Department of Health, Education, and Welfare
Public Health Service
Food and Drug Administration
Rockville, Maryland 20857

Subject: NDA 83-397, NDA 83-546, NDA 83-547, NDA 83-599
NDA 83-714, NDA 83-826, NDA 83-840, NDA 84-032
NDA 85-239, NDA 85-620, NDA 85-666, NDA 85-673
NDA 85-703, NDA 85-704, NDA 85-865

Dear Dr. Seife:

In accordance with your two letters of October 28th, 1977 covering the above NDA's which are Estrogen containing preparations, enclosed please find the Estrogen Patient Package Insert you requested.

This insert is in accord with the Federal Register notice of July 22nd, 1977.

Should you require further information please do not hesitate to write or call.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

Ronald M. Carter
President

RMC/sp

cc: Dr. Sam Fainberg
Governor Herschel Loveless
NDA Files

RECEIVED
NOV 03 1977
BUREAU OF DRUGS

GENERAL O. CES:
5160 WEST BETHANY HOME ROAD • GLENDALE, ARIZONA 85301
TELEPHONE (602) 939-7565 • TELEX 66-8304 (M-C LABS)

MEMO RECORD | AVOID ERRORS PUT IT IN WRITING | DATE 6-29-77

FROM: M.A. Jarsby (thru J.L. Meyer) | OFFICE HFD-530

TO: Mr. David H. Bryant, Office of Compliance | DIVISION HFD-322

SUBJECT: Inspection Request

SUMMARY

In conncetion with ANDA 85-865

for: Testosterone Enanthate and Estradiol Valearate Injection, 90/4.

Applicant:

Carter - Glogau Laboratories Division
5160 W. Bethany Home Road.
Glendale, AZ 85301.

AF -

REQUESTED: —

[✓] 1. Evaluation of compliance with CGMP for:

[✓] a. The applicant

[✓] b. Others all LAB tests are performed by

[✓] 2. Recommendation for approval/disapproval of the application/communication/supplement, based on your evaluation of compliance with CGMP

REMARKS:

ATURE

C. Cheng

DOCUMENT NUMBER 85-865

FD FORM 2034 (2/72)

OCT 14 1977

NDA 85-865

Carter-Glogau Laboratories Division
Chromalloy Pharmaceuticals, Inc.
Attn: Samuel M. Fainberg, Ph.D.
5160 W. Bethany Home Road
Glendale, AZ 85301

Gentlemen:

Reference is made to your abbreviated new drug application dated May 26, 1977, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testosterone Enanthate 90 mg. and Estradiol Valerate 4 mg. per ml. injection.

We have completed the review of this abbreviated new drug application and have the following comments regarding labeling and packaging:

1. The green color of the insert creates a degree of illegibility. The lengthy insert becomes more difficult to read.

2. The applicability of a 10 ml. multidose vial for this product has been referred to our Division of Metabolism and Endocrine Drug Products and we will correspond with you after their determination.

Other information required by 314.8(f) of the Regulations:

1. The rationale for using benzyl alcohol as a preservative in place of the reference product's chlorobutanol.

2. Manufacturers' certificates of analysis for the active ingredients.

3. The rationale for "Blank Page" in the application.

4. Adequate assurance of the identity, strength, quality and purity of the final dosage form. In this regard revise your specifications and tests in accord with the enclosure. Also, clarify your reference to chlorobutanol on page 22.

5. Adequate information on container-closure systems to assure their suitability for the intended use.

6. A complete description of, and data derived from, studies of the saability of the drug. The application should include a proposed expiration date to appear on the label together with data that furnish a sound basis for concluding the identity, strength, quality and purity of the drug will be preserved until used. Include some data at challenge conditions and evaluation of degredation products.

To expedite the processig of this application we are requesting samples of the drug product together with your analytical results.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

LOS-DO DUP HFD-614 10/12/77
VVKarusaitis/JLMeyer/MAJarski
R/DinitJMeyer/MSeife
ft/cjb10-11-77 rev w/f
Enclosure: Testosterone Enanthate and Estradiol Valerate Injection.

REVIEW OF ANDA

DATE COMPLETED: 7-11-77

ANDA #: 85-855

CO. NAME: Carter-Glogau Labs. Div.
Glendale, AZ 85301

F.R. DATE: 10-29-76

NAME OF DRUG: Testosterone Enanthate 90 mg. and Estradiol Valerate Injection, 4 mg.

DATE OF SUBMISSION: 6-7-77

TYPE OF SUBMISSION: ANDA

CLINICAL EVALUATION:

1. Review of Studies:

   Pertinent data is to be reviewed by the chemist.
   Bio requirement - not required.

2. Review of Labeling:

   a) container labels: Unsatisfactory
      vials of 10 ml. (multi-dose)

      *Reference product is 5 (five) ml. vial.

   b) Insert labeling: Unsatisfactory.
      Green color creates a degree of illegibility. Lengthy insert becomes more difficult to read!!!

CONCLUSION: Insert labeling is unsatisfactory. Container labels are unsatisfactory. Reference product is 5 ml. vials.

RECOMMENDATIONS: The firm is to be so notified.

V.V. Karusaitis, M.D.

cc:dup
VVK/wlb/7-15-77

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Statement Date

NDA Number 85-865

AF Number

Name and address of Applicant (City and State)
Carter-Glogau Laboratories Division
Chromalloy Pharmaceuticals Inc.
Glendale, AZ 85301

Original xxxxx
Amendment
Supplement
Resubmission
Correspondance
Report
Other

Purpose of Amendment/Supplement

Date(s) of Submission(s)
5-26-77

Pharmacological Category	Name of Drug	
androgen/estrogen	testosterone Enanthate and estradiol valerate	
Dosage Form(s)	Potency(ies)	How Dispensed
injection	90/4 mg. per ml.	R_x xxxxx OTC
Sterilization	Samples	Related IND/NDA/DMF
included	required	

Labeling see medical officer's revie of 7-11-77 and attached.

Biologic Availability
not required

Establishment Inspection
requested

Components, Composition, Manufacturing and Controls
per issuing letter

Packaging ~~xxx~~ 10 ml. multiple dose vial sent to Division

Stability
Protocol requested

Expiration Date requested.

Remarks and Conclusion
rev w/f majarski

M Majarski 10/12/77

REVIEWER

DATE

Conversation with Dr. V.V. Karusaitis on 10-6-77

Squibb has two androgen/estrogen products Deladumone 90/4 mg./ml and Deladumone OB 180/8 mg./ml. Each product has a specific use and there are separate package inserts and specific packaging for each. Dr. Karusaitis noted this in his memorandum of 6-6-77

However, generic manufacturers are proposing to manufacture the 90/4 mg./ml. and the 180/8 mg./ml. in 10 ml. multiple dose vials as interchangeable dosage forms for both uses and provide single package inserts.

At a meeting with Mr. Knapp, Dr. Karusaitis said it was decided that the Division of Metabolism and Endocrine Drug Products would be consulted as to the applicability of these generic products.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Marvin Seife, M.D.
(HFD-530)

DATE: June 6, 1977

FROM : V.V. Karusaitis, M.D.

SUBJECT: Deviations from Reference Product:

Reference Product			Proposed Product
Deladumone[R] NDA			Generic Label
Testosterone Enanthate Estradiol Valerate	90 mg. 4 mg.	INJ	. . . . .
How Supplied: 5 ml. vials 1 ml. vials			10 ml. multiple dose
Testosterone Enanthate Estradiol Valerate	180 mg. 8 mg.	INJ	
HOW SUPPLIED: 2 ml. vial			10 ml. multiple dose

Contents

Each ML

90 mg. Testosterone Enanthate
4 mg. Estradiol Valerate

0.5% Chlorobotanol . . . . . Preservative . . Benzyl Alcohol 2%

Sesame Oil Vehicle . . . . . Sesame Oil

**Unacceptable: 10 ml. vials (Multiple Dose) 180 mg.
8 mg.

Reference product is a 2 ml. vial specifically used for a singular indication: Prevention of Postpartum Breast Engorgement. Rationale for 2 cc vial: Large potency in small amount for injection

RECOMMENDATION: Separate submissions for potencies.

V.V. Karusaitis, M.D.

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MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 10-6-77
FROM: Mary Ann Jarski (thru J.L. Meyer)		OFFICE HFD-530
TO: Mr. David H. Bryant, Office of Compliance		DIVISION HFD-322

SUBJECT: Inspection Request

SUMMARY

In conncetion with ANDA 85-865

for: Testosterone Enanthate 90 mg. and Estradiol Valerate 4 mg./ml. Injection

Applicant:

Carter-Glogau Laboratories Division
Chromalloy Pharmaceuticals
Glendale, AZ 85301

AF -

REQUESTED:

[xxxx] 1. Evaluation of compliance with CGMP for:

[xxxx] a. The applicant

[xxxxx] b. Others

[xxxxx] 2. Recommendation for approval/disapproval of the application/communication/supplement, based on your evaluation of compliance with CGMP

REMARKS:

SIGNATURE

DOCUMENT NUMBER

JUN 27 1977

NDA 85-865

Carter-Glogau Laboratories Division
Chromalloy Pharmaceuticals, Inc.
Attention: Samuel M. Fainberg, Ph.D.
5160 W. Bethany Home Road
Glendale, AZ 85301

Gentlemen:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME OF DRUG: Testosterone Enanthate and Estradiol Valerate Injection, 90/4

DATE OF APPLICATION: May 26, 1977

DATE OF RECEIPT: June 7, 1977

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the NDA number shown above.

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

LOS-DO DUP HFD-614,HFD-616
JLMeyer/cjb/6-23-77 ack
JLMeyer 6/23/77

6/29/77

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

May 26, 1977

ABBREVIATED
NEW DRUG APPLICATION

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
Department of Health, Education, and Welfare
Public Health Service
Food and Drug Administration
Rockville, MD 20587

SUBJECT: TESTOSTERONE ENANTHATE AND ESTRADIOL VALERATE INJECTION 90/4.
ABBREVAITED NEW DRUG APPLICATION

Dear Dr. Seife:

Enclosed, in triplicate, is our abbreviated new drug application for Testosterone Enanthate and Estradiol Valerate Injection 90/4.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

Samuel M. Fainberg, Ph.D.
Director
Technical and Regulatory Affairs

SMF/jcw
encl

RECEIVED
JUN 7 1977
BUREAU OF DRUGS

GENERAL OFFICES:
5160 WEST BETHANY HOME ROAD • GLENDALE, ARIZONA 85301
TELEPHONE (602) 939-7565 • TELEX 66-8304 (M-C LABS)