CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

85239

CORRESPONDENCE

NDA 85-239

JUL 14 1976

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, nd Cosmetic Act for the following:

NAME OF DRUG: Estrone Suspension, 5 mg. per ml.

DATE OF APPLICATION: June 16, 1976

DATE OF RECEIPT: June 28, 1976

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,

/S/

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

7/14/76

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sented to have under the conditions of use prescribed, recommended, or suggested in the labeling. The holder of the new drug application has indicated that these preparations are no longer marketed.

A notice was published in the FEDERAL REGISTER of February 8, 1972 (37 F.R. 2851) withdrawing approval of NDA 7-249 on the grounds that reports required under section 505(j) of the Act and §§ 130.13 and 130.35 (e) and (f) of the new drug regulations (21 CFR 130.13 and 130.35) had not been submitted. Accordingly, no further action under the Drug Efficacy Study Implementation is indicated. However, if any related drug for human use, not the subject of an approved new drug application, is on the market, it may be affected by the effectiveness classification described above.

A copy of the Academy's report has been furnished to each firm referred to above. Communications forwarded in response to this announcement should be identified with the reference number DESI 7249, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Supplements (identify with NDA number): Office of Scientific Evaluation (BD-100), Bureau of Drugs.
Original new drug applications: Office of Scientific Evaluation (BD-100), Bureau of Drugs.
Requests for the Academy's report: Drug Efficacy Study Information Control (BD-67), Bureau of Drugs.
All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD-60), Bureau of Drugs.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: June 23, 1972.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.72-11392 Filed 7-24-72;3:46 am]

[DESI 1543; Docket No. FDC-D-405; NDA 1543 etc.]

CERTAIN ESTROGEN-CONTAINING DRUGS FOR ORAL OR PARENTERAL USE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drugs:

I. SHORT-ACTING ESTROGENS

1. *Preparations containing ethinyl estradiol.* a. [illegible] Tablets; Schering Corp., 60 Orange Street, Bloomfield, N.J. 07003 (NDA 5-252).

b. Lynoral Tablets; Organon, Inc., 375 [illegible], West Orange, N.J. 07052 (NDA 5-[illegible]).

2. *Preparations containing estradiol dipropionate.* a. Ovocyclin Dipropionate Injection; Ciba Pharmaceutical Co., 556 Morris Avenue, Summit, N.J. 07901 (NDA 740).

3. *Preparations containing estrone.* a. Theelin Aqueous Suspension; Parke, Davis and Co., Joseph Campau Avenue, At the River, Detroit, Mich. 48232 (NDA 3-977).

b. Estrugenone Suspension, Kremers-Urban Co., Post Office Box 2033, 5600 West County Line Road, Milwaukee, Wis. 53201 (NDA 1-543).

c. Estrone Aqueous Suspension; Abbott Laboratories, 14th and Sheridan Road, North Chicago, Ill. 60064 (NDA 4-823).

4. *Preparations containing conjugated estrogens.* a. Premarin Tablets; Ayerst Laboratories, Division American Home Products Corp., 685 Third Avenue, New York, N.Y. 10017 (NDA 4-732).

b. Premarin Intravenous; Ayerst Laboratories (NDA 10-402).

5. *Preparations containing methallenestril.* a. Vallestril Tablets; G. D. Searle and Co., Post Office Box 5110, Chicago, Ill. 60680 (NDA 8-579).

II. LONG-ACTING ESTROGENS

1. *Preparations containing chlorotrianisene.* a. Tace 12 and 25 mg. Capsules; Merrell-National Laboratories, Division of Richardson-Merrell, Inc., 110 East Amity Road, Cincinnati, Ohio 45215 (NDA 8-102 and NDA 11-444) (two reports).

2. *Preparations containing estradiol valerate.* a. Delestrogen; E. R. Squibb and Sons, Inc., Georges Road, New Brunswick, N.J. 08903 (NDA 9-402).

3. *Preparations containing polyestradiol phosphate.* a. Estradurin; Ayerst Laboratories (NDA 10-753).

Such drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. A new drug application is required from any person marketing such drug without approval.

The Food and Drug Administration is prepared to approve new drug applications and supplements to previously approved new drug applications for these drugs under the conditions described in this announcement.

I. SHORT-ACTING ESTROGENS

A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy's reports, as well as other available evidence, and concludes that these drugs are:

1. Effective or probably effective for the indications described in the labeling conditions which follow. The probably effective indication is "in selected cases of osteoporosis."

2. Possibly effective for disturbances of the menstrual cycle (dysmenorrhea, oligomenorrhea, irregular cycles); suppression of lactation, to minimize blood loss at surgery, lessen the incidence of postmenopausal hemorrhage, and [illegible] reduce capillary hemorrhage, reduce the oozing following multiple transfusions, and prevent or arrest delayed hemorrhage.

3. Lacking substantial evidence of effectiveness when labeled for "relief of pregnancy bleeding"; advanced cases of prostatic carcinoma resistant to other estrogens; hemorrhagic emergencies due to spontaneous bleeding; to reduce bleeding due to capillary hemorrhage during and after oral surgery and after dental extraction; pulmonary bleeding; and use in hyphema during and after ocular surgery.

B. *Conditions for approval and marketing*—1. *Form of drug.* Except for estradiol dipropionate and estrone, these preparations are in a form suitable for oral administration. Estradiol dipropionate, estrone, and conjugated estrogens may be in a form suitable for parenteral administration.

2. *Labeling conditions.* a. The labels bear the statement, "Caution: Federal law prohibits dispensing without prescription."

b. The drugs are labeled to comply with all requirements of the Act and regulations. The labeling bears adequate information for safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970 (35 F.R. 2656). The "Indications" sections are as follows (The possibly effective indications may also be included for 6 months.):

INDICATIONS

These drugs are indicated for replacement therapy of estrogen deficiency associated with: Menopausal syndrome, female hypogonadism (hypodgenitalism), amenorrhea, female castration, or primary ovarian failure. They are also indicated for the prevention of postpartum breast engorgement; abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology; and in osteoporosis—depending upon the etiology and then only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures.

The following indications may be included provided the recommended dosage schedules of these preparations are consistent with those recommended by the Academy:

Senile vaginitis; kraurosis vulvae with or without pruritus; inoperable progressing prostatic cancer (for palliation only when castration is not feasible or when castration failures or delayed escape following a response to castration have not occurred); breast cancer (for palliation only in women with progressing inoperable or recurrent resistant disease who are more than 5 years postmenopausal; and in men, in those inoperable cases in which bilateral orchidectomy cannot be performed because of an independent surgical contraindication.)

The dosages for any of these indications which are to be used in [illegible] must be supported by adequate data [illegible] indication was not included in the labeling which the Academy reviewed for that particular preparation.

c. The labeling for all short-acting estrogens must contain the following [illegible]:

WARNING

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

II. Long-Acting Estrogens

A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy's reports, as well as other available evidence, and concludes that these drugs are:

1. Effective or probably effective for the indications described in the labeling conditions which follow. The probably effective indication is "in selected cases of osteoporosis."

2. Possibly effective for disturbances of the menstrual cycle (hypomenorrhea, oligomenorrhea, irregular cycles); suppression of lactation; to minimize blood loss at surgery, lessen the incidence of postoperative hemorrhage, and avoid the risk of multiple transfusions; and to reduce capillary hemorrhage, reduce the oozing following multiple transfusions, and prevent or arrest delayed hemorrhage.

3. Lacking substantial evidence of effectiveness when labeled for "relief of pregnancy bleeding"; advanced cases of prostatic carcinoma resistant to other estrogens; hemorrhagic emergencies due to spontaneous bleeding; to reduce bleeding due to capillary hemorrhage during and after oral surgery and after dental extraction; pulmonary bleeding; and use in hyphema during and after ocular surgery.

In addition, because of the possibility of untoward effects and consequent need for prompt cessation of the drug effect, the long-acting estrogens are classified as lacking substantial evidence of effectiveness for their labeled indications relating to their use in neoplastic diseases other than prostatic carcinoma.

B. *Conditions for approval of marketing*—1. *Form of drug.* Chlorotrianisene preparations are in capsule form suitable for oral administration. Estradiol valerate and polyestradiol phosphate are in sterile oleaginous solution or sterile dry powder with sterile diluent form suitable for parenteral administration.

2. *Labeling conditions.* a. The labels bear the statement, "Caution: Federal law prohibits dispensing without prescription."

b. The drugs are labeled to comply with all requirements of the Act and regulations. The labeling bears adequate information for safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the [illegible] (35 F.R. [illegible]). The "Indications" sections are as follows (The possibly effective indications may also be included for [illegible] months):

[illegible]

These drugs are indicated for replacement therapy of estrogen deficiency associated with: [illegible], female hypogonadism (hypogenitalism) amenorrhea, female castration, or primary ovarian failure. They are also indicated for the prevention of postpartum breast engorgement; abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology; and in osteoporosis—depending upon the etiology and then only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures.

The following indications may be included provided the recommended dosage schedules of these preparations are consistent with those recommended by the Academy: Senile vaginitis and kraurosis vulvae with or without pruritus; inoperable progressing prostatic cancer (for palliation only when castration is not feasible or when castration failures or delayed escape following a response to castration have not occurred).

The dosages for any of these indications which are to be used in labeling must be supported by clinical data if the indication was not included in the labeling which the Academy reviewed for that particular preparation.

c. The labeling for all long acting estrogens must contain the following warning:

WARNING

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

III *Marketing status.* Marketing of such drugs may be continued under the conditions described in the notice entitled "Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study," published in the FEDERAL REGISTER July 14, 1970 (35 F.R. 11273), as follows:

a. For holders of "deemed approved" new drug applications (i.e., an application which became effective on the basis of safety prior to October 10, 1962), the submission of a supplement for revised labeling, an abbreviated supplement for updating information as described in paragraphs (a)(1) (i) and (iii) of the notice of July 14, 1970.

b. For any person who does not hold an approved or effective new drug application, the submission of an abbreviated new drug application as described in paragraph [illegible] of that notice.

c. For any distributor of the drug, the use of labeling in accord with this announcement for any such drug [illegible] as described in paragraph [illegible] of that notice.

d. For indications for which the drug has been classified as probably effective [illegible] above) and possibly effective [illegible] included in the "Indications" sections above), continued use as described in paragraphs (c), (d), (e), and (f) of that notice.

IV. *Opportunity for a hearing.* 1. The Commissioner of Food and Drugs proposes to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act withdrawing approval of all new drug applications and all amendments and supplements thereto providing for the indications for which substantial evidence of effectiveness is lacking as described in paragraphs I. A. and II. A. of this announcement. An order withdrawing approval of the applications will not issue if such applications are supplemented in accord with this notice, to delete such indications. Any related drug for human use, not the subject of an approved new drug application, offered for the indications for which substantial evidence of effectiveness is lacking may be affected by this action.

2. In accordance with the provisions of section 505 of the Act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the holders of any such applications, and any interested person who would be adversely affected by such an order, an opportunity for a hearing to show why such indications should not be deleted from the labeling. A request for a hearing must be filed within 30 days after the date of publication of this notice in the FEDERAL REGISTER.

3. A request for a hearing may not rest upon mere allegations or denials but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing together with a well organized and full factual analysis of the clinical and other investigational data that the objector is prepared to prove in a hearing. Any data submitted in response to this notice must be previously unsubmitted and include data from adequate and well-controlled clinical investigations (identified for ready review) as described in § 130.12(a)(5) of the regulations published in the FEDERAL REGISTER of May 8, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained under uncontrolled or partially controlled situations are not acceptable as a sole basis for approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety.

4. If a hearing is requested and is justified by the response to this notice, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence.

A copy of the Academy's report has been furnished to each firm [illegible]. Communications forwarded in response to this announcement should be

identified with the reference number [illegible] the appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852:

- Supplements (identify with NDA number): Office of Scientific Evaluation (BD-100), Bureau of Drugs.
- Original abbreviated new drug applications (identify as such): Drug Efficacy Study Implementation Project Office (BD-60), Bureau of Drugs.
- Request for hearing (identify with docket number): Hearing Clerk, Office of General Counsel (GC-1), Room 6-88, Parklawn Building.
- Requests for the Academy's report: Drug Efficacy Study Information Control (BD-67), Bureau of Drugs.
- All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD-60), Bureau of Drugs.

Received requests for a hearing may be seen in the office of the hearing clerk (address given above) during regular business hours, Monday through Friday.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: June 29, 1972.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.72-11364 Filed 7-24-72;8:46 am]

[DESI 3943; Docket No. FDC-D-206; NDA 8-943, etc.]

CERTAIN CARBONIC ANHYDRASE INHIBITORS

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drugs:

1. Cardrase Tablets containing ethoxzolamide; The Upjohn Co., 7171 Portage Road, Kalamazoo, Mich. 49002 (NDA 11-047).

2. Diamox Tablets containing acetazolamide; Lederle Laboratories Division, American Cyanamid Co., Post Office Box 500, Pearl River, N.Y. 10965 (NDA 8-943).

3. Diamox Parenteral (powder for reconstitution) containing sodium acetazolamide; Lederle Laboratories Division, American Cyanamid Co. (NDA 9-388).

4. Oratrol Tablets containing dichlorphenamide; Alcon Laboratories, Inc., 6201 South Freeway, Box 1959, Fort Worth, Tex. 76101 (NDA 12-449).

5. Neptazane Tablets containing methazolamide; Lederle Laboratories Division, American Cyanamid Co. (NDA 11-721).

6. [illegible] Dohme, Division of Merck and Co., West Point, Pa. 19486 (NDA 11-366).

7. Diamox Sequels (sustained release [illegible]) Lederle Laboratories Division, American Cyanamid Co. (NDA 12-6-8).

Such drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. A new drug application is required from any person marketing such drug without approval.

I. ETHOXZOLAMIDE; ACETAZOLAMIDE (IN CONVENTIONAL TABLET OR PARENTERAL FORMS); DICHLORPHENAMIDE; METHAZOLAMIDE

A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy's reports, as well as other available evidence, and concludes that:

1. These drugs are effective for the indications described in the "Indications" sections below, except that;

2. Ethoxzolamide is probably effective for its recommended use as an adjunct in the centrencephalic epilepsies (petit mal, unlocalized seizures).

3. Ethoxzolamide lacks substantial evidence of effectiveness for the management of premenstrual edema and toxemia of pregnancy.

4. Acetazolamide lacks substantial evidence of effectiveness for the treatment of obesity, edema of pregnancy, premenstrual edema, Meniere's disease, and in adjunctive therapy for postpartum breast engorgement.

5. Dichlorphenamide lacks substantial evidence of effectiveness for the treatment of chronic pulmonary insufficiency with respiratory acidosis.

6. Except for the indications referred to above, ethoxzolamide and dichlorphenamide are regarded as possibly effective for other labeled indications.

B. *Conditions for approval and marketing.* The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated supplements to previously approved new drug applications under conditions described in this announcement.

1. *Form of drug.* Preparations of these drugs are in conventional tablet form suitable for oral administration except that acetazolamide as the sodium salt is in sterile powder form suitable for reconstitution and parenteral administration.

2. *Labeling conditions.* a. The labels bear the statement, "Caution: Federal law prohibits dispensing without prescription."

b. The drugs are labeled to comply with all requirements of the Act and regulations. Their labeling bears adequate information for safe and effective use of the drugs. The "Indications" sections are as follows:

INDICATIONS

Ethoxzolamide:

For adjunctive treatment of: edema due to congestive heart failure; chronic simple (open angle) glaucoma, secondary glaucoma, and preoperatively in acute angle closure glaucoma where delay of surgery is desired in order to lower intraocular pressure; centrencephalic epilepsies (petit mal, unlocalized seizures).

Acetazolamide (in conventional tablet and parenteral forms):

For adjunctive treatment of: edema due to congestive heart failure, drug-induced edema; centrencephalic epilepsies (petit mal, unlocalized seizures); chronic simple (open angle) glaucoma, secondary glaucoma, and preoperatively in acute angle closure glaucoma where delay of surgery is desired in order to lower intraocular pressure.

Dichlorphenamide and Methazolamide:

For adjunctive treatment of: chronic simple (open angle) glaucoma, secondary glaucoma, and preoperatively in acute angle closure glaucoma where delay of surgery is desired in order to lower intraocular pressure.

3. *Marketing status.* Marketing of such drugs may be continued under the conditions described in the notice entitled "Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study," published in the FEDERAL REGISTER July 14, 1970 (35 F.R. 11273), as follows:

a. For holders of "deemed approved" new drug applications (i.e., an application which became effective on the basis of safety prior to October 10, 1962), the submission of a supplement for revised labeling, an abbreviated supplement for updating information, and adequate data to show the biologic availability of the drug in the formulation which is marketed as described in paragraphs (a)(1) (i), (ii), and (iii) of the notice of July 14, 1970. Clinical trials which have established effectiveness of the drug may also serve to establish the bioavailability of the drug if such trials were conducted on the currently marketed formulation.

b. For any person who does not hold an approved or effective new drug application, the submission of an abbreviated new drug application, to include adequate data to assure the biologic availability of the drug in the formulation which is or is intended to be marketed, as described in paragraph (a)(3)(ii) of that notice.

c. For any distributor of the drug, the use of labeling in accord with this announcement for any such drug shipped within the jurisdiction of the Act as described in paragraph (b) of that notice.

d. For indications for which the drug has been classified as probably effective (included in the "Indications" section above) and possibly effective (not included in the "Indications" section above), continued use as described in (c), (d), (e), and (f) of that notice.

C. *Opportunity for a hearing.* 1. The Commissioner of Food and Drugs proposes to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act withdrawing approval of all new drug applications and all amendments and supplements thereto providing for the indications for which substantial evidence of effectiveness is lacking as described in paragraph A above. An order withdrawing approval of the applications will not issue if such applications are supplemented, in accord with this notice, to delete such indications. Any related drug for human use not the subject of

APR 18 1977

NDA 85-239

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

Gentlemen:

Reference is made to your abbreviated new drug application dated December 9, 1976, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estrone Aqueous Suspension 5 mg/ml.

Review of generic estrone suspensions indicates a great variety in formula parameters - at variance with reference product. Present knowledge of suspensions requires a rationale for deviations - or formulae in accord with the following:

1. Estrone in solution with preservatives: benzyl alcohol buffered/unbuffered; and/or structured/unstructured).

2. Added specifications and tests:
   (a) estrone: particle size and density; crystalline form
   (b) vehicle: density and viscosity
   (c) final suspension: pH: in neutrality range; density and viscosity; syringability

Other information required for applications:

1. Labeling:
   (a) in accord with accompanying labeling guidelines
   (b) supply supportative data for Dosage regimen for "Postpartum Breast Engorgement."
   (c) directions for resuspension and syringability

2. Manufacturing:
   (a) complete instructions for preparation of the suspension: initial dispersion of particles; milling of dispersed particles (evaluate milling time); final combination in a vehicle.

(b) sterilization procedures: types of sterilization for all phases of manufacturing - operating parameters and parameter monitoring, validation of sterilization cycles, sterility confidence; product sterility tersing - number of units tested, % of lot tested, elapsed time between removal from sterilizer and testing; quarantine period; microbial burden of environment.

3. Packaging evaluation for:
   (a) light sensitivity of estrone
   (b) drainage characteristics

4. A protocol for stability studies which follows:
   (a) degradation of estrone
   (b) the retained physical integrity of the suspension and basis for establishing your expiration date.

Please let us have your response promptly.

Sincerely yours,

/S/ 4/8/77

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

cc: LOS-DO

Enclosure:
Labeling Guidelines

4/8/77 HFD-614 HFD-616
VVKarusaitis/JLmeyer/MAdarski 4/8/77
R/D ~~init~~. JLMeyer/MSeife/4/13/77
rev w/f
ca/4/14/77 JLMeyer 4/18/77

OCT 28 1977

NDA 85-239
NDA 85-620
NDA 85-865

Carter-Wallace Laboratories Division
Cheesebrough Pharmaceuticals, Inc.
Attention: Samuel M. 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. 10/28/77
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs

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

JMeyer 10/28/77

Enclosure:
F.R. July 22, 1977

NOV 9 1977

NDA 85-239

Chromalloy Pharmaceuticals, Inc.
Carter-Glogau Laboratories Division
Attn: 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 Estrone Suspension, 5 mg/ml.

Reference is also made to your amendment dated June 28, 1977.

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:

   Container labels: Appropriate storage and use recommendations and expiration dating for the used as well as unused multidose vials (see below).

   Package insert: Submit the required patient package insert.

2. The specification/test sheets in use by your Quality Control Laboratory(ies) for active ingredients, components and final dosage form.

3. Complete information on containers and closures and your methods for checking drainage characteristics.

4. It will be necessary for you to determine the chemical and physical characteristics of your suspension and to assure that these parameters are preserved until used. In this regard - for representative lots - submit data on (citing/describing methodology and test conditions):

   compendial parameters
   density
   pH
   viscosity

   sedimentation or
   settling rate

   estrone; suspension
   estrone; suspension
   suspension
   suspension - resistance to flow upon shear
   (rheograms)

   suspension - speed by which the suspended
   particles settle in an undisturbed
   sample product

particle size distribution	estrone; suspension - at sensitivity levels ≥5 μ, ≥10 μ, ≥25 μ and ≥40 μ
syringability	suspension - force-displacement profiles
detection of possible polymorphs	estrone; suspension - IR, microscopic examination
degree of flocculation	suspension

5. Evaluation of the compatability of the suspension with the closure

6. The application should contain a formal stability protocol indicating tests for chemical and physical stability of the product (cite/describe methodology). In this regard:

   a. the protocol should define/identify:

      formula
      container-closure systems
      sampling procedures
      number of lots under test: several
      storage conditions: controlled room temperature; some cyclic storage
      test procedures
      test intervals: 3,6,9,12,18,24...mo; then yearly studies thereafter

   b. Test procedures to determine chemical stability should also include (1) for estrone degredation; (2) evaluation of the preservatives. We request the rationale for estrone and preservative tolerances of %.

   c. Test procedures to determine physical stability should also include determinations for:

      particle size evaluation
      crystalline structure (polymorphism)
      syringability
      resuspendability/sedimentation

   d. also include test procedures for sterility of multidose vials after initial use.

7. With respect to expiration dating:

   a. Propose an expiration term for the multidose vial after initial use, i.e. "Use within..." and submit data in support of it.

   b. In our opinion the limited amount of data submitted fails to furnish a sound basis for a five year expiration term for the unused product. We recommend a current two year expiration term (from the date of the quality control release) and your commitment to check the stability of production batches of the product - per your protocol - submit results of these studies as they become available, and withdraw from the market any batches that fall out of specification or whose physical characteristics demonstrate radical change.

8. With respect to recommendations on labeling (a) we recommend that you add "Store at Controlled Room Temperature" (b) add storage conditions for multidose vials after inital use.

9. Include data/information on representative microbiological burden of your sterile manufacturing environment.

Relative to reference products on the market, the NAS/NRC Panel evaluated the Parke-Davis product Theelin, which is a suspension of estrone in isotonic sodium chloride solution with benzethonium chloride 0.1 mg. and benzyl alcohol 2% added as preservatives. We request rationale/information/data on your (a) lack of isotonicity; (b) pH below 7.0; (c) choice of preservatives - their suitability and effective concentrations.

Please let us have your response promptly.

Sincerely yours,

/S/ 11/9/77

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

LOS-DO DUP HFD-614
VVKarusaitis/JLMeyer/MAJarski 11/7/77
R/DinitJMeyer/MSeife
ft/cjb/11-7-77 XXXXX rev w/f

VVK/MS 11/8/77
JMeyer 11/8/77

JAN

NDA 85-239

Chromalloy Pharmaceuticals, 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 Estrone Suspension, 5 mg./ml.

Reference is also made to (1) your communication dated March 27, 1978 and (2) our letter of November 9, 1977.

We have completed the review of this abbreviated new drug application and have the following comment:

The labeling is satisfactory.

However, it will be necessary for you to supply the information in our referenced letter. A complete characterization of the chemical and physical characteristics of the suspension are necessary as well as assurance that these characteristics are maintained throughout the shelf life offthe product.

Please let us have your response promptly.

Sincerely yours,

/S/ 1/9/79

/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
R/D init JMeyer/MSeife/1/5/79
ps/1/5/79
rev w/f

1/8/79
1/8/79
1/8/79

JAN 6 1978

NDA 85-239

Chromalloy Pharmaceuticals, Inc.
Carter-Glogau Laboratories Division
Attention: Ronald M. Carter
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 Estrone Suspension, 5 mg./ml.

Reference is also made to (1) your communication dated October 31, 1977, enclosing a Patient Package Insert and (2) our letter of November 9, 1977, requesting additional information.

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. Approval of all estrogen products listed in the HOW SUPPLIED Section of labeling.

2. The information in our referenced letter.

Please let us have your response promptly.

Sincerely yours,

/S/ 1/6/78

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
R/D init JMeyer/MSeife/1/4/78
ns/1/4/78

1/4/78

1/5/78

RWF

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

March 27, 1978

RESUBMISSION
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, MD 20857

SUBJECT: ESTRONE SUSPENSION, 5 MG/ML
NDA 85-239

Dear Dr. Seife:

Reference is made to your letter of January 6, 1978 regarding our submission of a Patient Package Insert in our communication dated October 31, 1977.

In your above referenced letter you indicated that "...before we are able to reach a final conclusion the following additional information is necessary: 1. Approval of all estrogen products listed in the HOW SUPPLIED Section of labeling..."

We fail to understand why the Patient Package insert cannot be reviewed and commented on for future use upon approval of the NDA? We also question the need for a How Supplied Section in a Patient Package insert since this information is for the physician's use and information only and already appears on the physician insert.

We would greatly appreciate your comments and review of the Patient Package insert.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

RECEIVED
APR 06 1978
GENERIC DRUGS

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

JCW

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

Oriz

CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

RESUBMISSION

October 31, 1977

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 83-547,
NDA 83-714,
NDA 85-239, NDA 85-620,
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

ENCLOSURES
IN DUPLICATE

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

ESTROGEN DRUG PRODUCTS
PATIENT INFORMATION

WHAT YOU SHOULD KNOW ABOUT ESTROGENS

Estrogens are female hormones produced by the ovaries. The ovaries make several different kinds of estrogens. In addition, scientists have been able to make a variety of synthetic estrogens. As far as we know, all these estrogens have similar properties and therefore much the same usefulness, side effects, and risks. This leaflet is intended to help you understand what estrogens are used for, the risks involved in their use, and how to use them as safely as possible.

This leaflet includes the most important information about estrogens, but not all the information. If you want to know more, you can ask your doctor or pharmacist to let you read the package insert prepared for the doctor.

USES OF ESTROGEN

Estrogens are prescribed by doctors for a number of of purposes, including:

1. To provide estrogen during a period of adjustment when a woman's ovaries no longer produce it in order to prevent certain uncomfortable symptoms of estrogen deficiency. (All women normally stop producing estrogens, generally between the ages of 45 and 55; this is called the menopause.)

2. To prevent symptoms of estrogen deficiency when a woman's ovaries have been removed surgically before the natural menopause.

3. To prevent pregnancy. (Estrogens are given along with a progestagen, another female hormone; these combinations are called oral contraceptives or birth control pills. Patient labeling is available to women taking oral contraceptives and they will not be discussed in this leaflet.)

4. To treat certain cancers in women and men.

5. To prevent painful swelling of the breasts after pregnancy in women who choose not to nurse their babies.

THERE IS NO PROPER USE OF ESTROGENS IN A PREGNANT WOMAN

ESTROGENS IN THE MENOPAUSE

In the natural course of their lives, all women eventually experience a decrease in estrogen production. This usually occurs between ages 45 and 55 but may occur earlier or later. Sometimes the ovaries may need to be removed before natural menopause by an operation, producing a "surgical menopause."

When the amount of estrogen in the blood begins to decrease, many women may develop typical symptoms: Feelings of warmth in the face, neck, and chest or sudden intense episodes of heat and sweating throughout the body (called "hot flashes" or "hot flushes"). These symptoms are sometimes very uncomfortable. A few women eventually develop changes in the vagina (called "atrophic vaginitis") which cause discomfort, especially during and after

You may have heard that taking estrogens for long periods (years) after the menopause will keep your skin soft and supple and keep you feeling young. There is no evidence that this is so, however, and such long-term treatment carries important risks.

ESTROGENS TO PREVENT SWELLING OF THE BREASTS AFTER PREGNANCY

If you do not breast feed your baby after delivery, your breast may fill up with milk and become painful and engorged. This usually begins about 3 to 4 days after delivery and may last for a few days to up to a week or more. Sometimes the discomfort is severe, but usually it is not and can be controlled by pain relieving drugs such as aspirin and by binding the breasts up tightly. Estrogens can be used to try to prevent the breasts from filling up. While this treatment is sometimes successful, in many cases the breasts fill up to some degree in spite of treatment. The dose of estrogens needed to prevent pain and swelling of the breasts is much larger than the dose needed to treat symptoms of the menopause and this may increase your chances of developing blood clots in the legs or lungs (see below). Therefore, it is important that you discuss the benefits and the risks of estrogen used with your doctor if you have decided not to breast feed your baby.

THE DANGERS OF ESTROGENS

1. *Cancer of the uterus.* If estrogens are used in the postmenopausal period for more than a year, there is an increased risk of *endometrial cancer* (cancer of the uterus): Women taking estrogens have roughly 5 to 10 times as great a chance of getting this cancer as women who take no estrogens. To put this another way, while a postmenopausal women not taking estrogens has 1 chance in 1,000 each year of getting cancer of the uterus, a woman taking estrogens has 5 to 10 chances in 1,000 each year. For this reason *it is important to take estrogens only when you really need them.*

The risk of this cancer is greater the longer estrogens are used and also seems to be greater when larger doses are taken. For this reason *it is important to take the lowest dose of estrogen that will control symptoms and to take it only as long as it is needed.* If estrogens are needed for longer periods of time, your doctor will want to reevaluate your need for estrogens at least every six months.

Women using estrogens should report any irregular vaginal bleeding to their doctors; such bleeding may be of no importance, but it can be an early warning of cancer of the uterus. If you have undiagnosed vaginal bleeding, you should not use estrogens until a diagnosis is made and you are certain there is no cancer of the uterus.

If you have had your uterus completely removed (total hysterectomy), there is no danger of develop-

5. To prevent painful swelling of the breasts after pregnancy in women who choose not to nurse their babies.

THERE IS NO PROPER USE OF ESTROGENS IN A PREGNANT WOMAN

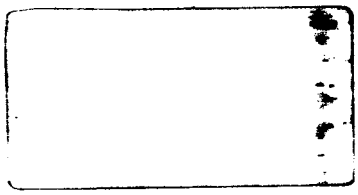
ESTROGENS IN THE MENOPAUSE

In the natural course of their lives, all women eventually experience a decrease in estrogen production. This usually occurs between ages 45 and 55 but may occur earlier or later. Sometimes the ovaries may need to be removed before natural menopause by an operation, producing a "surgical menopause."

When the amount of estrogen in the blood begins to decrease, many women may develop typical symptoms: Feelings of warmth in the face, neck, and chest or sudden intense episodes of heat and sweating throughout the body (called "hot flashes" or "hot flushes"). These symptoms are sometimes very uncomfortable. A few women eventually develop changes in the vagina (called "atrophic vaginitis") which cause discomfort, especially during and after intercourse.

Estrogens can be prescribed to treat these symptoms of the menopause. It is estimated that considerably more than half of all women undergoing the menopause have only mild symptoms or no symptoms at all and therefore do not need estrogens. Other women may need estrogens for a few months, while their bodies adjust to lower estrogen levels. Sometimes the need will be for periods longer than six months. In an attempt to avoid over-stimulation of the uterus (womb), estrogens are usually given cyclically during each month of use, that is three weeks of pills followed by one week without pills.

Sometimes women experience nervous symptoms or depression during menopause. There is no evidence that estrogens are effective for such symptoms and they should not be used to treat them, although other treatment may be needed.



each year of getting cancer of the uterus, a woman taking estrogens has 5 to 10 chances in 1,000 each year. For this reason *it is important to take estrogens only when you really need them.*

The risk of this cancer is greater the longer estrogens are used and also seems to be greater when larger doses are taken. For this reason *it is important to take the lowest dose of estrogen that will control symptoms and to take it only as long as it is needed.* If estrogens are needed for longer periods of time, your doctor will want to reevaluate your need for estrogens at least every six months.

Women using estrogens should report any irregular vaginal bleeding to their doctors; such bleeding may be of no importance, but it can be an early warning of cancer of the uterus. If you have undiagnosed vaginal bleeding, you should not use estrogens until a diagnosis is made and you are certain there is no cancer of the uterus.

If you have had your uterus completely removed (total hysterectomy), there is no danger of developing cancer of the uterus.

2. *Other possible cancers.* Estrogens can cause development of other tumors in animals, such as tumors of the breast, cervix, vagina, or liver, when given for a long time. At present there is no good evidence that women using estrogen in the menopause have an increased risk of such tumors, but there is no way yet to be sure they do not; and one study raises the possibility that use of estrogens in the menopause may increase the risk of breast cancer many years later. This is a further reason to use estrogens only when clearly needed. While you are taking estrogens, it is important that you go to your doctor at least once a year for a physical examination. Also, if members of your family have had breast cancer or if you have breast nodules or abnormal mammograms (breast x-rays), your doctor may wish to carry out more frequent examinations of your breasts.

3. *Gall bladder disease.* Women who use estrogens after menopause are more likely to develop gall bladder disease needing surgery as women who do not use estrogens. Birth control pills have a similar effect.

4. *Abnormal blood clotting.* Oral contraceptives increase the risk of blood clotting in various parts of the body. This can result in a stroke (if the clot is in the brain), a heart attack (clot in a blood vessel or the heart), or a pulmonary embolus (a clot which forms in the legs or pelvis, then breaks off and travels to the lungs). Any of these can be fatal.

At this time use of estrogens in the menopause is not known to cause such blood clotting, but this has not been fully studied and there could still prove to be such a risk. It is recommended that if you have had clotting in the legs or lungs or a heart attack or stroke while you were using estrogens or birth control pills, you should not use estrogens (unless they are being used to treat cancer of the breast or prostate). If you have had a stroke or heart attack or if you have angina pectoris, estrogens should be used with great caution and only if clearly needed (for example, if you have severe symptoms of the menopause).

The larger doses of estrogen used to prevent swelling of the breasts after pregnancy have been reported to cause clotting in the legs and lungs.

SPECIAL WARNING ABOUT PREGNANCY

You should not receive estrogen if you are pregnant. If this should occur, there is a greater than usual chance that the developing child will be born with a birth defect, although the possibility remains fairly small. A female child may have an increased risk of developing cancer of the vagina or cervix later in life in the teens or twenties). Every possible effort should be made to avoid exposure to estrogens during pregnancy. If exposure occurs see your doctor.

OTHER EFFECTS OF ESTROGENS

In addition to the serious known risks of estrogens described above, estrogens have the following side effects and potential risks:

1. *Nausea and vomiting.* The most common side effect of estrogen therapy is nausea. Vomiting is less common.

2. *Effects on breasts.* Estrogens may cause breast tenderness or enlargement and may cause the breasts to secrete a liquid. These effects are not dangerous.

3. *Effects on the uterus.* Estrogens may cause benign fiboid tumors of the uterus to get larger.

Some women will have menstrual bleeding when estrogens are stopped. But if the bleeding occurs on days you are still taking estrogens you should report this to your doctor.

4. *Effects on liver.* Women taking oral contraceptives develop on rare occasions a tumor of the liver which can rupture and bleed into the abdomen. So

SUMMARY

Estrogens have important uses, but they have serious risks as well. You must decide, with your doctor, whether the risks are acceptable to you in view of the benefits of treatment. Except where your doctor has prescribed estrogens for use in special cases of cancer of the breast or prostate, you should not use estrogens if you have cancer of the breast or uterus, are pregnant, have undiagnosed abnormal vaginal bleeding, clotting in the legs or lungs, or have had a stroke, heart attack or angina, or clotting in the legs or lungs in the past while you were taking estrogens.

You can use estrogens as safely as possible by understanding that your doctor will require regular physical examinations while you are taking them and will try to discontinue the drug as soon as possible and use the smallest dose possible. Be alert for signs of trouble including:

1. Abnormal bleeding from the vagina.

2. Pains in the calves or chest or sudden shortness of breath, or coughing blood (indicating possible clots in the legs, heart or lungs).

3. Severe headache, dizziness, faintness or changes in vision (indicating possible developing clots in the brain or eye).

4. Breast lumps (you should ask your doctor how to examine your own breasts).

5. Jaundice (yellowing of the skin).

6. Mental depression.

Based on his or her assessment of your medical needs, your doctor has prescribed this drug for you. Do not give the drug to anyone else.

HOW SUPPLIED

This informational leaflet refers to various estrogenic drug products which may be administered by your physician. These estrogenic drug products may include various natural and/or synthetic forms of estrogen such as Estradiol, Estrone, Estrogenic substances, Estradiol Cypionate, Estradiol Valerate, Potassium Estrone Sulfate, etc. either alone, in combination or with other drugs. The determination as to which product to administer by injection and necessary to produce the desired therapeutic response is left to the discretion of the physician and is based upon his evaluation of your medical condition and the treatment required.

Literature Revised: August 1977

CARTER-GLOGAU LABORATORIES
Division Chromalloy Pharmaceuticals, Inc.
Glendale, Arizona 85301

small. A female child may have an increased risk of developing cancer of the vagina or cervix later in life in the teens or twenties). Every possible effort should be made to avoid exposure to estrogens during pregnancy. If exposure occurs see your doctor.

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1. *Nausea and vomiting.* The most common side effect of estrogen therapy is nausea. Vomiting is less common.

2. *Effects on breasts.* Estrogens may cause breast tenderness or enlargement and may cause the breasts to secrete a liquid. These effects are not dangerous.

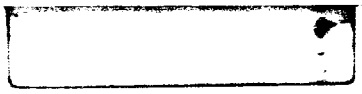
3. *Effects on the uterus.* Estrogens may cause benign fiboid tumors of the uterus to get larger.

Some women will have menstrual bleeding when estrogens are stopped. But if the bleeding occurs on days you are still taking estrogens you should report this to your doctor.

4. *Effects on liver.* Women taking oral contraceptives develop on rare occasions a tumor of the liver which can rupture and bleed into the abdomen. So far, these tumors have not been reported in women using estrogens in the menopause, but you should report any swelling or unusual pain or tenderness in the abdomen to your doctor immediately.

Women with a past history of jaundice (yellowing of the skin and white parts of the eyes) may get jaundice again during estrogen use. If this occurs, stop taking estrogens and see your doctor.

5. *Other effects.* Estrogens may cause excess fluid to be retained in the body. This may make some conditions worse, such as epilepsy, migraine, heart disease, or kidney disease.



Do not give the drug to anyone else.

HOW SUPPLIED

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Literature Revised: August 1977

CARTER-GLOGAU LABORATORIES
Division Chromalloy Pharmaceuticals, Inc.
Glendale, Arizona 85301

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

January 26, 1979

ORIG NEW CORRES

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: ESTRONE SUSPENSION, 5 mg/ml
NDA 85-239

Dear Dr. Seife:

In reference to our phone conversation of today with Jack Meyer informing us that our filing for NDA 85-239, Estrone Suspension, 5 mg/ml., dated April 21, 1978 has been misplaced, we are sending you duplicate copies of all filings and correspondence of that date and subsequent dates.

This material will be hand carried to your office by Mr. Scott D. Ballin, our Washington representative.

We grealty appreciate your prompt review and approval of this NDA since all information you have requested has been submitted.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

RECEIVED
JAN 29 1979
GENERIC DRUGS

CONFIRMATION TELEX
DATED JANUARY 25, 1979

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

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

January 18, 1979

ORIG NEW CODES

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 20857

SUBJECT: ESTRONE SUSPENSION, 5 mg/ml
NDA 85-239

Dear Dr. Seife:

Reference is made to your letter of January 9, 1979 regarding Estrone Suspension, 5 mg/ml.

On April 21, 1978 and September 12, 1978, we have responded fully to your letter of November 9, 1977 including all requested information regarding characterization of the chemical and physical characteristics of the suspension, and will greatly appreciate prompt approval of the ANDA.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC

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

/edc

RECEIVED
JAN 29 1979
GENERIC DRUGS

NERAL OFFICES:
5360 WEST BETHANY HOME ROAD • GLENDALE, ARIZONA 85301
TELEPHONE (602) 939-7565 • TELEX 66-8304 (M-C LABS)

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

September 12, 1978

RESUBMISSION

NDA ORIG AMENDMENT

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: ESTRONE SUSPENSION, 5 mg/ml.
NDA 85-239

Dear Dr. Seife:

In reference to our letter of April 21, 1978 in response to your communication of November 9, 1977 regarding Estrone Suspension, 5 mg/ml., we are enclosing additional information in reference to our commitment to submit the additional data when it becomes available.

We are enclosing the results of the Preservative Challenge Test and the Summary Table of Physical Properties of the product.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

RECEIVED
SEP 15 1978
GENERIC DRUGS

SMF/edc
encls:

5161 WEST BETHANY HOME ROAD • GLENDALE, ARIZONA 85301
TELEPHONE (602) 939-7565 • TELEX 66-8304 (M-C LABS)

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

Drug

CONFIDENTIAL

ORIG NEW CORRES

May 12, 1978

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 20857

SUBJECT: ESTRONE SUSPENSION, 5 MG/ML
NDA 85-239

Dear Dr. Seife:

Attached please find our letter of March 10, 1978 regarding Patient Package insert for estrogen containing products which was returned.

We are resubmitting the letter in reference to NDA 85-239 for Estrone Suspension, 5 mg/ml.

We would appreciate it if you would review and comment on our letter of March 10, 1978.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

RECEIVED
MAY 22 1978
GENERIC DRUGS

JCW
encl

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

Drug

CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

April 21, 1978

RESUBMISSION
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, MD 20857

SUBJECT: ESTRONE SUSPENSION, 5 MG/ML
NDA 85-239

Dear Dr. Seife:

Reference is made to your letter of November 9, 1977 regarding Estrone Suspension, 5 mg/ml, NDA 85-239.

We are supplying the following as requested:

1. Container label, revised as you requested, is attached. The Patient Package Insert was submitted to you in our letter of October 31, 1977 and our letters must have crossed in the mail.

2. The specification/test sheets in use by our Quality Control Laboratory are attached for the active ingredient, components and final dosage form.

3. Container and closure specifications and tests are attached.

Method for Drainage Characteristics: Drainage characteristics of vials are

We further run the volume withdrawal test specified by USP XIX on the final product, in order to insure that the full number of doses can be withdrawn. At this point we check the vial for a satisfactory appearance, i.e., a uniform suspension free of clumps with no significant residue sticking to vial sides. Further, after inspection of final-filled-vials, an AQL sample of the product is shaken up and inverted for six hours after which satisfactory drainage and absence of any leakers is confirmed by a Quality Control inspector.

RECEIVED
MAY 02 1978
GENERIC DRUGS

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

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

4. The full physical characteristics for this product as outlined by your letter are being studied by and will be submitted when completed. A draft copy is attached to our Master Formula Card (page 3 and 4), enclosed. We would hope all these tests would not be required on a routine basis since we believe that some of these tests are of more academic than practical interest and were originally devised by in order to publish a paper or select the best from alternate formulas. You will find few Quality Control departments willing to set pass/fail parameters from suspensions based on density, rheogram viscosity, sedimentation or degree of flucculation since these properties will vary from lot to lot depending on crystal form of raw materials used, process, agitation, air bubble entrapment, shipping or shaking history of an individual vial. Slight, but within USP range, differences in viscosity of a suspending raw material such as sodium carboxymethylcellulose makes such tests dubious at best. Please note that the Parke-Davis Theelin refence product does NOT contain a suspending agent hence the tests you suggest are more critical for it. We feel the tests described in number 6 of your letter fit our situation adequately.

5. Evaluation of the compatibility of the suspension with the closure is carried out following the attached PMA guidelines and by preliminary screening of various stoppers recommended by the stopper manufacturer who has the benefit of the research experience of many manufacturers. He also knows the full composition of his rubber stock fillers, anti-oxidants, water extractables, cytotoxicity, et al. We test the stability of the above versus similar stoppers already used in our plant. We prefer to use a stock stopper where possible for obvious reasons. We take stability vials apart after significant time and temperature and study the closure for changes in appearance (swelling, softening, discoloration, etc.) and, if necessary, run stopper measurements. We particularly study the ability of the stopper to retain volatile components

We further study development of cores or particles found in the product. See also attached protocol on coring, resealing and penetration pressure. Please note we have not found these latter properties change significantly from product to product.

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

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

We have written the stopper manufacturer, for assistance with evaluation of product compatibility with the closure. Attached are their physical, chemical and cytoxicity test reports for the stopper used. Additional coring tests, penetration, water extraction tests, cytotoxicity tests, moisture vapor transmission rates at room temperature and other stopper data are available in Master File.

The current product packaging shows no significant change in stopper appearance or measurement when exposed to the product for 48 months. Our stability tests further show satisfactory retention of the benzyl alcohol or used as preservatives plus acceptable pH, product appearance and estrone assays.

6. Our formal stability protocol for physical/chemical stability, including methodology reference is attached. These include formula-tested container/closure system, sampling procedure and the time intervals as suggested.

A test for estrone degradation has now been added and assays of retained samples show no significant degradation.

Our assays for preservatives are USP method which have improved in accuracy and predictability over the years as we have obtained new equipment. The range of % of label is indeed wider than limits now required and we propose limits of % of label.

Attached is our revised test protocol for suspension physical stability for: Particle Size, Crystalline Structure (polymorphism), Syringeability, Resuspendability/Sedimentation.

Our test procedure for sterility of multi-dose vials after initial use involves

All samples show the product to remain sterile.

7. a. We have tested the stopper vial on these products and found 1 to 0 cores visable when 20 or 25 gauge needles are inserted 10 times into the stopper.

We are running an additional test now on the actual product where multiple entries are made over a month's time, then test the product for sterility at 30 and 60 days, then run an infrared curve on the hormone versus initial assay to show no change. Accordinly we plan to label the product "Use

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CARTER-GLOGAU LABORATORIES DIVISION

within 90 days after first withdrawal".

b. Updated physical and chemical test results available on typical stability lots are attached. We believe these results are adequate to support an expiration date of 36 months.

We believe the tests we currently do are adequate to substantiate the predictability of our product; especially since our formula has been in safe and effective use for many years.

We will check stability of production batches of product for the foregoing protocols, submit the results of these studies as they become available and withdraw from the market any batch which falls out of specifications.

9. a. Regarding our choice of preservative, we use

Our results using the USP preservative effectiveness test for this product are being collected and will be submitted when available.

In conclusion, please note our June 28, 1977 comments on the manufacture of suspension. We should also point out this product has been packaged in clear glass vials, placed in cardboard cartons for many years without any problems, and most of our generic customers prefer this package. We have noted no significant changes when such vials are even exposed to light for several months so we currently plan to continue to protect the product from light during manufacturing, packaging, and cartoning.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

SMF/jcw
encl

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A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

June 28, 1977

RESUBMISSION
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, MD 20857

SUBJECT: ESTRONE AQUEOUS SUSPENSION, 5 MG/ML
NDA 85 239

Dear Dr. Seife:

Reference is made to your letter of April 19, 1977 regarding Estrone Aqueous Suspension, 5 mg/ml NDA 85-239.

"A pharmaceutically elegant sterile suspension product will consist of sterile uniform size particles free of aggregation or clumpling, homogeneously resuspendable in a sterile vehicle with minimal shaking and which sediment slowly enough to permit accurate dosage."

To acheive these ideal properties we use a number of procedures with require different in-process and end product testing procedures.

Many companies still manufacture suspensions by

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Redacted 1

pages of trade secret and/or confidential commercial information

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

Marvin Seife, M.D.
Food and Drug Administration

June 28, 1977

Full details of all manufacturing, sterilizing and testing procedures are given in the step by step manufacturing directions on our master formula cards for each product.

We run full USP or NF monographs specifications for all raw materials and final products and add these other in-house specifications as required to produce a consistent product. It might be emphasized that initial crystal form or size determinations on the powder are not too important in our preferred procedures since this process apparently converts the insoluble drug to the proper size and most thermodynamically stable form. Also, since our vehicle ingredients are added at several different processing stages (e.g. part in the suspension concentrate slurry, part in the final q.s., etc.), it is not practical to do density, viscosity, pH and other in-process tests on these steps and try to compare the partial results to the final product. Indeed, since we are working with sterile components here such sampling might result in accidential microbiological contamination of the product.

Validation procedures have previously been submitted to the FDA. These include manufacturing operation parameters, validation of sterilization cycles (with biological indicators, recording thermocouples, maximum reading thermometers, etc.) sterility confidence improvement using increased sampling and 28 day sterility testing.

We follow or exceed USP sampling requirements but do not test a set percentage of each lot for sterility. Our Quality Control department uses in inspecting and releasing our products after they have been 100% inspected by our production department.

Samples for testing are never tested for sterility or assay until at least 24 to 72 hours after they have reached room temperature. All vials are quarantined until USP or NF sterility, assay, inspection and other testing is complete - usually at least a month after filling. Quality Control reinspection and physical identification is then done on a at time of shipment.

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CARTER-GLOGAU LABORATORIES DIVISION

Marvin Seife, M.D.
Food and Drug Administration

June 28, 1977

page 4

The microbiological burden of the sterile manufacturing environment is checked daily on the rooms used using a particle counter and and settling plates as previously documented.

Our estrone products are packaged in amber glass bottles and packaged in individual cardboard cartons. All products are checked for drainage and fill volume as a condition for release by Quality Control and stability lots are checked at 3, 6, 9, 12, 18, 24, 36, 48 and 60 months after manufacture.

Stability studies include testing for degredation of estrone using the NF assay, pH, appearance and assay of preservatives. Our assay results show the estrone content is unchanged for at least three (3) years after manufacture with older assays pending. The pH and appearance are likewise not significantly changed during this period. Graphical plots suggest the product will be satisfactory for at least five (5) years. See attached data.

Insert, revised as you requested is attached.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

SMF/jcw
encl

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Orig

CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

December 9, 1976

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 20852

NDA ORIG AMENDMENT

FPL

SUBJECT: ESTRONE SUSPENSION, 5 mg/ml
NDA 85-239

Dear Dr. Seife:

We hereby amend our NDA 85-239 for Estrone Suspension, 5 mg. to provide for a revised insert in accord with the Notice published in the Federal Register, Volume 41, Number 210, Friday, October 29, 1976.

Attached is the revised insert. There is no other change or addition to this NDA.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

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CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

June 16, 1976

ABBREVIATED
NEW DRUG APPLICATION
85-239

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

SUBJECT: ESTRONE SUSPENSION,
2 mg. and 5 mg. per ml.

Dear Dr. Seife:

Reference is made to your communication of February 8, 1974 regarding NDA 83-397 for Estrone Suspension 2 mg. and 5 mg. per ml.

We are enclosing separate Abbreviated NDA's as requested in the above communication.

Sincerely,

CARTER-GLOGAU LABORATORIES
CHROMALLOY PHARMACEUTICALS, INC.

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

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FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

OMB No. 77-R0003

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

(Title 21, Code of Federal Regulations, § 130.4)

Name of applicant CARTER-GLOGAU LABORATORIES DIVISION, CHROMALLOY PHARMACEUTICALS, INC.

Address 5160 W. Bethany, Glendale, AZ 85301

Date June 16, 1976

Name of new drug Estrone Suspension, 5 mg.per ml.

- ☐ Original application (regulation § 130.4).
- ☐ Amendment to original, unapproved application (regulation § 130.7).
- ☒ Abbreviated application (regulation § 130.4(f)).
- ☐ Amendment to abbreviated, unapproved application (regulation § 130.7).
- ☐ Supplement to an approved application (regulation § 130.9).
- ☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, hazards, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in accord with §1.106(b) (21 CFR 1.106(b)). It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the change is made in conformance with other provisions of §130.9 of the new-drug regulations.

Attached hereto, submitted in the form described in §130.4(e) of the new-drug regulations, and constituting a part of this application are the following:

1. Table of contents. The table of contents should specify the volume number and the page number in which the complete and detailed item is located and the volume number and the page number in which the summary of that item is located (if any).

2. Summary. A summary demonstrating that the application is well-organized, adequately tabulated, statistically analyzed (where appropriate), and coherent and that it presents a sound basis for the approval requested. The summary should include the following information: (In lieu of the outline described below and the evaluation described in item 3, an expanded summary and evaluation as outlined in §130.4(d) of the new-drug regulations may be submitted to facilitate the review of this application.)

a. Chemistry.

i. Chemical structural formula or description for the new-drug substance.

ii. Relationship to other chemically or pharmacologically related drugs.

iii. Description of dosage form and quantitative composition.

b. Scientific rationale and purpose the drug is to serve.

c. Reference number of the investigational drug notice(s) under which this drug was investigated and of any notice, new-drug application, or master file of which any contents are being incorporated by reference to support this application.

d. Preclinical studies. (Present all findings including all adverse experiences which may be interpreted as incidental or not drug-related. Refer to date and page number of the investigational drug notice(s) or the volume and page number of this application where complete data and reports appear.)

i. Pharmacology (pharmacodynamics, endocrinology, metabolism, etc.).

ii. Toxicology and pathology: Acute toxicity studies; subacute and chronic toxicity studies; reproduction and teratology studies; miscellaneous studies.

e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose-range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. *a.* Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

b. If the drug is to be offered over the counter, labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to the layman. If the drug is intended or offered for uses under the professional supervision of a practitioner licensed by law to administer it, the application should also contain labeling that includes adequate information for all such uses, including all the purposes for which the over-the-counter drug is to be advertised to, or represented for use by, physicians.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with §1.106(b) (21 CFR 1.106(b)). The application should include any labeling for the drug intended to be made available to the layman.

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug.

f. No application may be approved if the labeling is false or misleading in any particular.

(When mailing pieces, any other labeling, or advertising copy are devised for promotion of the new drug, samples shall be submitted at the time of initial dissemination of such labeling and at the time of initial placement of any such advertising for a prescription drug (see §130.13 of the new-drug regulations). Approval of a supplemental new-drug application is required prior to use of any promotional claims not covered by the approved application.)

5. A statement as to whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

6. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

7. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed (for example, amount per tablet or per milliliter) and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

8. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form, as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging, labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and, if so, at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling storage and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of the batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including the control numbers that appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container in which it is to be marketed, including any proposed multiple-dose container, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. State the expiration date(s) that will be used on the label to preserve the identity, strength, quality, and purity of the drug until it is used. (If no expiration date is proposed, the applicant must justify its absence.)

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

9. Samples of the drug and articles used as components, as follows: a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing and, if any such sample is not from a commercial-scale production batch, such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in §130.1(g), from the batch(es) employed in the production of such dosage form(s).

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug: *Provided, however,* That samples of reference standards recognized in the official U.S. Pharmacopeia or The National Formulary need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics, to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to Item 9a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of Item 9a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

f. If samples of the drug are sent under separate cover, they should be addressed to the attention of the Bureau of Medicine and identified on the outside of the shipping carton with the name of the applicant and the name of the drug as shown on the application.

10. Full reports of preclinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and effectiveness of the drug under the conditions of use suggested in the proposed labeling.

b. Detailed reports of the preclinical investigations, including all studies made on laboratory animals, the methods used, and the results obtained, should be clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or women of child-bearing potential.

c. Detailed reports of any pertinent microbiological and *in vitro* studies.

d. Summarize and provide a list of literature references (if available) to all other preclinical information known to the applicant, whether published or unpublished, that is pertinent to an evaluation of the safety or effectiveness of the drug.

11. List of investigators. a. A complete list of all investigators supplied with the drug including the name and post office address of each investigator and, following each name, the volume and page references to the investigator's report(s) in this application and in any documents incorporated by reference, or the explanation of the omission of any reports.

b. The unexplained omission of any reports of investigations made with the new drug by the applicant, or

submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, whether or not it would bias an evaluation of the safety of the drug or its effectiveness in use, may constitute grounds for the refusal or withdrawal of the approval of an application.

12. Full reports of clinical investigations that have been made to show whether or not the drug is safe for use and effective in use. a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the labeling.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. An application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639, Drug Experience Report (obtainable, with instructions, on request from the Department of HEW. Food and Drug Administration. Bureau of Drugs *(BD-200)* Rockville, Maryland 20852), for each adverse experience or, if feasible, for each subject or patient experiencing one or more adverse effects, described in Item 12c, whether or not full information is available. Form FD-1639 should be prepared by the applicant if the adverse experience was not reported in such form by the investigator. The Drug Experience Report should be cross-referenced to any narrative description included in Item 12c. In lieu of a FD Form 1639, a computer-generated report may be submitted if equivalent in all elements of information with the identical enumerated sequence of events and methods of completion; all formats proposed for such use will require initial review and approval by the Food and Drug Administration.

e. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commerical marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §130.38 of the new-drug regulations, about related drugs; a bibliography will suffice. Include any evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.

Observe the provisions of §130.9 of the new-drug regulations concerning supplemental applications.

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.
(Applicant)

Per _____
(Responsible official or agent)

SAMUEL M. FAINBERG, PH.D., DIRECTOR
TECHNICAL AND REGULATORY AFFAIRS
(Indicate authority)

(Warning: A willfully false statement is a criminal offense. U.S.C. Title 18, sec. 1001.)

NOTE: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States.