CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

83-547

Generic Name: Estradiol Valerate Injection, 20mg/mL

Sponsor: Chromalloy Pharmaceuticals, Inc.

Approval Date: February 28, 1979

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APPLICATION NUMBER:

83-547

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-547

APPROVAL LETTER

NDA 83-547

FEB 28 1979

Chromalloy Pharmaceuticals, Inc.
Carter-Glogau Laboratories Division
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 Estradiol Valerate Injection, 20 mg/ml.

Reference is also made to (1) our letter of September 2, 1977, (2) the FEDERAL REGISTER Notice of October 7, 1977 and (3) your communications dated October 17, 1977, October 31, 1977, May 19, 1978, July 31, 1978 and February 15, 1979.

The product will carry a current two year expiration term.

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

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

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

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

An Abbreviated New Drug Application is approved on the basis of a determination that the subject drug is as safe and as effective as the referenced New Drug Application product. Claims of superior safety or efficacy for an Abbreviated New Drug Application product cannot be made unless such superiority has been demonstrated by adequate and well controlled studies which have been submitted to and approved by FDA.

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

Sincerely yours,

2/28/79

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

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

LOS-DO DUP HFD-614
MSeife/JLMeyer/MAJarski
R/DinitJMeyer/MSeife
ft/cjb/2-27-79 approved

2/27/79

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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FINAL PRINTED LABELING

ESTRADIOL VALERATE INJECTION

WARNING

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

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

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

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

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

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestagens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] This risk has been estimated as not greater than 4 per 1000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis[8-12] with epithelial changes of vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it is reasonable to presume they would induce similar changes.

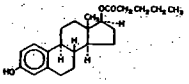
Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7 fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. These data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000.

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

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

DESCRIPTION: A sterile solution of Estradiol Valerate (a long-acting estrogen) for intramuscular injection.

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



$C_{23}H_{32}O_3$ 356.50

Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate.
Estradiol 17-valerate

Available as: Sterile Estradiol Valerate Injection 10 mg. per ml. in 10 ml. multiple dose vials. Each ml. contains: Estradiol Valerate 10 mg., Chlorobutanol (Chloral derivative) 0.5% as preservative in Sesame Oil.

Sterile Estradiol Valerate Injection 20 mg. per ml. in 10 ml. multiple dose vials. Each ml. contains: Estradiol Valerate 20 mg., Benzyl Benzoate 20%, Benzyl Alcohol 2% as preservative in Castor Oil.

Sterile Estradiol Valerate Injection 40 mg. per ml. in 10 ml. multiple dose vials. Each ml. contains: Estradiol Valerate 40 mg., Benzyl Benzoate 40%, Benzyl Alcohol 2% as preservative in Castor Oil.

CATEGORY: ESTROGEN

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

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

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

INDICATIONS: Estradiol Valerate is indicated in the treatment of:

1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma — palliative therapy of advanced disease.

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

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

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

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

At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[18] although a recent long-term followup of a single physician's practice has raised this possibility.[18A] Because of the animal data, there is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms.

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

3. Effects similar to those caused by estrogen-progestagen oral contraceptives. There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement are more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[20-23]

a. Thromboembolic disease. It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[24-31] Cases of retinal thrombosis, mesenteric thrombosis and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug.[32/33] An increased risk of post-surgery thromboembolic complications has also been reported in users of oral contraceptives.[34/35] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

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

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

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

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

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

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

PRECAUTIONS: A. General Precautions.

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

2. Fluid retention — Because estrogens may cause some degree of fluid retention, conditions might be influenced by

this factor such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

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

4. Oral contraceptives appear to be associated with an increased incidence of mental depression.[24] Although it is not clear whether this is due to the estrogenic or progestagenic component of the contraceptive, patients with a history of depression should be carefully observed.

5. Preexisting uterine leiomyomata may increase in size during estrogen use.

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

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

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

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

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

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

a. Increased sulfobromophthalein retention.

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

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

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

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

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

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

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

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

DOSAGE AND ADMINISTRATION: Care should be taken to inject deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration.

1. Given cyclically for short term use only:
For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause.

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

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

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

The usual dosage is 10 to 20 mg. Repeat two or three weeks after initial injection. Continuous therapy with estrogen alone may induce dysfunctional bleeding.

2. Given cyclically:
Female hypogonadism; female castration; primary ovarian failure.

10 to 20 mg. I.M. Repeat in two to three weeks after initial injection.

3. Given chronically:
Inoperable progressing prostatic cancer.

30 mg. or more every 1 to 2 weeks. Close medical supervision is mandatory. Suspend therapy if there is a relapse. Soreness of the breasts or gynecomastia may occur; hypercalcemia may develop.

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

HOW SUPPLIED: Multiple dose vials of 10 ml. containing 10 mg., 20 mg. and 40 mg. per ml. PROTECT FROM LIGHT.

CAUTION: Federal law prohibits dispensing without prescription.

Literature Revised: March 1977

Product No. 0026-10, 0027-10, 0244-10.

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Labeling: ORIG

NDA No: 83-547 Rc'd. 8-27-75

Reviewed by: majorsky 2/28/79

Sterile 10 ml. NDC 0381-0027-10 Multi-dose

ESTRADIOL VALERATE INJECTION
20 mg./ml.

FEB 28 1979

Each ml. contains: Estradiol Valerate 20 mg., Benzyl Benzoate 20%, Benzyl Alcohol 2% as preservative in Castor Oil.
USUAL ADULT DOSE: Intramuscular. See package insert.
CAUTION: Federal law prohibits dispensing without prescription.
873/0027-10

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

APPROVED

Sterile 10 ml. NDC 0381-0027-10 Multi-dose

ESTRADIOL VALERATE INJECTION
20 mg./ml.

FEB 28 1979

Each ml. contains: Estradiol Valerate 20 mg., Benzyl Benzoate 20% Benzyl Alcohol 2% as preservative in Castor Oil.
USUAL ADULT DOSE: Intramuscular. See package insert.
CAUTION: Federal law prohibits dispensing without prescription.
873/0027-10

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

APPROVED

Sterile 10 ml. NDC 0381-0027-10 Multi-dose

ESTRADIOL VALERATE INJECTION
20 mg./ml.

FEB 28 1979

Each ml. contains: Estradiol Valerate 20 mg., Benzyl Benzoate 20%, Benzyl Alcohol 2% as preservative in Castor Oil.
USUAL ADULT DOSE: Intramuscular. See package insert.
CAUTION: Federal law prohibits dispensing without prescription.
873/0027-10

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

APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-547

CHEMISTRY REVIEW(S)

CHEMIST's REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT	Statement Date:	NDA NUMBER: 83-547

NAME AND ADDRESS OF APPLICANT

Chromalloy Pharmaceuticals, Inc.
Glendale, AZ 85301

ORIGINAL
AMENDMENT XXX
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

labeling, manufacturing

DATE(s) of SUBMISSION(s)

see issuing letter

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
estrogen	estradiol valerate	RX XX OTC
DOSAGE FORM(S)	**POTENCY(IES)**	**RELATED IND/NDA/DMF**
injection	20 mg/ml	83-546 83-547 83-714
STERILIZATION	**SAMPLES**	
included		

LABELING

See Medical Officer's review of 2-26-79

BIOLOGIC AVAILABILITY

not required

ESTABLISHMENT INSPECTION

related HFD-322 memo of 11-20-78; Carter-Glogau profile of 8-11-78; of 7-17-78

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

included

PACKAGING

included

STABILITY

Protocol:

Exp. Date: 24 mo.

REMARKS AND CONCLUSION: approved MAJarski

MAJarski 7/27/79

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Federal Register Statement Date

NDA Number 83-547

AE Number 9-931

Name and Address of Applicant (City and State)

Carter-Glogau Laboratories Division
Glendale, AZ 85301

Original
Amendment XXXXXX
Supplement
Resubmission
Correspondance
Report
Other

Purpose of Amendment/Supplement

consolidation of Myers-Cater with Glogau

Date(s) of Submission(s)

3-5-75

Pharmacological Category	Name of Drug	How Dispensed
estrogen	estradiol valerate	R_x XXXXX OTC
Dosage Form(s) **injection**	Potency(ies) 20 mg. /ml.	
Packaging/Sterilization	Samples	Related IND/NDA/MF 83-546 83-547 83-714

Labeling

Biologic Availability

Establishment Inspection

Components, Composition, Manufacturing and Controls

Remarks **firm to provide response to FDA letter of**
firm to provide for Melrose park facility

ack majarski

majarski 6/11/75

Conclusion

REVIEWER DATE

CHECKLIST - REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Federal Register Statement Date

ORIGINAL ☐

SUPPLEMENT ☐

Name & Address of Applicant (City & State)
Myers-Carter
Glendale, Arizona

NDA Number
83-547

Supplement Date and Number

Name of Drug
estradiol valerate

Nonproprietary Name

Amendment Date(s)
xxxxxxxxxxxxx original

Purpose of Supplement

Other Date(s)

Pharmacological Category
estrogen

How Dispensed
Rx XX O.T.C. ☐

AF Number
9-931

Related IND/NDA/AF(s)
83-546

Dosage Form(s)
injection

Potency (ies)
20 mg./ml.

Satisfactory ☐ Labeling
Date Due ~~revise per medical officer~~

Satisfactory ☐ Components, Composition, Manufacturing and Controls
Date Due additional information

Satisfactory ☐ Biologic Availability
Date Due deferred
Is data on current formulation? YES ☐ NO ☐

Satisfactory ☐ Probably or Possibly Effective Indications (if in labeling)
Date Data Due _____

Establishment Inspection
E.I. 3-14/17-72 satisfactory
referred to compliance 4-19-73

Recalls

Relabeling of drug in commercial channels required? YES ☐ NO ☐
If so, what level:

Remarks
revise container labels and package insert
clarify manufacturing procedure
information on containers and closures
solution or suspension?
why formulation in _____ rather than castor oil?

Conclusions
rev w/f majarski

M.O. Jarski 5/14/73

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-547

ADMINISTRATIVE DOCUMENTS

REVIEW OF RESUBMISSION

DATE COMPLETED: 9-25-75

ANDA #: 83-547

F.R. DATE: 6-25-72

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

NAME OF DRUG: Generic: Estradiol Valerate Injection 20 mg/ml

DATE OF SUBMTSSION: 8-15-75

TYPE OF SUBMISSION: Resubmission (reply to FDA letter 4-23-75)

CLINICAL EVALUATION:

1. Review of STudies:

Bioavailability Requirement: NOT required
Pertinent data is to be reviewed by the chemist

2. Review of Labeling:

a) Container Labels: Satisfactory
*Castor oil as vehicle
10 ml vial

b) Insert Labeling: Not submitted

CONCLUSION: Labeling is satisfactory for container labels

RECOMMENDATIONS: The firm is to be so notified

V. V. Karusaitis, M.D.

cc:
Dup
HFD-530
VVKarusaitis/rt/9-29-75

MEMORANDUM OF A TELEPHONE CONVERSATION

February 14, 1979

BETWEEN

Marvin Seife, M.D., Director
Division of Generic Drug Monographs, FDA

AND

Mr. Jack Dale, Director
Quality Control
Carter-Glogau Laboratories
Glendale, AZ 85301

SUBJECT: Physician's Package Insert

1. 83-714 Estradiol Valerate Injection, USP, 40 mg/ml.
2. 83-546 Estradiol Valerate Injection, USP, 10 mg/ml.
3. 83-547 Estradiol Valerate Injection, USP, 20 mg/ml.

Mr. Dale was informed that the physician's package insert dated Nov. 1976, in each of the above submissions contained 9 INDICATIONS for use. He was requested to delete indication #9 which allowed the drug to be used for

Mr. Dale stated that the aforementioned indication had been deleted in the reprinted Estradiol Valerate insert dated March, 1977. Unfortunately, the firm had failed to forward copies of the revised physician's package insert to this Division, but was doing so today.

Marvin Seife

Marvin Seife, M.D.

cc:
83-714 (orig.dup.)
83-546 " "
83-547 " "
MS/wlh/2-22-79

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 4-19-73
FROM: m.a. jarski (thru Jack L. Meyer)		OFFICE BD-69
TO: Mr. J.L. Bassen (thru Stan Stringer BD-105)		DIVISION BD-340

SUBJECT: Collaborative draft(s)

SUMMARY

In connection with NDA 83-545 & 83-547 for **Estradiol Valerate Injection, 10mg./ml. and 20 mg./ml.**

The applicant:

Myers-Carter Laboratories, Inc.
Glendale, Arizona 85301

AF: **9-931**

We acknowledge receipt on **February 16, 1973**

of **ANDA's (2)**

dated **February 5, 1973**

for **as above**

In accordance with the 2/27/73 directive, Office of Compliance a request is made for:

REQUESTED

( ) 1. establishment inspection report on

[ ] a. the applicant

[ ] b. others

(XX) 2. evaluation of compliance with CGMPR

(XX) 3. recommendation for approval/disapproval of the application/communication/supplement based on your evaluation of compliance with CGMPR

PLEASE EXPEDITE

SIGNATURE

DOCUMENT NUMBER

REVIEW OF ANDA

DATE COMPLETED: 3/19/73

ANDA #: 83-547

F.R. STATEMENT DATE: 7/25/72

CO. NAME: Myers-Carter Labs., Inc.
ADDRESS : 5160 West Bethany Home Rd.
Glendale, Arizona 85301

Name of Drug: Trade:

Estradiol Valerate 20 mg/ml

Generic:

Date of Submission: Feb. 5, 1973

Type of Submission: ANDA

Clinical Evaluation:

1. Review of Studies: Pertinent data is to be reviewed by chemist.

Bioavailability status: Deferred

Formulation:	Delestrogen	Estradiol Valerate Product
20 mg/ml	Castor Oil	Sesame Oil
	20% Benzyl Benzoate	2% Benzyl Alcohol

2. Review of Labeling: a. Container Label: Unsatisfactory
20 mg/ml multiple dose vial
*Does not state size of vial

b. Insert Labeling: Unsatisfactory

Dosage and Administration: Submitted dosage levels are inadequate; ineffective and demonstrate lack of knowledge of product.

Conclusion: Labeling is not satisfactory for the safe and effective use of this product.

Recommendations: The firm is to be so notified.

V. V. Karusaitis, M.D.

cc: BD-69, Orig, Dup, VVKarusitis/ih/4/17/73

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER 83-547

DATE APPROVAL LETTER ISSUED

TO:

Press Relations Staff (HFI-40)

FROM:

X Bureau of Drugs FEB 28 1979

☐ Bureau of Veterinary Medicine

ATTENTION

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

ORIGINAL ABBREVIATED

TYPE OF APPLICATION

☐ ORIGINAL NDA ☐ SUPPLEMENT TO NDA XX ABBREVIATED ORIGINAL NDA ☐ SUPPLEMENT TO ANDA

CATEGORY

XX ☐ HUMAN ☐ VETERINARY

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

Estradiol Valerate

DOSAGE FORM

Injection

HOW DISPENSED

XX ☐ RX ☐ OTC

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

Estradiol Valerate 20 mg/ml

NAME OF APPLICANT *(Include City and State)*

Chromalloy Pharmaceuticals, Inc. - Glendale, AZ 85301

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

estrogen

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME MAJarski DATE

FORM APPROVED BY

NAME JJMeyer DATE

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-547

CORRESPONDENCE

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

Feburary 15, 1979

Marvin Seife, M.D.
Director
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs
Department of Health, Education & Welfare
Public Health Service
Food and Drug Administration
Rockville, Maryland 20852

NDA ORIG AMENDMENT

PU

SUBJECT: NDA 83-546 Estradiol Valerate Inj. 10 mg./ml.
NDA 83-547 Estradiol Valerate Inj. 20 mg./ml.
NDA 83-714 Estradiol Valerate Inj. 40 mg./ml.

Dear Dr. Seife:

In response to your telephone call today, I am enclosing 25 physicians package inserts for Estradiol Valerate Injection 10, 20 and 40 mg./ml.

These inserts were revised in March 1977 and show only the 8 indications you specified. I can find no record that they were submitted to you previously so I assume we were holding them anticipating additional indications would be approved.

Sincerely,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

JKD/ht

enc.

RECEIVED
FEB 28 1979
GENERIC DRUGS

TELEPHONE (602) 939-7565 • TELEX 66-8304 (M-C LABS)

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

July 31, 1978

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
Rockville, MD 20857

SUBJECT: ESTRADIOL VALERATE INJECTION USP, 20 mg/ml.
NDA 83-547

Dear Dr. Seife:

We are updating our Abbreviated New Drug Application for Estradiol Valerate Injection USP, 20 mg/ml.

Attached are the Master Formula Card, Manufacturing Procedure and the change of specification for Estradiol Valerate Injection as required in USP XIX, page 180-181.

As we have submitted all the required informations, we would greatly appreciate prompt approval of this ANDA.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

SMF/edc
encls:

RECEIVED
AUG 03 1978
GENERIC DRUGS

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

Orig

CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

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

May 19, 1978

ORIG NEW CORRES

SUBJECT: ESTRADIOL VALERATE INJECTION, 20 MG/ML
NDA 83-547

Dear Dr. Seife:

Reference is made to our letter of October 17, 1977 in which we requested approval of this ANDA based on the Federal Register Notice of October 7, 1977 amending DESI 1543 allowing the approval of an abbreviated new drug application for this product.

Reference is also made to our submission of October 31, 1977 in which we supplied the patient package insert as you requested in your letter of October 28, 1977.

To date we have not received an answer to either of these communications. As we have submitted all required information we would appreciate prompt approval of this ANDA.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

RECEIVED
MAY 22 1978
GENERIC DRUGS

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

Ops

CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

October 31, 1977

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
Public Health Service
Food and Drug Administration
Rockville, Maryland 20857

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

Dear Dr. Seife:

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

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

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

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

Ronald M. Carter
President

RMC/sp

cc: Dr. Sam Fainberg
Governor Herschel Loveless
NDA Files

RECEIVED
NOV 03 1977
BUREAU OF DRUGS

GENERAL OFFICES:
5760 WEST BETHANY HOME ROAD • GLENDALE, ARIZONA 85301
TELEPHONE (602) 939-7565 • TELEX 66-8304 (M-C LABS)

83-547

HERSCHEL C. LOVELESS
7523 17TH STREET, N.W.
WASHINGTON, D. C. 20012

June 1, 1978

TO WHOM IT MAY CONCERN:

This is to advise that the undersigned is no longer associated with Chromalloy American Corporation, Chromalloy Pharmaceuticals, Inc., or any units of these corporations.

Sincerely,

Herschel C. Loveless

HCL/jhr

OCT 28 1977

NDA 83-397
NDA 83-546
NDA 83-547
NDA 83-599
NDA 83-714
NDA 83-825
NDA 83-840
NDA 84-032

Carter-Glogau Laboratories Division
Chromalloy Pharmaceuticals, Inc.
Attention: Samuel M. Fainberg, Ph.D.
5160 W. 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 10/28/77

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

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

Enclosure:
F.R. July 22, 1977

Orig

CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

October 17, 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, MD 20857

ORIG NEW CORRES

SUBJECT: ESTRADIOL VALERATE INJECTION, 20 MG/ML
NDA 83-547

Dear Dr. Seife:

Reference is made to your communication of August 25, 1977 regarding NDA 85-547 for Estradiol Valerate Injection, 20 mg/ml making reference to the Federal Register Notice of September 29, 1976. In this letter your informed us that a full new drug application was required.

We call your attention to the Federal Register Notice, Volume 42, No. 195 dated Friday, October 7, 1977 DESI 1543. In this Federal Register Notice DESI 1543 is amended to allow the approval of an abbreviated new drug application.

We respectfully call to your attention that this ANDA has been on file since 1973 and full manufacturing information as required by items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of the new drug application FD Form 356H (21 CFR 314.1(c)) have been submitted and the ANDA has been approvable since the later part of 1975 and therefore we respectfully request prompt approval of this ANDA.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

RECEIVED
OCT 21 1977
BUREAU OF DRUGS

SMF/jcw

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

SEP 2

NDA 83-547

Chromalloy Pharmaceuticals, Inc.
Carter-Glogau Laboratories Division
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 Estradiol Valerate Injection.

Reference is also made to the FEDERAL REGISTER notice of September 29, 1976, relating to estrogenic products.

In accord with the FEDERAL REGISTER notice, page 43116, "For estradiol valerate sterile oleaginous solution, approval of a full new drug application (21 CFR 314.4(c)(2) must be obtained prior to marketing such a product".

Accordingly, if you elect to file for this product a full new drug application should be appropriately submitted.

Your material is not being evaluated but will be retained in the file.

Sincerely yours,

Marvin Seife 9/2/77

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

cc:
LQS-DO
HFD-614
VVKarusaitis/JMeyer/MJarski
R/D init JMeyer/MSeife/8/31/77
ps/8/31/77 chel 9/1/77
ack
JMeyer 9/1/77

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

Orig

June 24, 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, MD 20857

SUBJECT: ESTRADIOL VALERATE INJECTION USP. 20 MG/ML
NDA 83-547

Dear Dr. Seife:

We hereby amend our NDA 83-547 for Estradiol Valerate Injection USP, 20 mg/ml.

This amendment provides for an additional batch size of _____ Master Formula Card reflecting this change is attached.

There are no other changes or additions to this NDA.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

SMF/jcw
encl

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

Orig

June 3, 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, MD 20857

NDA ORIG AMENDMENT

SUBJECT: ESTRADIOL VALERATE INJECTION 20 mg/ml
NDA 83-547

Dear Dr. Seife:

We hereby amend our application for Estradiol Vaterate Injection 20 mg/ml NDA 83-547.

This amendment provides for a change in the vial type from ——— to "Amber". The Master Formula Card reflecting this change is attached.

There are no other changes or additions to this application for Estradiol Valerate Injection, 20 mg/ml.

Sincerely Yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

SMF/jcw
encl

RECEIVED
JUNO 7 1977
BUREAU OF DRUGS

GENER 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

Orig

June 1, 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, MD 20857

NDA ORIG AMENDMENT

SUBJECT: ESTRADIOL VALERATE INJECTION, 20 MG/ML
NDA 83-547

Dear Dr. Seife:

We hereby amend our application for Estradiol Valerate Injection, 20 mg/ml. NDA 83-547.

This amendment provides for _____ for the product rather than _____ The Master Formula Card and Manufacturing Instructions reflecting this change are attached.

There are no other changes or additions to this application for Estradiol Valerater Injection NDA 83-547.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CRHOMALLOY PHARMACEUTICALS, INC.

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

SMF/jcw
encl

RECEIVED
JUN 07 1977
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

December 16, 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: ESTRADIOL VALERATE INJECTION, 20 mg/ml
NDA 83-547

Dear Dr. Seife:

We hereby amend our NDA 83-547 for Estradiol Valerate Injection, 20 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

SMF/jcw
encl

DEC23

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

CHROMALLOY PHARMACEUTICALS, II
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

August 15, 1975

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 20852

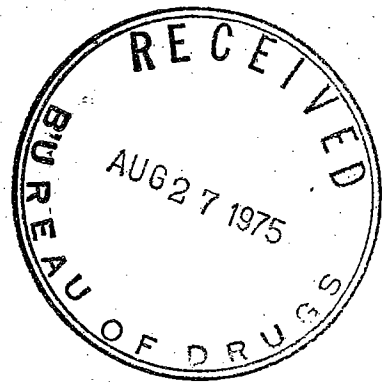
SUBJECT: NDA 83-547
ESTRADIOL VALERATE INJECTION
20 mg. per ml.

Dear Dr. Seife:

We are supplementing our abbreviated NDA for Estradiol Valerate Injection, 20 mg. per ml., NDA 83-547 to provide for an alternate ——— castor oil and an additional batch size of ———

We are supplying the following information:
1. Master formula card for ——— batch.
2. Manufacturing instructions for ——— batch.
3. Revised labels reflecting the use of castor oil.
4. Stability data on the formulation using castor oil.
5. Assurance that the drug dosage form and components will meet specifications.

No other information contained in our NDA has been changed.



Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVIS
CHROMALLOY PHARMACEUTICALS, INC.

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

SMF/jw
encl: FD Form 356H

GENERAL OFFICES:
5160 WEST BETHANY HOME ROAD • GLENDALE, ARIZONA 85301
TELEPHONE (602) 939-1426 • TELEX 66-8304 (M-C LABS)

ORIG NEW CORRES Orig

CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

June 23, 1975

No Reply
MaJanka 7/24/75

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

SUBJECT: NDA 83-547
ESTRADIOL VALERATE INJECTION
20 mg. per ml.

Dear Dr. Seife:

We are attaching hereto our supplement and FD Form 356H for NDA 83-547 for Estradiol Valerate Injection, 20 mg. per ml.

This supplement provides for _____ to be performed by:

_____

_____

_____

Letter of Certification from _____ is attached.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICAL, INC.

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

RECEIVED
JUL 09 1975
BUREAU OF DRUGS

SMF/jw

Enc: FD Form 356H, _____ Letter,
_____ Letter of Certification

GENERAL OFFICES:
5160 WEST BETHANY HOME ROAD • GLENDALE, ARIZONA 85301
TELEPHONE (602) 939-1426 • TELEX 66-8304 (M-C LABS)

Orig

CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

June 23, 1975

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
Public Health Service
Food and Drug Administration
Rockville, MD 20852

No Reply
MeJarvis
8/1/75

SUBJECT: NDA 83-547
Estradiol Valerate Injection
20 mg. per ml.

Dear Dr. Seife:

Reference is made to your letter of June 12, 1975, regarding NDA 83-547 Estradiol Valerate Injection, 20 mg. per ml. and a letter we sent you March 5, 1975 , advising you of the consolidation of Chromalloy pharmaceuticals, Inc. Division - Meyers-Carter Laboratories Division and Glogau and Company, Inc., into the consolidated company, Carter-Glogau Division, Chromalloy Pharmaceuticals, Inc.

On May 30, 1975, we submitted a letter to you withdrawing the communication of March 5, 1975 and submitted another supplement advising you of the consolidation.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICAL, INC.

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

RECEIVED
JUL 01 1975
BUREAU OF DRUGS

SMF/jw

GENERAL OFFICES:
5160 WEST BETHANY HOME ROAD • GLENDALE, ARIZONA 85301
TELEPHONE (602) 939-1426 • TELEX 66-8304 (M-C LABS)

NDA 83-547

AF 9-931

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

JUN 12 1975

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 Estradiol Valerate Injection, 20 mg./ml.

Reference is also made to (1) your communication dated March 5, 1975, amending the application and (2) our letter of April 23, 1975, commenting on your application.

Your communication:

a) advised of the consolidation of Chromalloy Pharmaceuticals, Inc. Divisions - Myers-Carter Laboratories Division and Glogau and Company, Inc. - into the consolidated company, Carter-Glogau Division, Chromalloy Pharmaceuticals, Inc.

b) included a completed form FD 356H so amending the application

c) stated that all labeling will be revised to reflect the name change

d) provided for a Melrose Park, IL location for manufacturing

We have reviewed the material submitted. However, before we are able to take any further action on this application, it will be necessary for you to (1) reply to our comments and (2) submit appropriate information for operations at the Melrose Park facility.

The material submitted is being retained in the file.

Sincerely yours,

Marvin Seife 6/12/75

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

cc:
LOS-DO
Dup
HFD-530
HFD-614
HFD-616
JLMeyer/MAJarski
R/D init. MSeife/JMeyer/6-10-75
Final typing/rt/6-10-75
Ack.

MAJarski 6/11/75

JLMeyer 6/11/75

NDA ORIG AMENDMENT

CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

June 2, 1975

No Reply
Majumdar
7/2/75

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

SUBJECT: NDA 83-547
ESTRADIOL VALERATE INJECTION,
20 mg./ml.

Dear Dr. Seife:

We are attaching hereto FD Form 356H to supplement our NDA 83-547 for Estradiol Valerate Injection, 20 mg. per ml.

Also attached is a copy of the letter executed by Mr. Ronald M. Carter, President, Carter-Glogau Laboratories Division, Chromalloy Pharmaceutical, Inc., which indicates the consolidation of Meyers-Carter Laboratories Division and Glogau and Company, Inc. and provides for their name change, effective immediately.

There has been no change in the physical location of the plant facilities in Glendale, Arizona. There is also no change in company operations and personnel. Changes in the signature lines on labeling will be made at the next printing or within six months, whichever date is first.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICAL, INC.

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

SMF/jw
Enc: FD Form 356H, Mr. R. Carter's Letter

GENERAL OFFICES:
5160 WEST BETHANY HOME ROAD • GLENDALE, ARIZONA 85301
TELEPHONE (602) 939-1426 • TELEX 66-8304 (M-C LABS)

WITHDRAWN dkg

CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

May 30, 1975

No Reply
MaJarvis
7/2/75

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

SUBJECT: NDA 83-547
ESTRADIOL VALERATE INJECTION,
20 mg. per ml.

Dear Dr. Seife:

On the date of March 5, 1975, I submitted a letter to you advising you of a name change effecting the former Meyers-Carter facility in Glendale, Arizona.

The terminology of the letter of March 5, is incorrect and I hereby withdraw it and request that the attachment hereto be made a part of that file for NDA 83-547.

Sincerely yours,

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

SMF/jw
Enc

RECEIVED
JUN 19 1975
BUREAU OF DRUGS

GENERAL OFFICES:
5160 WEST BETHANY HOME ROAD • GLENDALE, ARIZONA 85301
TELEPHONE (602) 939-1426 • TELEX 66-8304 (M-C LABS)

NDA 83-546
NDA 83-547
NDA 83-714

AF 9-931

Myers-Carter Laboratories Division
Chromalloy Pharmaceutical, Inc.
Attention: Samuel M. Fainberg
5160 West Bethany Home Road
Glendale, AZ 85301

APR 23 1975

Gentlemen:

Reference is made to your abbreviated new drug applications submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for (1) Estradiol Valerate Injection 10 mg./ml., re: 83-546, (2) Estradiol Valerate Injection, 20 mg./ml. re: 83-547; and (3) Estradiol Valerate Injection, 40 mg./ml.

Reference is also made to your communication dated February 14, 1975, relating to these application, i.e., comments relating to assay procedures.

We have completed our review of these abbreviated new drug applications and have the following comments:

1. Final printed vial labels are lacking from all applications.

2. No provision has been made for an assay of estradiol valerate, active ingredient.

3. No provision has been made for a castor oil formulation for the 20 mg./ml. dosage form (re: 83-547, formulation as submitted 2-5-73 indicates ———— .

Your referenced communication indicates the USP XVIII assay procedure will now be used, in lieu of the modified —— procedure. An objection to the USP procedure has been that high assay values are often obtained because of interferences from ———— The —— procedure separates the active ingredient from ———— by using a ————

Therefore, in order to determine that the tests applied to the drug dosage form are adequate to assure identity, strength, quality and purity we are requesting:

(a) recovery studies which verify the absolute strength of the drug dosage form relative to your assay procedures (including a complete account of the procedure) and,

(b) an evaluation of the extent of interference from ——— on your procedure.

Please let us have your response promptly.

Sincerely yours,

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

cc:
LOS-DO
Dup
HFD-530
HFD-614
HFD-616 MaJarski 4/22/75
JLMeyer/MAJarski
R/D init. MSeife/GMillar/4-17-75
Final typing/rt/4-21-75
rev w/f
JMeyer 4/22/75

NDA ORIG AMENDMENT

CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

March 5, 1975

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 20852

SUBJECT: NDA 83-547
ESTRADIOL VALERATE INJECTION,
20 mg. per ml.

Dear Dr. Seife:

We are attaching hereto FD Form 356H to amend our NDA 83-547 for Estradiol Valerate Injection, 20 mg. per ml.

Also attached is a copy of the letter executed by Mr. Ronald M. Carter, President, Carter-Glogau Laboratories Division, Chromalloy Pharmaceutical, Inc. which indicates the consolidation of Myers-Carter Laboratories Division and Glogau and Company, Inc. and provides for their name change, effective immediately.

There has been no change in the physical location of the plant facilities in Glendale, Arizona and/or Melrose Park, Illinois. There is also no change in company operations and personnel at either facility. Changes in the signature lines on labeling will be made at the next printing or within six months, whichever date is first.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICAL, INC.

Samuel M. Fainberg,
Director,
Technical and Regulatory Affairs

MP

Enclosures: FD Form 356H
Mr. Ron Carter's Letter

GENERAL OFFICE
5160 WEST BETHANY HOME ROAD • GLENDALE, ARIZONA 85301
TELEPHONE (602) 939-1426 • TELEX 66-8304 (M-C LABS)

ORIG NEW CORRES

ORIG

MYERS-CARTER LABORATORIES

Division of Chromalloy Pharmaceuticals, Inc. • A Subsidiary of Chromalloy American Corporation

February 14, 1975

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 20852

SUBJECT: NDA 83-546
ESTRADIOL VALERATE INJECTION,
10 mg. per ml.

We refer to your communication dated September 19, 1974 regarding the following NDAs:

NDA 83-546	Estradiol Valerate Injection, 10 mg./ml.
NDA 83-547	Estradiol Valerate Injection, 20 mg./ml.
NDA 83-714	Estradiol Valerate Injection, 40 mg./ml.

The comment in the referenced communication does not apply to the 20 mg./ml. and the 40 mg./ml. dosage forms since they are in castor oil , not .

In reference to the 10 mg./ml. dosage form, because we do not have a available for our use, we believe that the USP XVIII analytical procedure gives us better accuracy on our . Attached is a letter from regarding the analytical method for Estradiol Valerate Injection, 10 mg. per ml.

Sincerely yours,

MYERS-CARTER LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICAL, INC.

Samuel M. Feinberg,
Director,
Technical and Regulatory Affairs

MP

Enclosure: Letter

Enclosures in 83-546

RECEIVED
FEB 20 1975
BUREAU OF DRUGS

NDA 83-546
83-547
83-714

AF 9-931

SEP 10 1974

Myers-Carter Laboratories Division
Chromalloy Pharmaceuticals, Inc.
Attention: Mr. Samuel M. Fainberg
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 (1) Estradiol Valerate Injection, 10 mg./ml., re: 83-546, (2) Estradiol Valerate Injection, 20 mg./ml., re: 83-547, and (3) Estradiol Valerate Injection, 40 mg./ml., re: 83-714.

Reference is also made to your communication dated June 14, 1974 (re: 83-714) relating to methodology of testing.

We have reviewed the material submitted and again call to your attention the remarks elicited from our Laboratories:

> We feel that this technique may be suitable as an in-house quality control procedure, but may not be suitable as a regulatory procedure since the needed sesame oil would not be available to all other analytical laboratories.

We therefore recommend that you adopt the procedure as outlined in JAOAC Vol. 56, No. 2, page 511 (1973).

Please let us have your response promptly.

Dup
HFD-107 HFD-106 HFD-13 HFD-8
JLMeyer/MJarski
R/D init. by JMeyer/MSeife 9-11-74
Final typing/wlb/9-11-74
Rev w/f

MJarski 9/12/74

Sincerely yours,

Marvin Seife, M.D.
Director
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs

cc:
LOS-DO

REVIEW OF AMENDMENT

DATE COMPLETED: 2-26-79

ANDA #: 83-546 10 mg/ml.
83-547 20 mg/ml.
83-714 40 mg/ml.

F.R. DATE: 7-25-72; 7-22-77

CO. NAME: Carter-Glogau Laboratories
5160 W. Bethany Home Rd.
Glendale, AZ 85301

NAME OF DRUG: Estradiol Valerate Injection, 10 mg/ml., 20 mg/ml., 40 mg./ml. (in 10 ml. multiple dose vial)

DATE OF SUBMISSION: 2-15-79

TYPE OF SUBMISSION: Amendment

CLINICAL EVALUATION:

1. Review of Studies: NONE SUBMITTED

2. Review of Labeling:

FPL, physician's package insert, dated March, 1977, was submitted as per the telephone conversation dated 2/14/79 between Marvin Seife, M.D., and Jack K. Dale, Ph.D. The [redacted] indication has been deleted and the insert is now acceptable.

CONCLUSION: Satisfactory physician's package insert.

RECOMMENDATIONS: Approve ANDA's 83-546, 83-547, and 83-714.

Marvin Seife

Marvin Seife, M.D.

cc:dup
MS/wlh/2-26-79

NDA 83-546
NDA 83-547
NDA 83-714
AF 9-931

MAY 28 1974

Myers-Carter Laboratories, Inc.
Attention: Mr. Samuel Fainberg
5160 West Bethany Home Road
Glendale, AZ 85301

Gentlemen:

Reference is made to your abbreviated new drug applications submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

(1) Estradiol Valerate Injection, 10 mg./ml., re: 83-546
(2) Estradiol Valerate Injection, 20 mg./ml., re: 83-547
(3) Estradiol Valerate Injection, 40 mg./ml., re: 83-714

In relation to 83-546 and 83-547, reference is also made to your communications dated March 8, 1974, adopting the revised assay procedure for all Estradiol Valerate drug dosage forms.

In relation to 83-546, we acknowledge receipt of your communication dated January 23, 1974, enclosing an acceptably revised printed package insert and information relative to samples.

We have reviewed the material submitted relative to your assay procedure and call to your attention the following remarks elicited from our laboratories (in connection with 83-714):

1. Preparation of Blank and Standard Solutions:

[redacted]

APPEARS THIS WAY
ON ORIGINAL

2. Standard Preparation:

[redacted]

In view of these comments, the rationale for nonconformity with the procedure as outlined in JAOAC Vol. 56, No. 2, pg. 511 (1973) is requested.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 5/28/74

Marvin Seife, M.D.
Director
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs

cc:
LOS-DO
Dup
HFD-107
HFD-106
HFD-13
HFD-8
VVKarusaitis/JIMeyer/MAJaraki 5/20/74
R/D init. MSeife/JMeyer/5-17-74
Final typing/rt/5-17-74
rev w/f

JMeyer 5/21/74

Rec'd 3/8 E

ORIG

RESUBMISSION

NDA ORIG AMENDMENT

MYERS-CARTER LABORATORIES INC.
SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

March 8, 1974

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, Maryland 20852

SUBJECT: NDA 83-547
ESTRADIOL VALERATE INJECTION, 20 mg. per ml.

Dear Dr. Seife:

In view of your letter dated December 1, 1973 requesting as assay revision for our NDA 83-714 for _____ (estradiol valerate) Injection, 40 mg. per ml., we are enclosing a description of the complete methodology of the assay procedure for our NDA 83-547 for Estradiol Valerate Injection, 20 mg. per ml.

Sincerely yours,

MYERS-CARTER LABORATORIES, INC.

Samuel M. Fainberg,
Director,
Technical and Regulatory Affairs

MP

Enclosure: Assay Procedure

GENERAL OFFICES and PLANT: 5160 WEST BETHANY HOME ROAD, GLENDALE, ARIZONA 85301 TELEPHONE - (602) 939-1426
CABLE ADDRESS – "M-C LABS PHX" TELEX 668 - 304

identified with the reference number DESI 1543, 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 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.72-11394 Filed 7-24-72;8:46 am]

[DESI 8943; Docket No. FDC-D-306; 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; Laderle 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. Daranide Tablets containing dichlorphenamide; Merck Sharp and Dohme, Division of Merck and Co., West Point, Pa. 19486 (NDA 11-366).

7. Diamox Sequels (sustained release capsules) containing acetazolamide; Lederle Laboratories Division, American Cyanamid Co. (NDA 12-945).

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. *Effectivenes. 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 gaumoca, 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 withapplications and all amendments and drawing approval of all new drug supplements thereto providing for theindications 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

c. The labeling for all short-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.

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 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 (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 (a) (3) (i) 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" sections above) and possibly effective (not 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 referred to above. Communications forwarded in response to this announcement should be

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 (i) 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 28, 1972.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.72-11392 Filed 7-24-72;8:46 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. Estinyl Tablets; Schering Corp., 60 Orange Street, Bloomfield, N.J. 07003 (NDA 5-292).

b. Lynoral Tablets; Organon, Inc., 375 Mount Pleasant Avenue, West Orange, N.J. 07052 (NDA 5-490).

2. *Preparations containing estradiol dipropionate.* a. Ovocylin 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 2038, 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 4-782).

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 (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.

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 roentgen 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 labeling must be supported by clinical data if the indication was not included in the labeling which the Academy reviewed for that particular preparation.

CHROMALLOY PHARMACEUTICALS, INC.
A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

Feburary 15, 1979

Marvin Seife, M.D.
Director
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs
Department of Health, Education & Welfare
Public Health Service
Food and Drug Administration
Rockville, Maryland 20852

NDA ORIG AMENDMENT

PU

SUBJECT: NDA 83-546 Estradiol Valerate Inj. 10 mg./ml.
NDA 83-547 Estradiol Valerate Inj. 20 mg./ml.
NDA 83-714 Estradiol Valerate Inj. 40 mg./ml.

Dear Dr. Seife:

In response to your telephone call today, I am enclosing 25 physicians package inserts for Estradiol Valerate Injection 10, 20 and 40 mg./ml.

These inserts were revised in March 1977 and show only the 8 indications you specified. I can find no record that they were submitted to you previously so I assume we were holding them anticipating additional indications would be approved.

Sincerely,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

JKD/ht

enc.

RECEIVED
FEB 28 1979
GENERIC DRUGS

TELEPHONE (602) 939-7565 • TELEX 66-8304 (M-C LABS)

NDA 83-547

AF 9-931

MAY 15 1973

Myers-Carter Laboratories, Inc.
Attention: Mr. Samuel Fainberg
5160 W. Bethany Home Road
Glendale, Arizona 85301

Gentlemen:

Reference is made to your abbreviated new drug application dated February 5, 1973, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estradiol Valerate Injection, 20 mg./ml.

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

1. Container label: Include the vial size.

2. Package insert:

[redacted]

b) DOSAGE AND ADMINISTRATION: The submitted dosage levels are inadequate, ineffective and demonstrate a lack of knowledge of the product.

Enclosed is a copy of the labeling guidelines for your reference.

Other information required by 130.4(f) of the regulations:

1. A more complete outline of the methods used in, and the facilities, and controls used for the manufacture and processing of the drug since it is noted that the active ingredient, estradiol valerate, requires special handling.

2. Clarification of a formulation deviating from that of the reference drug product.

3. 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 its suitability for the intended use.

4. Clarify whether the drug dosage form is a solution or a suspension.

Further, The Bureau of Drugs, Office of Compliance is currently evaluating your status with regard to compliance with current Good Manufacturing Practice regulations. We will correspond with you after their review is complete.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 5/15/73

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

Enclosure:
Labeling guidelines
cc:
Dms DO

Dup
BD-69
BD-66
BD-106
BD-242
BD-340 M.A. Jarski 5/14/73
VVKarusaitis/JMeyer/MJarski 5/14/73
R/D init. by MSeife/JMeyer 4-23-73
Final typing/wlb/5-9-73
Rev w/f JMeyer 5/14/73

NDA 83-547
AF 9-931

MAR 02 1973

Myers-Carter Laboratories, Inc.
Attention: Mr. Samuel M. Fainberg
5160 West Bethany Home Road
Glendale, Arizona 85301

Gentlemen:

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

NAME of DRUG: Estradiol Valerate Suspension, 20 mg./ml.

DATE of APPLICATION: February 5, 1973

DATE of RECEIPT: February 16, 1973

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

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

Sincerely yours,

Marvin Seife 3/2/73

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

cc:
LOS-DO
Dup
BD-69
BD-66 JLMeyer 3/1/73
BD-106BD-310
JLMeyer/wlb/2-28-73
Ack.

PERSONALLY SUBMITTED BY
Mr H Loveless
Read by Loveless
2-16-73

MYERS-CARTER LABORATORIES INC.
SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

ABBREVIATED
NEW DRUG APPLICATION

February 9, 1973

83-547

RECEIVED
FEB 16 1973
BUREAU OF DRUGS

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Implementation Project Office
Bureau of Drugs (BD-69)
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Food and Drug Administration
Rockville, Maryland 20852

SUBJECT: ABBREVIATED NEW DRUG APPLICATION FOR
ESTRADIOL VALERATE SUSPENSION 20 MG/ML
FEDERAL REGISTER RULING OF TUESDAY,
JULY 25, 1972, VOL. 37, NO. 143, DESI 1543

Dear Dr. Seife:

We are enclosing our Abbreviated New Drug Application for Estradiol Valerate Injection, 20 mg./ml.

Sincerely yours,

MYERS-CARTER LABORATORIES, INC.

Samuel M. Fainberg, Director,
Technical and Regulatory Affairs

PB

Enclosure: Abb. NDA

C.C.

GENERAL OFFICES and PLANT: 5160 WEST BETHANY HOME ROAD, GLENDALE, ARIZONA 85301 TELEPHONE - (602) 939-1426
CABLE ADDRESS – "M-C LABS PHX" TELEX 668 - 304