

**CENTER FOR DRUG
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RESEARCH**

Approval Package for:

APPLICATION NUMBER:

83-714

Generic Name: Estradiol Valerate Injection, 40mg/mL

Sponsor: Chromalloy Pharmaceuticals, Inc.

Approval Date: February 28, 1979

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APPLICATION NUMBER:

83-714

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APPLICATION NUMBER:

83-714

APPROVAL LETTER

FEB 28 1979

NDA 83-714

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, 40 mg/ml.

Reference is also made to (1) our letter of August 25, 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,

Marvin Seife 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

MAJarski
2/27/79
JMeyer 2/27/79

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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 1960 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 15.5 times greater than in nonusers. The risk appears to depend on both duration of treatment¹ 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.⁵⁻⁹ 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 adenosis⁸⁻¹² 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 available with the use of other estrogens, it is reasonable to presume they would induce similar changes.

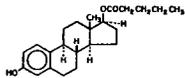
Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.¹³⁻¹⁶ One case control study¹⁶ estimated a 4.7 fold increased risk of limb reduction defects in infants exposed in utero 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:



C₂₃H₃₂O₃ 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 oral administration.

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

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,¹⁴ although a recent long-term followup of a single physician's practice has raised this possibility.^{15A} 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 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 disease, 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 men³⁷ 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 menopause⁴¹ 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 pre-treatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed.

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

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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.¹⁴ Although it is not clear whether this is due to the estrogenic or progestogenic 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:

- Increased sulfobromophthalein retention.
- Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
- 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.
- Impaired glucose tolerance.
- Decreased pregnandiol excretion.
- Reduced response to metyrapone test.
- Reduced serum folate concentration.
- 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:

- Gonitourinary 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.
- Breasts.
Tenderness, enlargement, secretion.
- Gastrointestinal.
Nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice.
- Skin.
Chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.
- Eyes.
Steepening of corneal curvature; intolerance to contact lenses.
- CNS.
Headache, migraine, dizziness; mental depression; chorea.
- 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 gynecostasia 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.

PHYSICIAN REFERENCES: ¹Ziel, H. K. and W. D. Finkel, "Increased Risk of Endometrial Carcinoma Among Users of Conjugated Estrogens," *New England Journal of Medicine*, 292:1167-1170, 1975.

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2/28/79

Sterile 10 ml. NDC 0381-0244-10 Multi-dose
ESTRADIOL VALERATE INJECTION
40 mg./ml.

Each ml. contains: Estradiol Valerate 40 mg., Benzyl Benzoate 40%, Benzyl Alcohol 2% as preservative in Castor Oil.
USUAL ADULT DOSE: Intramuscular. See package insert.
CAUTION: Federal law prohibits dispensing without prescription.
474/0244-10

mf FEB 28 1979

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

APPROVED

Sterile 10 ml. NDC 0381-0244-10 Multi-dose
ESTRADIOL VALERATE INJECTION
40 mg./ml.

Each ml. contains: Estradiol Valerate 40 mg., Benzyl Benzoate 40%, Benzyl Alcohol 2% as preservative in Castor Oil.
USUAL ADULT DOSE: Intramuscular. See package insert.
CAUTION: Federal law prohibits dispensing without prescription.
474/0244-10

mf FEB 28 1979

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

APPROVED

Sterile 10 ml. NDC 0381-0244-10 Multi-dose
ESTRADIOL VALERATE INJECTION
40 mg./ml.

Each ml. contains: Estradiol Valerate 40 mg., Benzyl Benzoate 40%, Benzyl Alcohol 2% as preservative in Castor Oil.
USUAL ADULT DOSE: Intramuscular. See package insert.
CAUTION: Federal law prohibits dispensing without prescription.
474/0244-10

mf FEB 28 1979

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

APPROVED

mf Sterile 5 ml. NDC 0381-0244-05 Multi-dose
ESTRADIOL VALERATE INJECTION
40 mg./ml.

Each ml. contains: Estradiol Valerate 40 mg., Benzyl Benzoate 40%, Benzyl Alcohol 2% as preservative in Castor Oil.
USUAL ADULT DOSE: Intramuscular. See package insert.
CAUTION: Federal law prohibits dispensing without prescription.
673/0244-05

mf FEB 28 1979

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

APPROVED

Sterile 5 ml. NDC 0381-0244-05 Multi-dose
ESTRADIOL VALERATE INJECTION
40 mg./ml.

Each ml. contains: Estradiol Valerate 40 mg., Benzyl Benzoate 40%, Benzyl Alcohol 2% as preservative in Castor Oil.
USUAL ADULT DOSE: Intramuscular. See package insert.
CAUTION: Federal law prohibits dispensing without prescription.
673/0244-05

mf FEB 28 1979

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

APPROVED

Sterile 5 ml. NDC 0381-0244-05 Multi-dose
ESTRADIOL VALERATE INJECTION
40 mg./ml.

Each ml. contains: Estradiol Valerate 40 mg., Benzyl Benzoate 40%, Benzyl Alcohol 2% as preservative in Castor Oil.
USUAL ADULT DOSE: Intramuscular. See package insert.
CAUTION: Federal law prohibits dispensing without prescription.
673/0244-05

mf FEB 28 1979

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

APPROVED

**CENTER FOR DRUG EVALUATION
AND RESEARCH**

APPLICATION NUMBER:

83-714

**MEDICAL OFFICER
REVIEW(S)**

REVIEW OF ANDA

DATE COMPLETED: 8-2-77

ANDA#: 83-714

CO. NAME: Chromalloy Pharmaceuticals, Inc.
Carter-glogau Labs. Division
ADDRESS: Glendale, AZ 85301

NAME OF DRUG: Estradiol Valerate Injection 40 mg./ml (Yellow, Oleagenous Liquid)

DATE OF SUBMISSION: 6-3-77

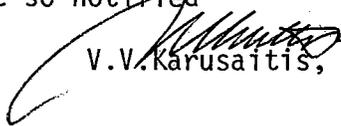
TYPE OF SUBMISSION: ANDA

CLINICAL EVALUATION:

1. Review of Studies:
Pertinent Data is to be reviewed by the chemist
Bioavailability Requirement: Required
2. Review of Labels:
 - a) Container Labels: Satisfactory
* FR 1029. 1976 Quote:
(ii) For Estradiol Valerate Sterile Oleagenous Solution, approval of a full New Drug Application (21CFR 314.1(c)(2) Must be obtained prior to marketing such product
 - b) Insert Labeling: Satisfactory

CONCLUSION: Insert Labelins is satisfactory

RECOMMENDATIONS: * Requires Full NDA
The firm is to be so notified


V.V. Karusaitis, M.D.

cc:
DUP
VVKarusaitis/ps/8/16/77

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF RESUBMISSION, FPL

DATE COMPLETED: 3-8-74

ANDA #: 83-714

CO. NAME: Myers-Carter Laboratories
Glendale, AZ 85301

NAME OF DRUG: Trade: Injection

Generic: Estradiol Valerate Injection (40 mg/ml)

DATE OF SUBMISSION: 1-30-74

TYPE OF SUBMISSION: Resubmission (reply to FDA letter, 1-23-74)

CLINICAL EVALUATION:

1. Review of Studies:

Pertinent data is to be reviewed by the chemist.

Bioavailability Requirement: Deferred

2. Review of Labeling:

- a. Container Labels: Satisfactory
(M.O.R. 5-31-73)
- b. Insert Labeling: Satisfactory
F.P.L.

CONCLUSION: Labeling is satisfactory for the safe and effective use
of this drug.

RECOMMENDATIONS: The firm is to be so informed.
Medically approvable.


V. V. Karusaitis, M.D.

cc:
Dup
HFD-107
VVKarusaitis/rt/3-12-74

REVIEW OF RESUBMISSION

DATE COMPLETED: 1-2-74

ANDA #: 83-714

F.R. DATE:

CO. NAME: Myers-Carter
Glendale, AZ 85301

NAME OF DRUG: Trade: _____
Generic: Estradiol Valerate Injection

DATE OF SUBMISSION: 11-20-73

TYPE OF SUBMISSION: ANDA resubmission (reply to FDA letter 11-8-73)

CLINICAL EVALUATION:

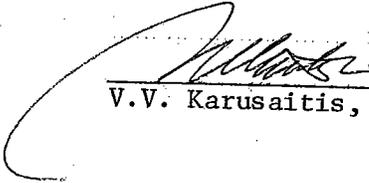
1. Review of Studies: Pertinent data is to be reviewed by chemist.
Bioavailability data: Deferred

2. Review of Labeling: a. Container labels: Satisfactory (MOR 5-31-73)
10 mg. multiple dose vials:
10 mg./ml. : 20 mg/ml: 40 mg/ml.

- b. Insert Labeling: Satisfactory (draft copy)

CONCLUSION: Draft copy of insert labeling is satisfactory.

RECOMMENDATION: The firm is to be so notified. Send FPL.



V.V. Karusaitis, M.D.

cc:
Dup
HFD-107
VVKarusaitis, M.D./kim/1-6-74

REVIEW OF SUBMISSION

DATE COMPLETED: 10-30-73

ANDA #: 83-714

CO. NAME: Myers-Carter

NAME OF DRUG: Trade: _____ 40 mg./ml.
Generic: Estradiol Valerate Injection 40 mg./ml.

DATE OF SUBMISSION: 10-1-73

TYPE OF SUBMISSION: Resubmission (reply to FDA letter 9-24-73)

CLINICAL EVALUATION:

1. Review of Studies: Pertinent data is to be reviewed by the chemist.
Sept. 6, 1973 submission: Six samples submitted.

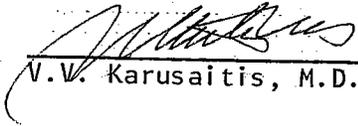
2. Review of Labeling:

a. Container label: Satisfactory (MOR 5-31-73)

b. Insert labeling: Unsatisfactory

CONCLUSION: *ANDA's 83-714: 83-547: 83-546 are to have the same insert
labeling. Instructions of 8-24-73 letter are to be followed.

RECOMMENDATION: The firm is to be so notified.


V.V. Karusaitis, M.D.

cc:

Dup

BD-69

VVKarusaitis, M.D./kim/10-30-73

REVIEW OF RESUBMISSION

DATE COMPLETED: 9-11-73

ANDAs #: 83-714

CO. NAME: Myers-Carter Laboratories
Glendale, Arizona 85301

NAME OF DRUG: Trade: _____ 40 mg./ml.

Generic: Estradiol Valerate — Injection 40 mg./ml.

DATE OF SUBMISSION: August 7, 1973

TYPE OF SUBMISSION: Resubmission (reply to F.D.A. 6-29-73 letter)

CLINICAL EVALUATION:

1. Review of Studies:

Pertinent data is to be reviewed by chemist.

Bioavailability status: Deferred

2. Review of Labeling:

(a) Container Labels: Satisfactory
5 ml. 40 mg./ml. (M.O.R. 5-31-73)

(b) Insert Labeling:

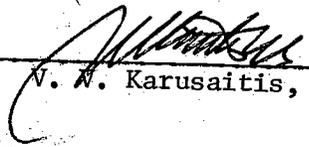
DOSAGE AND ADMINISTRATION: Unacceptable: FDA letter 6-29-73 asked
for revision of dose levels.

CONCLUSION: Labeling is NOT satisfactory for the safe and effective use of this product.

RECOMMENDATION: The firm is to be so notified.

Question: If the product is a long-acting estrogen product (effects last 2 to 3 weeks),
why advocate a dose per week, preferably in divided doses?

cc:
Dup
BD-69
VVKarusaitis/rt/9-12-73


N. N. Karusaitis, M.D.


V. Karusaitis, M.D.

cc:
Dup
BD-69
VVKarusaitis/rt/5-31-73

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

83-714

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW FOR
ABBREVIATED NEW DRUG APPLICATION
OR SUPPLEMENT

Statement Date:

NDA NUMBER:

83-714

NAME AND ADDRESS OF APPLICANT

Chromalloy Pharmaceuticals, Inc. - Glendale, AZ 85301

ORIGINAL
AMENDMENT^{XX}
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

Labeling, manufacturing

DATE(s) of SUBMISSION:

see issuing letter

PHARMACOLOGICAL CATEGORY

estrogen

NAME OF DRUG

estradiol valerate

HOW DISPENSED

RX xxx OTC

DOSAGE FORM(S)

injection

POTENCY(IES)

40 mg/ml

RELATED IND/NDA/DMF

83-546 83-547
83-714

STERILIZATION

included

SAMPLES

LABELING

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

BIOLOGIC AVAILABILITY

not requested

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

STABILITY

Protocol:

Exp. Date: 24 mo.

REMARKS AND
CONCLUSION:

approval MAJarski

MAJarski 2/27/79

OR SUPPLEMENT

Statement Date

83-714

AF Number

Name and Address of Applicant (City and State)

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

Original	_____
Amendment	_____
Supplement	_____
Resubmission	_____
Correspondance	xxxx
Report	_____
Other	_____

Purpose of Amendment/Supplement

Date(s) of Submission(s)

Pharmacological Category

estrogen

Name of Drug

estradiol valerate

Dosage Form(s)

oleaginous injection

Potency(ies)

How Dispensed

R_x xxxx

OTC

Packaging/Sterilization

Samples

Related IND/NDA/MF

Labeling

see medical officers review of 8-2-77

Biologic Availability

Establishment Inspection

Components, Composition, Manufacturing and Controls

Remarks

this drug requires a full new drug application.

ack majarski

Majarski 8/24/77

Inclusion

VIEWER

DATE

CHEMIST'S REVIEW FOR
ABBREVIATED NEW DRUG APPLICATION
OR SUPPLEMENT

Federal Register
Statement Date

NDA Number
83-714
9-931

AF Number
Original _____
Amendment XXXXX
Supplement _____
Resubmission _____
Correspondance _____
Report _____
Other _____

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

Purpose of Amendment/Supplement
provide for corporate changes.

Date(s) of Submission(s)
3-5-75

Pharmacological Category
estrogen

Name of Drug
estradiol valerate

Dosage Form(s)
injection

Potency(ies)
40 mg./ml.

How Dispensed
Rx XXXXX
OTC

Packaging/Sterilization

Samples

Related IND/NDA/IF

Labeling

Biologic Availability

Establishment Inspection

Components, Composition, Manufacturing and Controls

Remarks
firm requested additional information in FDA letter of 4-23-75
firm to respond
ack
majarski
majarski 5/27/75

Conclusion
REVIEWED

NEW DRUG APPLICATION
OR SUPPLEMENT

Statement Date

83-546
83-547

AE Number 83-714

Name and Address of Applicant (City and State)

Myers-Carter Laboratories, Inc.
Glendale, AZ 85301

Original _____
Amendment _____
Supplement _____
Resubmission XXXXX
Correspondance _____
Report _____
Other _____

Purpose of Amendment/Supplement

Date(s) of Submission
6-14-74

Pharmacological Category

estrogen

Name of Drug

estradiol valerate

Dosage Form(s)
injection

Potency(ies)

How Dispensed

R_x xxxx

Packaging/Sterilization

Samples

OTC

Related IND/UDA/NE

Labeling

Biologic Availability

Establishment Inspection

Components, Composition, Manufacturing and Controls

Remarks

Firm has submitted an ~~ax~~ analytical procedure which has been judged non-regulatory by our Laboratories. The firm is advised to use the officially published procedure.

rev w/f
majarski

Majarski 9/13/74

Conclusion

REVIEWER

DATE

Name and Address of Applicant (City and State)

Myers-Carter Laboratories, Inc.
Glendale, AZ 85301

Original _____
Amendment _____
Supplement _____
Resubmission xxxx _____
Correspondance xxxxx _____
Report _____
Other _____

Purpose of Amendment/Supplement

Date(s) of Submission(s)

1-23-74
3-8-74

Pharmacological Category

estrogen

Name of Drug

estradiol valerate

Dosage Form(s)

injection

Potency(ies)

10 mg. /ml.

How Dispensed
R_x xxxxxxx

OTC

Packaging

Samples

Related IND/NDA/MF

83-547 20 mg./ml.
83-714 40 mg./ml.

Labeling

satisfactory per medical officer's review of 2-12-74

Biologic Availability

Establishment Inspection

Components, Composition, Manufacturing and Controls

Remarks

comments on methodology for assay sent to firm
this is applicable to all three applications.

Conclusion

REVIEWER rev w/f majarski
DATE

CHEMIST'S REVIEW FOR
ABREVIATED NEW DRUG APPLICATION
OR SUPPLEMENT

Federal Register
Statement Date

NDA Number
83-546

9-931

AF Number

Name and Address of Applicant (City and State)

Myers-Carter Laboratories, Inc.
Glendale, AZ 85301

Original _____
Amendment _____
Supplement _____
Resubmission xxxx
Correspondance xxxxx
Report _____
Other _____

Purpose of Amendment/Supplement

Date(s) of Submission(s)

1-23-74
3-8-74

Pharmacological Category

estrogen

Name of Drug

estradiol valerate

Dosage Form(s)

injection

Potency(ies)

10 mg. /ml.

How Dispensed
R_x xxxxxx

OTC

Packaging

Samples

Related IND/NDA/MF

83-547 20 mg./ml.
83-714 40 mg./ml.

Labeling

satisfactory per medical officer's review of 2-12-74

Biologic Availability

Establishment Inspection

Components, Composition, Manufacturing and Controls

Remarks

comments on methodology for assay sent to firm
this is applicable to all three applications.

Conclusion

REVIEWER rev w/f majarski DATE

COMMITTEE'S REVIEW FOR
AMENDMENT NEW DRUG APPLICATION
OR SUPPLEMENT

Federal Register
Statement Date

INDA Number
83-714

AF Number 9-931

Name and Address of Applicant (City and State)

Myers-Carter Laboratories, Inc.
Glendale, AZ 85301

Original _____
Amendment _____
Supplement _____
Resubmission xxxxx
Correspondance _____
Report _____
Other _____

Purpose of Amendment/Supplement

Date(s) of Submission:

1-30-74
3-8-74

Pharmacological Category

Name of Drug

estrogen

(estradiol valerate)

Dosage Form(s)

Potency (ies)

injection

40 mg.

How Dispensed

Rx xxx

OTC

Environmental Impact Analysis
Report

Samples

Related IND/INDA/NEA#

submitted

83-547 10 mg.
83-546 20 mg.

Labeling

satisfactory per medical-officers review of 3-8-74

Biologic Availability

NA

Establishment Inspection

satisfactory per HFD 340 memo of 1-4-74

Components, Composition, Manufacturing and Controls

see below

Remarks

assay procedures sent to Los Angeles laboratories for comment on 3-29-74

Conclusion

ack majarski

Majarski 4/2/74

OWNER'S REVIEW FOR
PREPARED INDUSTRY APPLICATION
OR SUPPLEMENT

Federal Register
Statement Date

7-25-72

DA Number 83-714

AF Number 9-931

Name and Address of Applicant (City and State)
Myers-Carter Laboratories, Inc.
5160 West Bethany Home Road
Glendale, Arizona 85301

Original _____
Amendment _____
Supplement _____
Resubmission _____
Correspondance _____
Report _____
Other _____

Purpose of Amendment/Supplement

Manufacturing information

Date(s) of Submission(s)

1-18-74

Pharmacological Category

XXREstrogen

Name of Drug

Estradiol Valerate

Dosage Form(s)

Injectable

Potency (ies)

40 mg. per ml.

How Dispensed

R_x

CEC

Environmental Impact Analysis
Report

Submitted

Samples

Submitted

Related IND/IDA/AF(s)

83-547 & 83-546
10 mg. 20 mg.

Labeling

Satisfactory (VVKarusiaits)

Biologic Availability

Deferred

Establishment Inspection

Satisfactory HFD 340 memo 1-4-74

Components, Composition, Manufacturing and Controls
See below

Remarks

Request complete assay procedure and ~~xxxxx~~ FP as per our letter
of 1-23-74

rev w/f

Conclusion

RJW alters

APWalt 2-15-74

Name and Address of Applicant (City and State) Myers-Carter Laboratories, Inc. 5160 West Bethany Home Road Glendale, Arizona 85301	Original _____ Amendment _____ Resubmission <input checked="" type="checkbox"/> _____ Correspondence _____ Report _____ Other _____
--	--

Purpose of Amendment/Supplement	Date(s) of Submission(s)
---------------------------------	--------------------------

Pharmacological Category Glucocorticoid	Name of Drug Estradiol Valerate
---	---

Dosage Form(s)	Potency (ies)	How Dispensed Rx <input type="checkbox"/> OTC <input type="checkbox"/>
----------------	---------------	--

Environmental Impact Analysis Report	Samples	Related IND/NDA/IF(s)
--------------------------------------	---------	-----------------------

Labeling

Biologic Availability

Establishment Inspection

Components, Composition, Manufacturing and Controls

Remarks

Request firm to ~~REVISE~~ revise their assay procedures as per district recommendations.

Conclusion

Rev w/f

REVIEWER: **RJWalters** DATE: **11-27-73**

Name and address of Applicant (City and State)
Myers-Carter Laboratories, Inc.
5160 West Bethany Home Road
Glendale, AZ. 85301

Original _____
Amendment _____
Resubmission _____
Correspondence _____
Report _____
Other _____

Purpose of Amendment/Supplement
Draft labeling, samples and manufacturing information

Date(s) of Submission(s)
9-6-73 and 10-1-73

Pharmacological Category
Estrogen

Name of Drug
~~40 mg. per ml.~~
Estradiol Valerate

Dosage Form(s)
Injectable

Potency (ies)
40 mg. per ml.

How Dispensed
Rx
OTC

Environmental Impact Analysis Report
Submitted

Samples
Submitted

related IND/IDA/ID(s)
83-547 & 83-546
10 mg. and 20 mg./ml.

Labeling
To be revised (VVKarusaitis)

Biologic Availability
Deferred

Establishment Inspection
Unsatisfactory BD 340 memo 5-17-73

Components, Composition, Manufacturing and Controls
See below

Remarks
Request: Revised labeling as per MO's review and satisfactory inspection. -
NDA² ref product Squibb Estradiol Myers Carter product
Estradiol Valerate 40 mg./ml. 40 mg./ml.
Benzyl benzoate 40% 40%
Benzyl Alcohol 2% 2%
Castor Oil qs ~~40%~~ qs

Conclusion
rev w/f

REVIEWER
RJWalters *RJWalters* DATE 11-2-73

7-25-72

AF Number 9-931

Name and Address of Applicant (City and State)
Myers-Carter Laboratories, Inc.
5160 West Bethany Home Road
Glendale, Arizona 85301

Original _____
Amendment _____
Supplement _____
Report _____
Other _____

Purpose of Supplement / Amendment
Revised labeling and manufacturing information

Date(s) of Submission
8-7-73

Name of Drug
Estradiol Valerate

Pharmacological Category
~~Estrogenic~~
Estrogen

Dosage Form(s)
Injectable

Potency (ies)
40 mg./ml.

How Dispensed
Rx
OTC

Environmental Impact Analysis Report
Submitted

Samples
to be submitted

Related IND/NDA/AF(s)

Labeling
Revised as per MO's review (VVKarusaitis)

Components, Composition, Manufacturing and Controls
See below

Biologic Availability
Deferred

Establishment Inspection
Satisfactory Myers-Carter Unsatisfactory BD 340 m
memo 5-17-73

Remarks
Request: 1. Revised labeling as per MO's review.
2. Clarify HOW SUPPLIED section (potencies.)
3. Clarify tests perform on drug and active ingredient.
4. _____
5. _____
6. Samples
7. Inspection.

Conclusion
rev w/f

REVIEWER
RJW:lters *RJW alt 9-19-73*
DATE

CHEMIST'S REVIEW FOR
APPROVED NEW DRUG APPLICATION
OR SUPPLEMENT

Federal Register
Statement Date

NDA Number 83-714

7-25-72

AF Number 9-931

Name and Address of Applicant (City and State)
Myers-Carter Laboratories, Inc.
5160 West Bethany Home Road
Glendale, Arizona 85301

Original _____
Amendment _____
Supplement _____
Report _____
Other _____

Purpose of Supplement / Amendment

Revised labeling and manufacturing information

Date(s) of Submission

8-7-73

Name of Drug

Duta Estradiol
Estradiol Valerate

Pharmacological Category

~~Estrogenic~~
Estrogen

Dosage Form(s)

Injectable

Potency (ies)

5 40 mg./ml.

How Dispensed

Rx

OTC

Environmental Impact Analysis Report

Submitted

Samples

to be submitted

Related IND/NDA/TF(s)

Labeling

Revised as per MO's review (VVKarusaitis)

Components, Composition, Manufacturing and Controls

See below

Biologic Availability

Deferred

Establishment Inspection

Satisfactory Myers-Carter Unsatisfactory BD 340 m
memo 5-17-73

Remarks

- Request:
1. Revised labeling as per MO's review.
 2. Clarify HOW SUPPLIED section (potencies.)
 3. Clarify tests perform on drug and active ingredient.
 4. _____
 5. _____
 6. Samples
 7. Inspection.

Conclusion

rev w/f

RJWplters

RJW alt 9-19-73

REVIEWER

DATE

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

83-714

**ADMINISTRATIVE
DOCUMENTS**

MEMORANDUM OF A TELEPHONE CONVERSATION

February 14, 1979

BETWEEN

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

AND

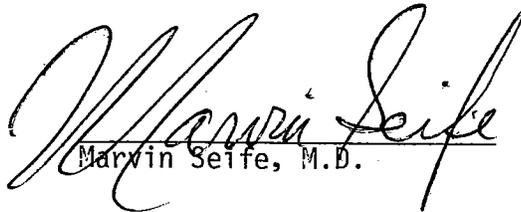
Dr. Jack Dale, Director
Quality Control
Carter-Glogau Laboratories
Glendale, AZ 85301

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.

Dr. 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

Dr. 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, M.D.

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

MORANDUM

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

BD-105

DATE: May 17, 1973

ATTN: Stanley Stringer

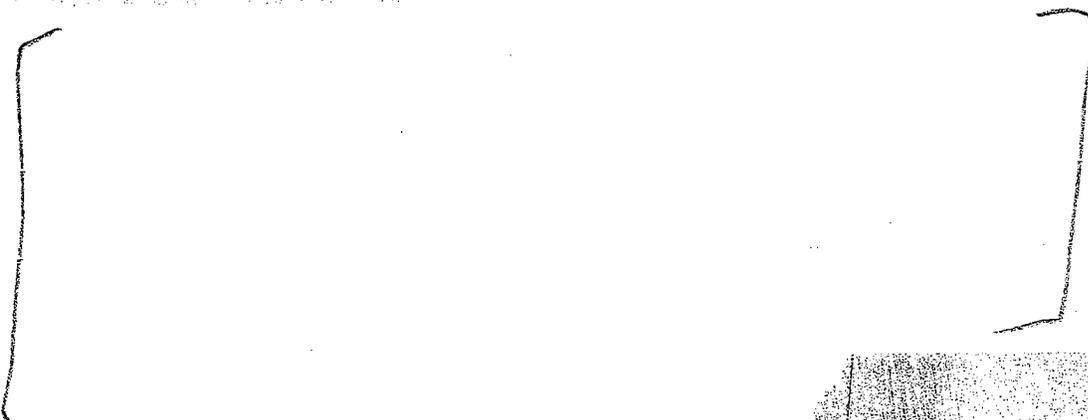
OM : BD-340

SUBJECT: Disapproval for pending ANDA's 83-397, 80-365, 83-546, 83-547

Applicant: Myers Carter Laboratories, Inc., Subsidiary Chromalloy Corporation, Glendale, Arizona

We have evaluated the operations of the above referenced applicant as they relate to conformity with Current Good Manufacturing Practice Regulations (21 CFR, Part 133). On the basis of this evaluation, we are not able to approve the subject ANDA's as the firm is not operating in compliance with Part 133 to assure that the product meets the requirements of the Federal Food, Drug, and Cosmetic Act as to safety, and has the identity and strength, and meets the quality and purity characteristics which it purports to possess.

The inspection of 4/17-20/73 revealed significant GMP deviations including:



Jonas L. Bassen
Jonas L. Bassen

cc:

ANDA File, NDA orig., NDA dup.

BD-105, BD-316, BD-340, Log

BD-340 Subject File

CA-226

LOS-DO (NDA trip.)

CGBROKER:lr

MEMORANDUM

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

TO : BD-105
ATTN: Stanley Stringer

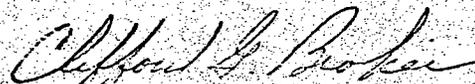
DATE: June 8, 1973

FROM : BD-340

SUBJECT: Applicant: Myers-Carter Laboratories, Inc., Glendale Arizona
Consultant Lab: _____

RE: Disapproval of ANDAs _____; 83-147; 83-714; 83-398; 83-702

Although we have no objection to your approving the subject ANDAs insofar as they relate to CGMP Compliance of _____ we find that Myers-Carter Laboratories, Inc. is not approvable based on our evaluation of that firm's compliance with CGMP Regulations. Our letter of 5/17 details deviations from GMP noted during an EI of 4/17 - 20/73.


Clifford G. Broker

RSL:jmv

cc:

ANDA File

NDA orig. ✓

NDA dup.

BD-105

BD-316

BD-340, Log

BD-340, Working File

BD-340, Laderman

VM-200

BD-145

CA-226

LOS-DO

KAN-FO

Dr. Seife
May 17, 1971

Present: Dr. Margaret Clark
Dr. Marvin Seife
Dr. Trieste Vitti
Dr. John Winkler

Dr. Alan Smith
Dr. John McMillen
Miss Jean Mansur

General discussion: Example, oral chlorpromazine available in several strengths. Should bioavailability studies be performed on each strength? Dr. Vitti recommended that if the formulation does not vary as to ingredients and proportions, testing the low and the high strengths should be adequate. However, if there are different proportions of ingredients (e.g. to maintain tablet size), the practical approach would be to perform the test on the highest ratio and lowest ratio excipient-to-active component. Also if liquid form is sold for mixing with diluent, studies should be conducted using recommended diluent. This should pick up problems of incompatibility.

Discussion and decisions:

1. Estrogens - ethinyl estradiol, estrone, estradiol, methallenestril, chlorotrianisene, conjugated estrogens, polyestradiol (oral and parenteral) (Unpublished, List #3, attached.)

Decision postponed from May 5 meeting. For most of these, methodology is a problem - endogenous material may interfere with measurements. At an earlier meeting it was decided to defer some estrogens, primarily diethylstilbestrol. If problems develop, the priority category can always be changed.

Decision: Defer bioavailability.

Category of Deferral: 3

2. Mercurial Diuretics (single entity and combination with procaine) -- Mercumatilin; sodium mercaptomerin; meralluride; merethoxylline procaine -- injectables. (Unpublished, List #2, p.2, attached)

Other diuretics have been considered as requiring bioavailability. However, these products are injectables, they have a rapid effect after i.v. administration.

Decision: Defer bioavailability.

Category of Deferral: 5

Ergotamine -- oral inhalation; dihydroergotamine mesylate -- aqueous solution for i.m. or i.v.; ergotamine tartrate with caffeine -- rectal suppository and oral. (Unpublished, List #4, attached)

Methodology is a problem. Clinical measurements would be difficult. Medical significance not great enough to warrant immediate efforts to perform studies.

Decision: Defer bioavailability.

Category of Deferral: 5

4. Chlorpromazine; prochlorperazine -- both rectal suppositories. (Unpublished, List #4)

At present clinical trials are required on oral forms. Limited market for rectal form. May have problems of formulation and proper administration. Because of variables, it may be more useful to perform clinicals for better results.

Decision: Require bioavailability.

5. Benzyl benzoate with benzocaine and chlorophenothane; crotamiton; gamma benzene hexachloride -- topical (DESI 4203, published 9/17/70).

Not medically significant to warrant immediate efforts to tie up personnel in testing program. Only methods available would be clinical trials.

Decision: Defer bioavailability.

Category of Deferral: 5

6. Antitussives: benzonatate; levopropoxyphene napsylate; chlorpheniramine with chloroform -- all oral (DESI 11210, published 4/29/71).

Probably not much competitive interest and low sales. Not medically significant.

Decision: Defer bioavailability.

Category of Deferral: 4

7. Antiparkinson Drugs -- biperiden lactate and hydrochloride; trihexyphenidyl HCl; benztropin mesylate; orphenadrine HCl; procyclidine HCl; cycrimine HCl; ethopropazine HCl; chlorphenoxamine HCl; hyoscyamine HBr; belladonna root -- all oral except biperiden lactate which is in injectable form and benztropine mesylate which is in both oral and injectable forms. (DESI 1403, published 11/7/70)

At least some of these have assay methodology. Others may be a problem.

Decision: Postpone so that Dr. Vitti can check on methodology.

8. Betazole HCl -- injectable - s.c., i.m. (DESI 9344, published 7/3/71).

This drug, used for testing gastric secretion, is similar to histamine which was previously considered (5/3/72) and for which the decision was to defer bioavailability (Category 5). This drug should be consistent with histamine.

Decision: Defer bioavailability.

Category of Deferral: 5

9. Triethanolamine polypeptide oleate condensate -- topical otic. (DESI 11340, published 10/15/70).

This drug has little medical significance. It is used to remove impacted cerumen prior to ear examination or therapy.

Decision: Waive bioavailability requirements.

10. Buclicline HCl -- oral (DESI 9295, published 3/9/71).

This drug, like certain other antihistamines considered, is indicated for prevention of motion sickness. Generally, the Committee has felt that lack of medical significance of such drugs warranted deferral and a low priority category.

Decision: Defer bioavailability.

Category of deferral: 5

11. Meclizine -- oral.

This drug was before the Committee because Anti-Vert, formerly meclizine with niacin and published as lacking substantial evidence of effectiveness (DESI 10721, published 3/27/70) has been reformulated. Niacin has been deleted from the formulation, leaving meclizine which has already been published (DESI 8993, 7/2/70) as effective for motion sickness. The Anti-Vert product is also being studied for vertigo. If the drug is to be handled other than through the OTC monograph procedure, a bioavailability determination is necessary.

Decision: Refer bioavailability.

Category of Deferral: 5

Jean Mansur
Jean Mansur

Attachments

cc:

BD-1/Dr. Crout
BD-100/Dr. Finkel
BD-60/Dr. Bryan
BD-110/Dr. Belton
BD-120/Dr. Gardner
BD-130/Dr. Ortiz
BD-140/Dr. Gibson

Each Committee Member:

BD-69/Dr. Clark
BD-69/Dr. Seife
BD-220/Dr. Vitti
BD-110/Dr. Winkler
BD-140/Dr. Smith
BD-130/Dr. McMillen
BD-68/Miss Mansur

APPEARS THIS WAY
ON ORIGINAL

Approved - Jk Crout - 5/30/72

MEMORANDUM

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

TO : Robert Wolters/BD-69

DATE: October 16, 1973

FROM : Scientific Coordinator
Field Sciences Branch/EDRO/RO-130

SUBJECT: ANDA 83-714 Estradiol Valerate Injection (Myers Carter, Ariz.)

1. This memo will confirm our telephone conversation of October 15, 1973 in which I designated the Los Angeles District laboratory as a validating agent for the above ANDA.

2. Estimated analytical time for the study is about 32 hours.

3. Please refer samples and method references to the attention of:

John R. Weatherwax
Laboratory Director
Los Angeles District

4. Attached is an ~~_____~~ The information may be only of an isolated case. According to James Kottemann, BD-OPRT(BD-420), a test to ~~_____~~

5. Please indicate the appropriate HIA/DCC number in your transmittal memo.


John R. Markus

ATTACHMENT

cc: LOS-D60 (Mr. Weatherwax)

Redacted 12

Page(s) of trade

secret and /or

confidential

commercial

information

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 11-8-73
FROM: Bob Walters DD-69	OFFICE	
TO: Joseph Levine BD-420	DIVISION	
SUBJECT: 83-714 Estriodiol Valerate Injection		
SUMMARY As per our telephone conversation of 11-8-73, enclosed is a copy of the memo from Los Angeles Dist. Please forward to USP for appropriate action.		
SIGNATURE: <i>Robert Walters</i> DOCUMENT NUMBER:		

APPEARS THIS WAY
ON ORIGINAL

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 2-6-74
FROM: Robert Walters		OFFICE
TO: Donald Dechert Los Do		DIVISION
SUBJECT: Estradiol Valerate Inj.		
SUMMARY		
<p>Mr. Tele con. 213 6883786</p> <p>Mr. Dechert requested that the complete assay procedure be submitted since the firm made some changes in it.</p> <p>Send procedure to Dist. when firm after it is received.</p>		
APPEARS THIS WAY ON ORIGINAL		
SIGNATURE Robert Walters		DOCUMENT NUMBER 83-714

Donald D. Dechert - Research Coordinator
LOS-D60

March 28, 1974

Mary Ann Jarski (HFD-107)

NDA 83-714

Per our telephone conversation of March 28, 1974, the enclosed procedures
are submitted for evaluation.

M.A. Jarski

cc:
LOS-DO
Orig. NDA 83-714
Dup
HFD-107

APPEARS THIS WAY
ON ORIGINAL

NOTICE OF APPROVAL NEW DRUG APPLICATION OR SUPPLEMENT		NDA NUMBER
		82-714 DATE APPROVAL LETTER ISSUED
TO:	FROM:	
Press Relations Staff (HFI-40)	<input checked="" type="checkbox"/> Bureau of Drugs <input type="checkbox"/> Bureau of Veterinary Medicine	FEB 28 1979
ATTENTION		
Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.		
TYPE OF APPLICATION <input type="checkbox"/> ORIGINAL NDA <input type="checkbox"/> SUPPLEMENT TO NDA <input checked="" type="checkbox"/> ORIGINAL NDA <input type="checkbox"/> SUPPLEMENT TO ANDA		CATEGORY <input type="checkbox"/> HUMAN <input type="checkbox"/> VETERINARY
TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG Estradiol Valerate		
DOSAGE FORM		HOW DISPENSED
		<input checked="" type="checkbox"/> RX <input type="checkbox"/> OTC
ACTIVE INGREDIENTS (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.) <p style="text-align: center;">Estradiol Valerate 40 mg/ml</p>		
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		DATE
MAJarski		
FORM APPROVED BY		
NAME		DATE
JIMeyer		

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

83-714

CORRESPONDENCE



CHROMALLOY PHARMACEUTICALS, INC. *ms*

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

February 15, 1979

NDA ORIG AMENDMENT

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

PH

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.

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



CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

My

CARTER-GLOGAU LABORATORIES DIVISION

July 31, 1978

RESUBMISSION
NDA ORIG AMENDMENT

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

SUBJECT: ESTRADIOL VALERATE INJECTION USP, 40 mg/ml.
NDA 83-714

Dear Dr. Seife:

We are updating our Abbreviated New Drug Application for Estradiol Valerate Injection USP, 40 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.

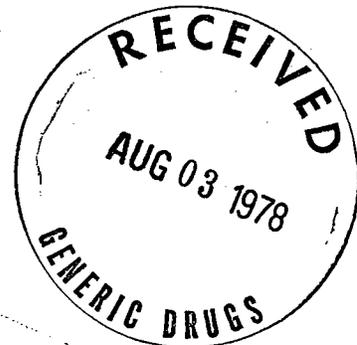
As we have submitted all the required informations, we would greatly appreciate prompt approval of this ANDA.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

SMF/edc
encls:



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

Orig

CARTER-GLOGAU LABORATORIES DIVISION

May 19, 1978

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs
Department of Health, Education, and Welfare
Public Health Service
Food and Drug Administration
Rockville, MD 02857

ORIG NEW CORRES

SUBJECT: ESTRADIOL VALERATE INJECTION, 40 MG/ML
NDA 83-714

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



GENERAL OFFICES:

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

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

83-714

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



CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CMS

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 _____
NDA 83-714, NDA _____, NDA _____, NDA _____
NDA 85-239, NDA 85-620, NDA _____, NDA 85-673
NDA _____, NDA _____, 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.

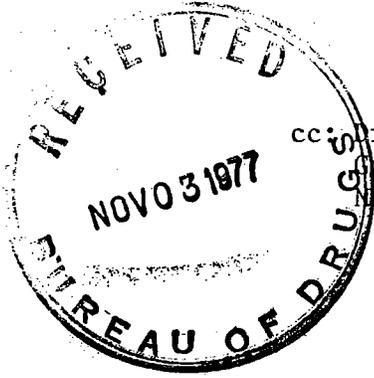
Should you require further information please do not hesitate to write or call.

Sincerely yours,

Ronald M. Carter
CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

Ronald M. Carter
President

RMC/sp



cc: Mr. Sam Fainberg
Governor Herschel Loveless
NDA Files

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

OCT 28 1977

NDA 63-397	NDA 63-714
NDA 63-546	NDA _____
NDA 63-547	NDA _____
NDA _____	NDA _____

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

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

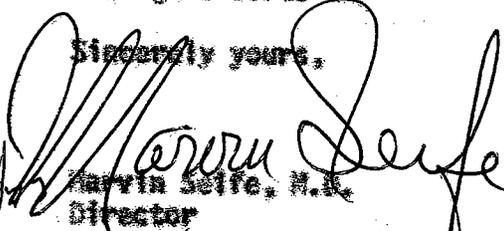
Gentlemen:

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

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

Please submit the required Patient Package Insert.

Sincerely yours,


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

cc: LOS-00
 Dup HFD-614
 VVKarasaitis/JMeyer/MJarski
 r/d/ init. JMeyer/MSeife 10-28-77
 f/t/wlb/10-28-77
 ACK

Enclosure:
 F.R. July 22, 1977

JMeyer r/d/10/28/77

10/28/77



CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

Upis

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, 40 MG/ML
NDA 83-714

Dear Dr. Seife:

Reference is made to your communication of August 25, 1977 regarding NDA 83-714 for Estradiol Valerate Injection, 40 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.

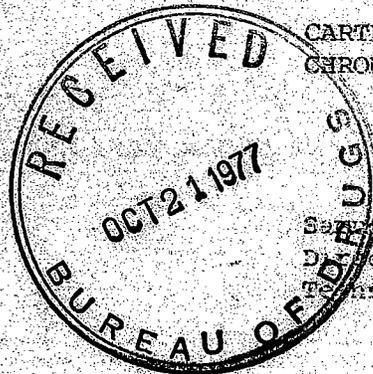
We call your attention to the Federal Register Notice, Volume 42, No. 195 dated Friday, October 7, 1977 DESI 1543. In this Federal Register Notice DESI 1543 is amended to allow the approval of an abbreviated new drug application.

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



SME/jcw

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

NDA 83-714

25 1977

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.

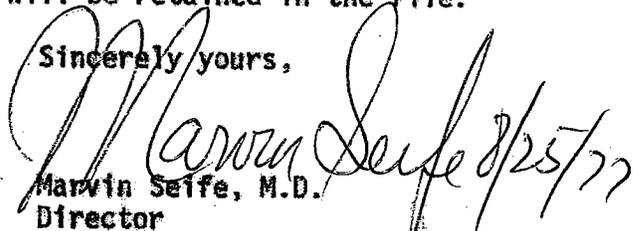
Reference is also made to the FEDERAL REGISTER notice of September 29, 1976 relating to estrogenic products.

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".

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,



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

cc:

L0S-D0

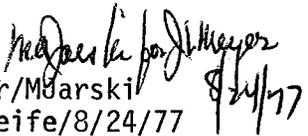
HFD-614

VVKarusaitis/JMeyer/Mbarski

R/D init JMeyer/MSeife/8/24/77

ps/8/24/77

ack





CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

CARTER-GLOGAU LABORATORIES DIVISION

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

Orig
NDA ORIG AMENDMENT

SUBJECT: ESTRADIOL VALERATE INJECTION 40 MG/ML.
NDA 83-714

Dear Dr. Seife:

We hereby amend our application for Estradiol Valerate Injection, 40 mg/ml, NDA 83-714.

This amendment provides for a change in the vial type from Amber 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 40 mg/ml.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

SMF/jcw
encl





CHROMALLOY PHARMACEUTICALS, INC.

A SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

Orig

CARTER-GLOGAU LABORATORIES DIVISION

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 40 MG/ML
NDA 83-714

Dear Dr. Seife:

We hereby amend our application for Estradiol Valerate Injection, 40 mg/ml NDA 83-714.

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

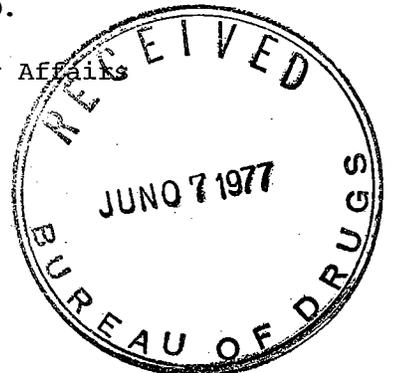
There are no other changes or additions to this application for Estradiol Valerate Injection, 40 mg/ml, NDA 83-714.

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

Orig

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, 40 mg./ml.
NDA 83-714

Dear Dr. Seife:

We hereby amend our NDA 83-714 for Estradiol Valerate Injection, 40 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/jw
encl



GENERAL OFFICES:
5160 N. 101ST 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

Orig

CARTER-GLOGAU LABORATORIES DIVISION

August 18, 1976

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, MD 20852

SUBJECT: ESTRADIOL VALERATE INJECTION 40 mg/ml
NDA 83-714

Dear Dr. Seife:

We hereby amend our NDA 83-714 for Estradiol Valerate Injection, 40 mg/ml., to provide for an additional batch size of _____

There are no other additions or changes to the NDA 83-714 for Estradiol Valerate Injection, 40 mg. per ml.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

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

SMF/jw

encl: FD Form 356H, Master Formula Card



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

Orig

CARTER-GLOGAU LABORATORIES DIVISION

August 3, 1976

NDA ORIG AMENDMENT

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

SUBJECT: ESTRADIOL VALERATE INJECTION
40 MG./ML.
NDA 83-714

Dear Dr. Seife:

We hereby amend our NDA 83-714 for Estradiol Valerate Injection, 40 mg./ml., to provide for an additional batch size of

There are no other additions or changes in this NDA for Estradiol Valerate Injection, 40 mg/ml.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.



Samuel M. Fainberg

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

SMF/jw
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

Beauf
Orin

CARTER-GLOGAU LABORATORIES DIVISION

August 3, 1976

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

RESUBMISSION
NDA ORIG AMENDMENT

FPL

SUBJECT: ESTRADIOL VALERATE INJECTION
40 MG/ML
NDA 83-714

Dear Dr. Seife:

Reference is made to your letter of April 23, 1975 and May 23, 1975, both regarding Estradiol Valerate Injection 40 mg./ml., NDA 83-714.

In response to your letter of April 23, 1975 we are supplying the following:

1. Final printed labels are attached.
2. Estradiol Valerate will be assayed as per USP XIX.

In response to your letter of May 23, 1975:

No manufacturing of this product will be done in the Melrose Park facility. If there is any change in this the proper filings will be made.

Sincerely yours,

CARTER-GLOGAU LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICALS, INC.

Samuel M. Fainberg

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



SMF/jw
encl

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

NDA 83-714

AF 9-931

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

MAY 23 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, 40 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, requesting additional information.

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 Laboratories 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 _____ 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) submit the additional information requested; (2) submit appropriate information for operations at the _____ facility.

The material submitted is being retained in the file.

cc:

LOS-DO

Dup

HFD-530 HFD-614 HFD-616

JLMeyer/MAJarski *MAJarski 5/22/75*

R/D init. JMeyer/MSeife/5-20-75

Final typing/rt/5-21-75

Ack.

JMeyer 5/22/75

Sincerely yours,

Harvin Seife 5/23/75
Harvin Seife, M.D.

Director

Division of Generic Drug Monographs

Office of Drug Monographs

Bureau of Drugs

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 sesame oil).

Your referenced communication indicates the USP XVIII assay procedure will now be used, in lieu of the modified AOAC procedure. An objection to the USP procedure has been that high assay values are often obtained because of interferences from _____ The _____

APPEARS THIS WAY
ON ORIGINAL

Myers-Carter Laboratories Division
Chromalloy Pharmaceutical, Inc.
NDA 83-546, NDA 83-547, NDA 83-714

-2-

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 _____
_____ 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

JLMeyer/MAJarski

R/D init. MSeife/GMiller/4-17-75

Final typing/rt/4-21-75

rev w/f

MAJarski 4/22/75

JLMeyer 4/22/75



NDA ORIG AMENDMENT

ORIG

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

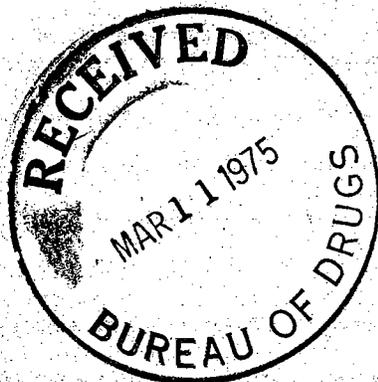
SUBJECT: NDA 83-714
 _____ (estradiol valerate) INJECTION,
 40 mg./ml.

Dear Dr. Seife:

We are attaching hereto FD Form 356H to amend our NDA 83-714
 for _____ (estradiol valerate) Injection, 40 mg./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 _____
 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
 Samuel M. Fainberg,
 Director,
 Technical and Regulatory Affairs

MP

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

GENERAL OFFICES:
 5160 WEST HAWTHORNE HOME ROAD • GLENDALE, ARIZONA 85301
 TELEPHONE (602) 939-1428 • TELEX 66-8304 (M-C LABS)



MYERS-CARTER LABORATORIES

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

ORIG NEW CORRES

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

Dear Dr. Seife:

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.

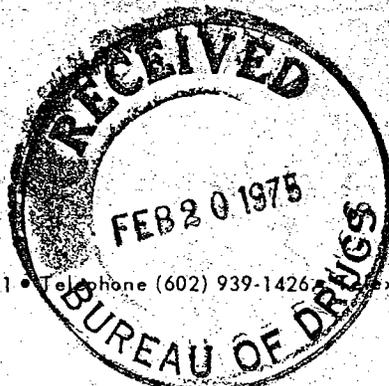
The comment in the referenced communication that the needed sesame oil would not be available for blanks for regulatory assays does not apply to the 20 mg. per ml. dosage form since this dosage form is in castor oil, not sesame oil.

Sincerely yours,

MYERS-CARTER LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICAL, INC.

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

MP



NDA 83-546
83-547
83-714 ✓

AF 9-931

SEP 19 1974

Nyers-Carter Laboratories Division
Chromalloy Pharmaceuticals, Inc.
Attention: Mr. Samuel H. 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



Ku.W.K

E
ORIG

RESUBMISSION

MYERS-CARTER LABORATORIES

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

NDA ORIG AMENDMENT

June 14, 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 83-714
_____ (estradiol valerate) INJECTION,
40 mg./ml.

Dear Dr. Seife:

In reference to your communication dated May 28, 1974 we are enclosing a letter from _____ responding to your comments regarding _____. Please note that:

- (1). Myers-Carter provides _____ with the Sesame Oil which is added to the _____. This Sesame Oil is _____.
- (2). _____ as reconfirmed that they have no difficulty in _____ 40 mg. of Estradiol Valerate in _____.

Sincerely yours,

MYERS-CARTER LABORATORIES DIVISION
CHROMALLOY PHARMACEUTICAL, INC.

Samuel M. [Signature]

Samuel M. [Signature]
Director,
Technical Regulatory Affairs

MP

Encl.: Letter from _____



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:

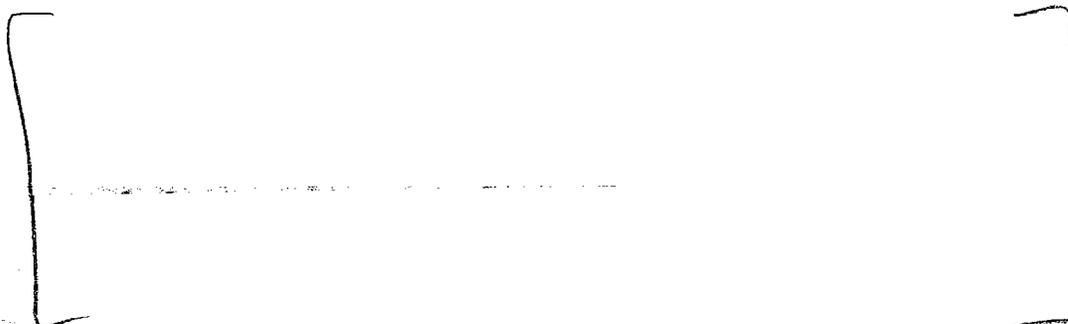
- (1) Estradiol Valerate Injection, 10 mg./ml., re: 83-546
- (2) Estradiol Valerate Injection, 20 mg./ml., re: 83-547
- (3) Estradiol Valerate Injection, 40 mg./ml., re: 83-714

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



APPEARS THIS WAY
ON ORIGINAL

Myers-Carter Laboratories, Inc.
NDA 83-546, NDA 83-547, NDA 83-714

-2-

2. Standard Preparation:

The manufacturer specifies the dissolution of 40 mg. of Estradiol Valerate in _____ Our experience has been that the 40 mg. will not dissolve in the _____ We would use _____ alcohol to dissolve this amount of Estradiol Valerate.

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,

Harvin Seife 5/28/74

Harvin 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

VVKarasaitis/JMeyer/MAJarski

R/D init. MSeife/JMeyer/5-17-74

Final typing/rt/5-17-74

rev w/f

MAJarski 5/20/74

JMeyer 5/21/74

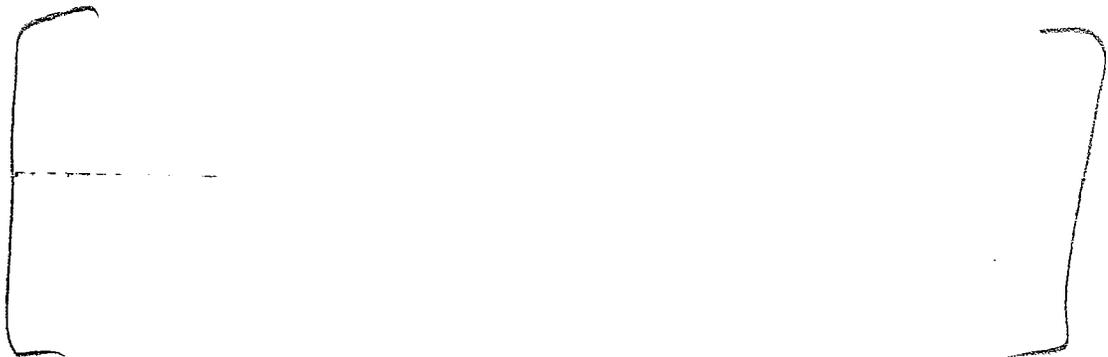
OFFICE OF PHARMACEUTICAL RESEARCH
AND TESTING (HFD-420)

May 8, 1974

LOS ANGELES DISTRICT
HFR-9260NDA 83-714, Estradiol Valerate Injection
Revised Analytical Methodology

We have reviewed the revised analytical procedure per the March 28, 1974 request of Mary Ann Jarski (HFD-107). We have the following comments:

1.



2. Standard Preparation:

The manufacturer specifies the dissolution of 40 mg. of Estradiol Valerate in . Our experience has been that the 40 mg. will not dissolve in the . We would use alcohol to dissolve this amount of Estradiol Valerate.

For your information, we are attaching a copy of the AOAC. Official First Action procedure for Estradiol Valerate.

If we can be of any further assistance, do not hesitate to call.

DONALD D. DECHERT
RESEARCH COORDINATORAttachment:
AOAC Procedure

cc: FSB/EDRO (HFD-130)

cc: HFD-107, Attn: Mary Ann Jarski

CHANGES IN METHODS

c (Vol. 56, No. 2, 1973)

and std eluates from 350
blank eluate. If liq. is
min) before detg A. Calc.
solus, ΔA and $\Delta A'$, resp.,
and max. A at ca 246 nm.

HCl/ml
= $(\Delta A/\Delta A') \times C \times F$,
F = diln factor.

and for the determination
lets was adopted official

Official First Action

6.018, 46.045, 46.054,
46.066.)

Reagents

Approx. 15 μ g/ml. Accu-
Dienestrol, dissolve in
to concn. Store in low-

acid.—Carefully add, with
50 ml MeOH, while
in ice D. Use reagent
table 3-4 days in g s flask.
s follows on day of use:
s air stream, mixt of 10.0
ca 200 ml H₂O-washed
10.0 ml MeOH. Proceed
in and 5.0 ml dienestrol
ould be clear and exhibit
and corrected A, 36.C14,

—Celite 545, acid-washed.

Preparation of Columns

—Celite and 3 ml 0.25M
 $\times 22$ mm glass chromatg
Tamp mixt. tightly and
Prewash column with 25
owed by 25 ml benzene.

ately weigh freshly ground
dienestrol into 150 ml
K₃PO₄ and wet sample
te and mix thoroly with

mixt. to 200 \times 22 mm
glass wool pad in 2 equal
ortion moderately tight.
g Celite and add rinse to
patula, and beaker with
d to top of column.

Chromatography

eluate from sample col-

umn passes into trap column. Add 25 ml benzene to
trap column; then add 175 ml benzene-isooctane
(9+1) to sample column, using several portions to
rinse sample beaker. Maintain layer of eluant over
trap column. (To maintain this reservoir in trap
column, connect the 2 columns with air-tight stop-
per, i.e., hollow No. 4 Nalgene stopper with hole
drilled to accommodate stem of sample column.)
Discard sample column when elution is complete.
Wash trap column with addnl 25 ml benzene-isoo-
octane (9+1) and discard eluates.

Elute dienestrol from trap column with 225 ml
H₂O-washed ether into 250 ml g-s conical flask contg
10 ml absolute alcohol. Without delay evap. to near
dryness, using air stream and gentle heat. Rinse flask
walls with small amt absolute alcohol and evap. soln
to dryness. Pipet 25 ml MeOH into flask, stopper
tightly, and let stand several min with frequent
vigorous swirling.

36.C13 Isomerization

Into sep. 25 ml g-s conical flasks pipet 5 ml di-
enestrol std soln, 5 ml sample prepn, and 5 ml MeOH
as reagent blank. Add 5.0 ml methanolic H₂SO₄ to
each flask with swirling (solns will become warm).
Stopper flasks tightly and shake vigorously; then
let cool ≥ 25 min at room temp.

36.C14 Determination

Det. A of sample and std solns between 400 and
240 nm in 1 cm cells against reagent blank. Correct
A at ca 303 nm by subtracting A at 360 nm.

mg Dienestrol/tablet = $[(A/A') \times C \times V \times W]/$
Q, where A and A' refer to sample and std solns,
resp.; C = exact concn of std in mg/ml; V = ml
sample diln (25 ml); W = av. tablet wt (g); and Q =
sample wt (g).

(7) The following fluorometric method for the
determination of estradiol valerate (979328) in
sesame oil or ethyl oleate injectables, JAOAC 54,
1192(1971), 56, 86(1973), was adopted official first
action:

Estradiol Valerate—Official First Action

36.C15 Principle

Oils are eluted with heptane from CH₃NO₂-Celite
column. Estradiol valerate is eluted with addnl hept-
ane, and detd by fluorometry at max. intensity, ca
328 nm.

36.C16 Apparatus

(a) Recording spectrophotofluorometer.—Aminco-
Bowman SPF, or equiv., with 1 cm cell path, Xe
lamp, slit arrangement No. 4, excitation wavelength
285 nm, meter multiplier 0.1, and sensitivity to pro-
duce 70% fluorescence for std soln at 328 nm.

(b) Glass chromatographic tubes.—250 \times 25 mm
id.

36.C17 Reagents

- (a) Heptane.—Redistd.
- (b) Nitromethane.—Spectral grade, or equiv.
- (c) Diatomaceous earth.—Celite 545, acid-washed.
- (d) Estradiol valerate std solns.—(1) Stock soln.—
0.4 mg/ml. Accurately weigh ca 40 mg USP Ref.
Std Estradiol Valerate in 100 ml vol. flask and dil.
to vol. with absolute alcohol. (2) Working soln.—16
 μ g/ml. Dil. 2 ml stock soln to 50 ml with absolute
alcohol.

36.C18 Preparation of Sample

Using "to contain" pipet (or hypodermic syringe
fitted with 1 $\frac{1}{2}$ " 18 gage needle), transfer accurately
measured vol. sample contg ca 40 mg estradiol
valerate to 100 ml vol. flask. Wash pipet with hep-
tane and add wash to vol. flask. Dil. to vol. with
heptane and mix.

36.C19 Preparation of Column

Place glass wool plug in base of chromatg tube.
To 10 g Celite in 250 ml beaker, add 11 ml CH₃NO₂.
(Caution: CH₃NO₂ is toxic and flammable. Wear
resistant rubber gloves when using it. Use effective
fume removal device.) Mix until fluffy and add to
tube in portions, packing moderately after each
addn. Place glass wool plug above column packing
and prewash column with 50 ml heptane.

36.C20 Determination

Transfer 2 ml sample soln to column. Wash with
5, 5, 10, 10, and 40 ml heptane (70 ml total), allowing
each portion to pass thru column before adding next.
Discard eluate. (Caution: See 46.011 and 46.039.)
Change receiver to 250 ml beaker and continue
eluting with heptane, collecting ca 150 ml. Evap.
eluate to dryness and quant. transfer residue to 50
ml vol. flask, using absolute alcohol. Dil. to vol. with
absolute alcohol.

Adjust spectrophotofluorometer to ca 70% fluor-
escence intensity at 328 nm with working std soln.
Scan sample and std solns from ca 280 to 450 nm,
reading % fluorescence at max. at ca 328 nm. Use
absolute alcohol as blank.

mg Estradiol valerate/ml = $100 \times C \times (F/F') \times$
(1/V), where C = concn of std soln (mg/ml); F and
F' = fluorescence of sample and std solns, resp., at
328 nm, each corrected for blank; and V = vol. of
sample taken.

(8) The following colorimetric method for the de-
termination of benzotropine mesylate (132172) in tab-
lets and injections was adopted official first action:

NDA 9883714

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

APR 02 1974

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, 40 mg.

Reference is also made to your communications dated January 30 and March 8, 1974, pertaining to the application.

We have reviewed the material submitted and have the following comment:

Your assay methodology has been submitted to our laboratories for evaluation and we will correspond with you after their review is completed.

The material submitted is being retained as part of your application for this article.

Sincerely yours,

M. Seife

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

cc:
LOS-DO
Dup
HFD-107
HFD-8
HFD-106
HFD-13
MAJarski/JLMeyer

MAJarski 4/2/74
Chill 4/2/74

Final typing/kim/4-1-74
Ack.

JAOAC 56 #2, (1973)

le and std eluates from 350
umn blank eluate. If liq. is
1 min) before detg A. Calc.
d solns, ΔA and $\Delta A'$, resp.,
and max. A at ca 246 nm.
e. HCl/ml
= $(\Delta A/\Delta A') \times C \times F$,
and F = diln factor.

umn passes into trap column. Add 25 ml benzene to
trap column; then add 175 ml benzene-isooctane
(9+1) to sample column, using several portions to
rinse sample beaker. Maintain layer of eluant over
trap column. (To maintain this reservoir in trap
column, connect the 2 columns with air-tight stop-
per, i.e., hollow No. 4 Nalgene stopper with hole
drilled to accommodate stem of sample column.)
Discard sample column when elution is complete.
Wash trap column with addnl 25 ml benzene-iso-
octane (9+1) and discard eluates.

(b) *Glass chromatographic tubes.*—250 × 25 mm
id.

ethod for the determination
tablets was adopted official

Official First Action

46.018, 46.045, 46.054,
and 46.066.)

Reagents

—Approx. 15 $\mu\text{g/ml}$. Accu-
Std Dienestrol, dissolve in
l. to concn. Store in low-

acid.—Carefully add, with
to 50 ml cold MeOH, while
xt. in ice-H₂O. Use reagent
stable days in g.s. flask.
as follows on day of use:
and air stream, mixt of 10.0
in ca 200 ml H₂O-washed
in 10.0 ml MeOH. Proceed
soln and 5.0 ml dienestrol
should be clear and exhibit
n, and corrected A, 36.C14,

i.—Celite 545, acid-washed.

Preparation of Columns

g Celite and 3 ml 0.25M
× 22 mm glass chromatg.
ug. Tamp mixt. tightly and
Prewash column with 25
followed by 25 ml benzene.
rately weigh freshly ground
g dienestrol into 150 ml
f K₃PO₄ and wet sample
dite and mix thoroly with

le mixt. to 200 × 22 mm
tg glass wool pad in 2 equal
portion moderately tight.
2 g Celite and add rinse to
spatula, and beaker with
pad to top of column.

Chromatography

at elu from sample col-

Elute dienestrol from trap column with 225 ml
H₂O-washed ether into 250 ml g-s conical flask contg
10 ml absolute alcohol. Without delay evap. to near
dryness, using air stream and gentle heat. Rinse flask
walls with small amt absolute alcohol and evap. soln
to dryness. Pipet 25 ml MeOH into flask, stopper
tightly, and let stand several min with frequent
vigorous swirling.

36.C13

Isomerization

Into sep. 25 ml g-s conical flasks pipet 5 ml di-
enestrol std soln, 5 ml sample prepn, and 5 ml MeOH
as reagent blank. Add 5.0 ml methanolic H₂SO₄ to
each flask with swirling (solns will become warm).
Stopper flasks tightly and shake vigorously; then
let cool ≥ 25 min at room temp.

36.C14

Determination

Det. A of sample and std solns between 400 and
240 nm in 1 cm cells against reagent blank. Correct
A at ca 303 nm by subtracting A at 360 nm.
mg Dienestrol/tablet = $[(A/A') \times C \times V \times W]/$
Q, where A and A' refer to sample and std solns,
resp.; C = exact concn of std in mg/ml; V = ml
sample diln (25 ml); W = av. tablet wt (g); and Q =
sample wt (g).

(7) The following fluorometric method for the
determination of estradiol valerate (979328) in
sesame oil or ethyl oleate injectables, JAOAC 54,
1192(1971), 56, 86(1973), was adopted official first
action:

Estradiol Valerate—Official First Action

36.C15

Principle

Oils are eluted with heptane from CH₃NO₂-Celite
column. Estradiol valerate is eluted with addnl heptane,
and detd by fluorometry at max. intensity, ca
328 nm.

36.C16

Apparatus

(a) *Recording spectrophotofluorometer.*—Aminco-
Bowman SPF, or equiv., with 1 cm cell path, Xe
lamp, slit arrangement No. 4, excitation wavelength
285 nm, meter multiplier 0.1, and sensitivity to pro-
duce 70% fluorescence for std soln at 328 nm.

36.C17

Reagents

(a) *Heptane.*—Redistd.
(b) *Nitromethane.*—Spectral grade, or equiv.
(c) *Diatomaceous earth.*—Celite 545, acid-washed.
(d) *Estradiol valerate std solns.*—(1) *Stock soln.*—
0.4 mg/ml. Accurately weigh ca 40 mg USP Ref.
Std Estradiol Valerate in 100 ml vol. flask and dil.
to vol. with absolute alcohol. (2) *Working soln.*—16
 $\mu\text{g/ml}$. Dil. 2 ml stock soln to 50 ml with absolute
alcohol.

36.C18

Preparation of Sample

Using "to contain" pipet (or hypodermic syringe
fitted with 1½"; 18 gage needle), transfer accurately
measured vol. sample contg ca 40 mg estradiol
valerate to 100 ml vol. flask. Wash pipet with heptane
and add wash to vol. flask. Dil. to vol. with
heptane and mix.

36.C19

Preparation of Column

Place glass wool plug in base of chromatg tube.
To 10 g Celite in 250 ml beaker, add 11 ml CH₃NO₂.
(*Caution:* CH₃NO₂ is toxic and flammable. Wear
resistant rubber gloves when using it. Use effective
fume removal device.) Mix until fluffy and add to
tube in portions, packing moderately after each
addn. Place glass wool plug above column packing
and prewash column with 50 ml heptane.

36.C20

Determination

Transfer 2 ml sample soln to column. Wash with
5, 5, 10, 10, and 40 ml heptane (70 ml total), allowing
each portion to pass thru column before adding next.
Discard eluate. (*Caution:* See 46.011 and 46.039.)
Change receiver to 250 ml beaker and continue
eluting with heptane, collecting ca 150 ml. Evap.
eluate to dryness and quant. transfer residue to 50
ml vol. flask, using absolute alcohol. Dil. to vol. with
absolute alcohol.

Adjust spectrophotofluorometer to ca 70% fluor-
escence intensity at 328 nm with working std soln.
Scan sample and std solns from ca 280 to 450 nm,
reading % fluorescence at max. at ca 328 nm. Use
absolute alcohol as blank.

mg Estradiol valerate/ml = $100 \times C \times (F/F') \times$
(1/V), where C = concn of std soln (mg/ml); F and
F' = fluorescence of sample and std solns, resp., at
328 nm, each corrected for blank; and V = vol. of
sample taken.

(8) The following colorimetric method for the de-
termination of benzotropine mesylate (132172) in tab-
lets and injections was adopted official first action:

NDA 83-714
AF 9-931

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

FEB 20 1974

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, 40 mg.

Reference is also made to your communication dated January 18, 1974, enclosing manufacturing information.

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

1. Submit the final printed labeling as per our letter dated January 23, 1974.
2. It is requested that the complete assay procedure for estradiol valerate be submitted for evaluation.

Please let us have your response promptly.

cc:
LOS-D0
Dup
HFD-107
HFD-8
HFD-106
HFD-13
JLMeyer/RJWolters/2-6-74
R/D init. by MSeife/JMeyer/2-8-74
Final typing/kim/2-8-74
Rev w/f

Sincerely yours,

Marvin Seife 2/20/74
Marvin Seife, M.D.
Director
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs

*RJWolters
2-15-74*

JMeyer 2/15/74

NDA 83-714

AF 9-931

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

JAN 23 1974

Gentlemen:

Reference is made to your abbreviated new drug application dated October 17, 1973, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for _____ (estradiol valerate) Injection, 40 mg.

We acknowledge the receipt of your communication dated November 20, 1973, enclosing draft labeling.

Reference is also made to our letter of November 28, 1973.

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

1. Submit twelve copies of the final printed package insert. The insert should be identical in content to the draft copy.
2. Revise the assay procedure as per our letter referenced above.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 1/23/74
Marvin Seife, M.D.

Director

Generic Drug Staff

Office of Scientific Evaluation

Bureau of Drugs

cc:

LOS-DO

Dup

HFD-107 HFD-106 HFD-12 HFD-8

VVKarusaitis/JLMeyer/RJWolters 1-10-74

R/D init. by Mseife/JMeyer/1-14-74

Final typing/rt/1-18-74

rev w/f

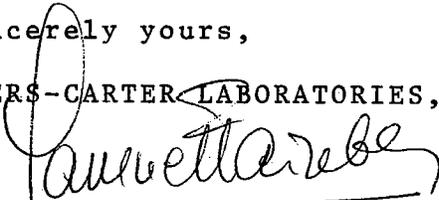
RM 1-21-74

JMeyer 1/22/74

Attached is a letter from _____
providing this information.

Sincerely yours,

MYERS-CARTER LABORATORIES, INC.


Samuel M. Fainberg,
Director,
Technical and Regulatory Affairs

MP

Enclosure: Letter form _____

C.C:

APPEARS THIS WAY
ON ORIGINAL

NDA 83-714
AF 9-931

NOV 28 1973

Myers-Carter Laboratories, Inc.
Attention: Mr. Samuel M. Fainberg
5160 West Bathany 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, 40 mg. per ml.

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

The drug dosage form has been analyzed, and our laboratory suggest that the assay procedure be revised as per the J.A.O.A.C., 58, 511 (1973).

Please let us have your response promptly.

Sincerely yours,

Harvin Seife 11/27/73
Harvin Seife, M.D.
Director
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs

cc:
LOS-DO
Dup
BD-69
BD-66
BD-106
BD-242

JLMeyer/RJWolters/11-20-73
R/D init. by MSeife/JMeyer/11-26-73
Final typing/kim/11-26-73
Rev w/f

*check for SLW
11/27/73*

*R. J. Wolters
11-27-73*



**MYERS-CARTER
LABORATORIES** INC.

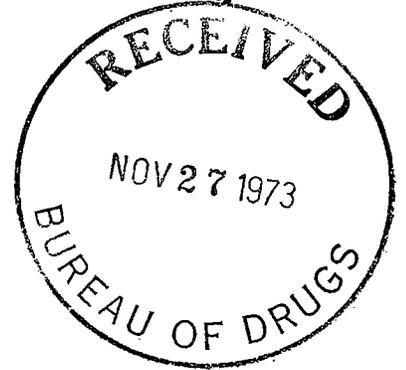
SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

PERSONALLY SUBMITTED BY
M. H. Hovell
Reidley BA
11-27-73

Rev # *ORIG* *E*

RESUBMISSION
NDA ORIG AMENDMENT

November 20, 1973



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 83-714 (ESTRADIOL VALERATE) INJECTION
40 mg./per ml.

Dear Dr. Seife:

In response to your letter, dated November 8, 1973, we are submitting the following information.

In the DOSAGE AND ADMINISTRATION section of the Package Insert, we have deleted _____ and have stated the dosage as follows:

Menopause: 10 to 20 mg. Estradiol Valerate Injection. Repeat two or three weeks after initial injection. Continuous therapy with estrogen alone may induce dysfunctional bleeding.

Kraurosis Vulvae: With or without pruritus, 10 to 20 mg., I.M. Repeat in two to three weeks after initial injection.

Amenorrhea: As part of Cyclic Therapy Schedule: 20 mg. Estradiol on day 1. The physician is to determine when a patient should have Estrogen-Progesterone therapy.

Draft of Package Insert enclosed. We will make the above corrections at the time of our next printing.

Sincerely yours,

MYERS-CARTER LABORATORIES, INC.

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

PB Enclosure: Draft of Package Insert

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

NDA 83-714

AP 9-931

NOV 08 1973

Myers-Carter Laboratories, 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 _____ (estradiol valerate) Injection, 40 mg. per ml.

Reference is also made to your communications dated September 6 and October 1, 1973, enclosing draft labeling, samples, and manufacturing information.

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

In the DOSAGE AND ADMINISTRATION section of the package insert, delete material on _____ and state the dosage as follows:

- Menopause: 10 to 20 mg. Estradiol Valerate Injection. Repeat two to three weeks after initial injection. Continuous therapy with estrogen alone may induce dysfunctional bleeding.
- Kraurosis Vulvae with or without pruritus: 10 to 20 mg. I.M. Repeat in two or three weeks after initial injection.
- Amenorrhea As part of Cyclic Therapy Schedule: 20 mg. Estradiol on day 1. The physician is to determine when a patient should have Estrogen-Progesterone therapy.

In addition, before the application can be approved, it is necessary to have a satisfactory establishment inspection report as requested in our communications since June 29, 1973.

Please let us have your response promptly.

cc:

LOS-DO

Dup

BD-69 BD-66 BD-106 BD-242

VVKarusaitis/JMeyer/RJWolters/10-31-73

R/D init. MSeife/JMeyer/11-1-73

Final typing/rt/11-1-73

rev w/f

Sincerely yours,

Marvin Seife, M.D.

Director

Generic Drug Staff

Office of Scientific Evaluation

Bureau of Drugs

RJWolters 11-2-73



**MYERS-CARTER
LABORATORIES INC.**

SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

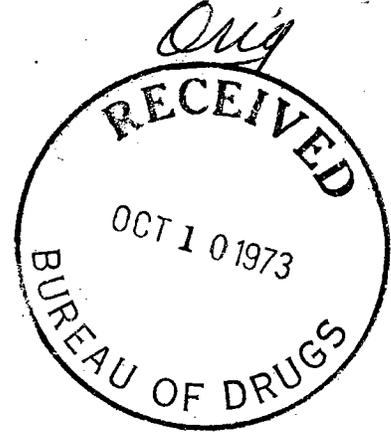
PERSONALLY SUBMITTED BY

Mr. H. Jones
Reid by BAO
10-10-73

October 1, 1973

Rev. WIF *E*
RESUBMISSION

NDA ORIG AMENDMENT



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 83-714 (ESTRADIOL VALERATE) — INJECTION
40 mg. per ml.

Dear Dr. Seife:

In response to your letter, dated September 24, 1973, we are submitting the following information.

1. Package Insert:
 - a. We have revised the dosage levels in the DOSAGE AND ADMINISTRATION section as requested.
 - b. We have clarified the dosage administration as requested.
 - c. We have clarified the potency in the HOW SUPPLIED section as requested.
2. The tests performed on the active ingredient, Estradiol Valerate, are as listed in the U.S.P. XVIII, Page 241. (Copy of U.S.P. Page 241 attached). The tests are as follows:

[]

Continued

Samples rec'd in DRSS 10-10-73

Redacted _____

Page(s) of trade

secret and /or

confidential

commercial

information

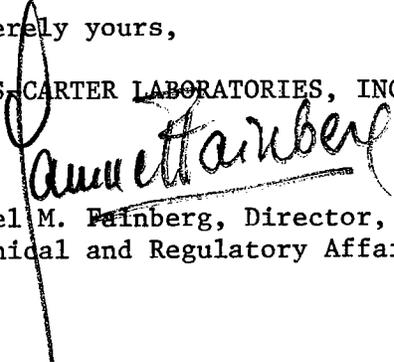
Page 3, Continued

NDA 83-714

October 1, 1973

Sincerely yours,

MYERS-CARTER LABORATORIES, INC.


Samuel M. Feinberg, Director,
Technical and Regulatory Affairs

PB

Enclosure: Page 8 of the revised Package Insert
Copies of pages from USP (3) & N.F. (1)
Copy of Certificate of Analysis

APPEARS THIS WAY
ON ORIGINAL

~~NDA 83-714~~

SEP 24 1973

AF 9-931

Myers-Carter Laboratories, Inc.
Attention: Mr. Samuel M. Fainberg
5160 West Bethany Home Road
Glendale, Arizona 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, 40 mg. per ml.

Reference is also made to your communication dated August 7, 1973, enclosing revised labeling and manufacturing information.

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

1. Package insert:

a) Revise the dosage levels in the DOSAGE AND ADMINISTRATION section as requested in our letter of June 29, 1973.

b) It is noted that the preparation is a long-acting estrogen product (effects last 2 to 3 weeks). However, the dose is to be administered weekly preferably in divided doses. Please clarify.

c) Clarify the potencies listed in the HOW SUPPLIED section as labels and manufacturing information for these potencies were not included and the 40 mg. per ml. potency was not listed.

2. Clarify which tests are performed on the drug dosage form and active ingredients.

3. It is recommended that the _____

Myers-Carter Laboratories, Inc.
NDA 83-714

-2-

4. []

5. Include samples of the drug dosage form and active ingredient (including the certificate of analysis) as per your commitment.

6. A satisfactory establishment inspection as requested in our letter of June 29, 1973.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 9/21/73

Marvin Seife, M.D.

Director

Generic Drug Staff

Office of Scientific Evaluation

Bureau of Drugs

cc:

LOS-DO

Dup

BD-69

BD-66

BD-106

BD-242

VVKarusaitis/JLMeyer/RJWolters/9-17-73

R/D init. MSeife/JMeyer/9-19-73

Final typing/rt/9-19-73

rev w/f

JMeyer 9/20/73

*RWalters
9-19-73*



**MYERS-CARTER
LABORATORIES INC.**

SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

PERSONALLY SUBMITTED BY
Mr. H. Kovelos
Rec'd by BAO
9-13-73

ORIG NEW CORRES

Original

September 6, 1973

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

SUBJECT: NDA 83-714 (CAC NO. 136)
(ESTRADIOL VALERATE)
— INJECTION, 40 mg./ml.

Dear Dr. Seife:

As stated in our letter to you, dated August 7, 1973,
Page 2, Number 5, we are submitting six samples of
NDA 83-714, (Estradiol Valerate) —
Injection for your approval.

Sincerely yours,

MYERS-CARTER LABORATORIES, INC.

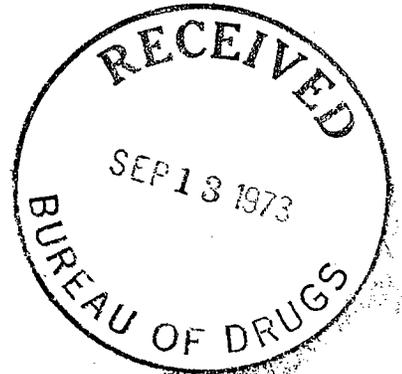
Samuel M. Fainberg

Samuel M. Fainberg, Director,
Technical and Regulatory Affairs

PB

Enclosure: Samples

C.C.



Samples rec'd in DRSS

9-13-73



**MYERS-CARTER
LABORATORIES INC.**

SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

PERSONALLY SUBMITTED BY

Mr. H. Hoveless
Rec'd by BAO
9-5-73

Rev. W/F
RESUBMISSION

NDA ORIG AMENDMENT

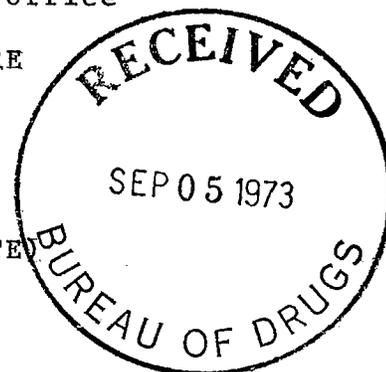
August 7, 1973

Orig

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

SUBJECT: NDA 83-714

--- (ESTRADIOL VALERATE)
--- INJECTION, 40 mg./ml,



Dear Dr. Seife:

In response to your letter, dated June 29, 1973,
we are submitting the requested information,

1. Package Insert:

- a. In the ACTIONS section, we have added the statement, "The estrogenic effects last for approximately two or three weeks after a single intramuscular injection" as suggested,
- b. In the DOSAGE AND ADMINISTRATION section, we have revised the dosage levels as suggested and in addition, we have deleted the statement, "Estrogen Deficiency:,,,individual patient", as suggested,

2. The drug will be manufactured, processed, packaged, and labeled at:

MYERS-CARTER LABORATORIES, INC.
5160 W. Bethany Home Road
Glendale, Arizona 85301

Continued

Page 2, Continued
 NDA 83-714
 Dr. Seife

3. We have included the actual analytical procedures used to assure that the drug dosage form and components will comply with the specifications and tests described in an official compendium, if such article differs from the compendium drug, that the specifications and tests applied to the drug and its components are adequate to assure their identity, strength, quality, and purity as requested.
4. (7 iv.) Methods used in, and the Facilities, and Controls used for the Manufacturing, Processing, and Packing of the Drug.

<u>Ingredients</u>	<u>Per Batch</u>
Estradiol Valerate	_____
Caster Oil	_____
Benzyl Benzoate	_____
Benzyl Alcohol	_____

CAUTION NOTICE IS POSTED AS FOLLOWS:

CAUTION: Hazardous Drug - Potent Estrogen. Can cause enlargement of breasts or high pitched voice in the male, etc. Precaution must be taken to avoid inhalation and all other contact. Wear protective gloves and clothing and wash thoroughly and immediately after any contact. Process so as to prevent cross-contamination of any other product.

5. Samples will be submitted in a separate mailing at a later date.

Sincerely yours,

MYERS-CARTER LABORATORIES, INC.

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

PB

Enclosures: Copy of revised Package Insert
 Test Procedures

Page 2, Continued

NDA 83-714

Dr. Seife

- 3. We have included the actual analytical procedures used to assure that the drug dosage form and components will comply with the specifications and tests described in an official compendium, ~~if such~~ article differs from the compendium drug, that the specifications and tests applied to the drug and its components are adequate to assure their identity, strength, quality, and purity as requested.
- 4. (7 iv.) Methods used in, and the Facilities, and Controls used for the Manufacturing, Processing, and Packing of the Drug.

Ingredients

Per Batch

Estradiol Valerate
 Caster Oil
 Benzyl Benzoate
~~Benzyl Alcohol~~

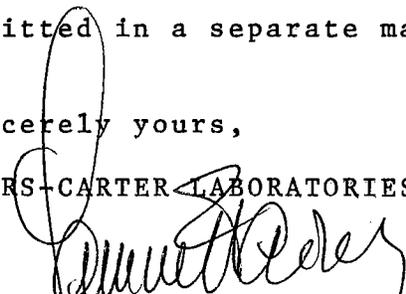
CAUTION NOTICE IS POSTED AS FOLLOWS:

CAUTION: Hazardous Drug - Potent Estrogen. Can cause enlargement of breasts or high pitch voice in the male, etc. Precaution must be taken to avoid inhalation and all other contact. Wear protective gloves and clothing and wash thoroughly and immediately after any contact. Process so as to prevent cross-contamination of any other product.

- 5. Samples will be submitted in a separate mailing at a later date.

Sincerely yours,

MYERS-CARTER LABORATORIES, INC.



Samuel M. Fainberg, Director,
 Technical and Regulatory Affairs

PB

Enclosures: Copy of revised Package Insert
 Test Procedures

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

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

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

Supplements (Identify with NDA number):
Office of Scientific Evaluation (BD-100),
Bureau of Drugs.
Original new drug applications: Office of Scientific Evaluation (ED-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. Ovocilin 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. Vallestrial Tablets; G. D. Searle and Co., Post Office Box 5110, Chicago, Ill. 60680 (NDA 8-579).

II. LONG-ACTING ESTROGENS

1. *Preparations containing chlorotri-anisene.* 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. Dellestrogen; 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 orchiectomy 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.

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 (hypogonitalism) 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" section above) and possibly effective (not included in the "Indications" section above), continued use as described in paragraphs (c), (d), (e), and (f) 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 or supplements thereto providing for indications for which substantial evidence of effectiveness is lacking as described in paragraphs I. A. and II. of this announcement. An order withdrawing approval of the application will not issue if such applications supplemented in accord with this notice, to delete such indications. A related drug for human use, not subject of an approved new drug application, offered for the indications which substantial evidence of effectiveness is lacking may be affected by this action.

2. In accordance with the provision of section 505 of the Act (21 U.S.C. 3) 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 be deleted from the labeling. A request for a hearing must be filed within 30 days after the date of publication of notice in the FEDERAL REGISTER.

3. A request for a hearing may not be upon mere allegations or denials. It 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 factual analysis of the clinical and/or investigational data that the objector prepared to prove in a hearing. Any such data submitted in response to this notice must be previously unsubmitted and include data from adequate and well-controlled clinical investigations (identified ready review) as described in § 130.115(5) of the regulations published in the FEDERAL REGISTER of May 3, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained in 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 will issue a written notice of the time and place at which the hearing will commence.

A copy of the Academy's report is being furnished to each firm referred to above. Communications forwarded in response to this announcement should

14828

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, 5609 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 (ED-60),
Bureau of Drugs.

Request for hearing (Identify with docket number): Hearing Clerk, Office of General Counsel (GC-1), Room 6-83, 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 (ED-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.

FER Dec 72 11394 Filed 7 24-23; 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; Lederle Laboratories Division, American Cyanamid Co., Post Office Box 500, Pearl River, N.Y. 10965 (NDA 8-943).

3. Diamox Parenteral (powder for reconstitution) containing sodium acetazolamide; Lederle Laboratories Division, American Cyanamid Co. (NDA 9-328).

4. Oratrol Tablets containing dichlorophenamide; 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 dichlorophenamide; Merck Sharp and Dohme, Division of Merck and Co., West Point, Pa. 19486 (NDA 11-356).

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

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

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

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

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

5. Dichlorophenamide 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 dichlorophenamide 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; cen-

trancephalic epilepsies (petit mal, unlocalized seizures).

Acetazolamide (in conventional tablet and parenteral forms):

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

Dichlorophenamide 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 FR. 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, 1969), 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 with applications and all amendments and drawing approval of all new drug supplements thereto providing for their indications for which substantial evidence of effectiveness is lacking as described in paragraph A above. An order with drawing approval of the application 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

NDA 83-714

AF 9-931

JUN 29 1973

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

Gentlemen:

Reference is made to your abbreviated new drug application dated February 9, 1973, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for _____ (estradiol valerate) — Injection, 40 mg. per ml.

Reference is also made to your communication dated May 22, 1973, enclosing an environmental impact statement.

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

1. Package insert:

- a) In the ACTIONS section, add the statement, "The estrogenic effects last for approximately two or three weeks after a single intramuscular injection."
- b) Revise the dosage levels in the DOSAGE AND ADMINISTRATION section as the levels are inadequate. In addition delete the statement _____

2. Identify the place where the drug will be manufactured, processed, packaged, and labeled.

3. Include the actual analytical procedures used to assure that the drug dosage form and components will comply with the specifications and tests described in an official compendium, if such article is recognized therein, or, if not listed or if the article differs from the compendium drug, that the specifications and tests applied to the drug and its components are adequate to assure their identity, strength, quality, and purity.

APPEARS THIS WAY
ON ORIGINAL

4. Outline the methods used in, and the facilities, and controls used for, the manufacture, processing, and packing of the drug. In this regard clarify (a) the facilities used for the manufacture, processing, and packing of the drug and (b) the raw material handling procedures.
5. Include samples of the drug dosage form and active ingredient to expedite the handling of this application.

At the present time, the requirement for adequate data to assure the bio-availability of this drug has been deferred.

The Bureau of Drugs, Office of Compliance, has reviewed your establishment inspection report and have the following comments:

We have evaluated the operations of the above referenced applicant as they relate to conformity with Current Good Manufacturing Practice Regulations (21 CFR, Part 133). On the basis of this evaluation, we are not able to approve this application as the firm is not operating in compliance with Part 133 to assure that the product meets the requirements of the Federal Food, Drug, and Cosmetic Act as to safety, and has the identity and strength, and meets the quality and purity characteristics which it purports to possess.

The inspection of 4-17-20/73 revealed significant GMP deviations including:



APPEARS THIS WAY
ON ORIGINAL

Myers-Carter Laboratories, Inc.
NDA 83-714

-3-

Such information indicates that there is a disagreement between actual GMP and the commitment in your application. Therefore, before we can take further action on this abbreviated new drug application, we should have a satisfactory inspection report.

Please let us have your response promptly.

Sincerely yours,

C. M. Carroll M.D. / for.

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

6/29/73

cc:

LOS-DO

Dup

BD-69

BD-66

BD-106

BD-242

BD-340

OMCarroll/JLMeyer/RJWolters/6-19-73

R/D init. MSeife/JMeyer/6-20-73

Final typing/rt/6-22-73

rev w/f

OM. Carroll, M.D. 6/25/73

JMeyer 6/25/73

APPEARS THIS WAY
ON ORIGINAL



**MYERS-CARTER
LABORATORIES INC.**

SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

Original
NDA ORIG AMENDMENT

May 22, 1973

Marvin Seife, M.D.
Director
Division of Actions 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: NDA 83-714, _____ INJECTION
(ESTRADIOL VALERATE)

Dear Dr. Seife:

In response to your correspondence, dated May 11, 1973, we are enclosing an Environmental Impact Statement as requested.

We also wish to correct errors in label (Page 5), insert (Page 13) and accompanying letter, the dosage form being a solution not _____. Copies of corrected pages attached.

Sincerely yours,

MYERS-CARTER LABORATORIES, INC.

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

PB

Enclosures: E.I.S.
Pages 5, 13, and cover page



NDA 83-714

AF 9-931

MAY 11 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) _____

DATE of APPLICATION: February 9, 1973

DATE of COVER LETTER: April 26, 1973

DATE of RECEIPT: May 1, 1973

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

We would also like to call to your attention the Federal Register of March 15, 1973 (38 F.R. 7001) regulations establishing procedures for preparation of Environmental Impact Statements (Part 6 - Environmental Impact Considerations). Section 6.1(e) of these regulations requires that the applicant include an environmental impact analysis report as part of any new-drug application. Failure to submit an environmental impact analysis report is grounds for refusing to file or to approve an application (21 CFR 130.4(a)(8) or 130.12(a)(7)).

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

cc:
LOS-DO
Dup
BD-69 BD-66
BD-106 BD-310
JLMeyer/kim/5-7-73
Ack

JLMeyer 5/9/73

Sincerely yours,

Marvin Seife 5/10/73

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



MYERS-CARTER LABORATORIES INC.

SUBSIDIARY OF CHROMALLOY AMERICAN CORPORATION

**ABBREVIATED
NEW DRUG APPLICATION**

PERSONALLY SUBMITTED BY

M. Seife
5/1/73
Paul [unclear]

April 26, 1973

83-714

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
40 MG./ML. FEDERAL REGISTER
RULING OF TUESDAY, JULY 25, 1972, VOLUME 37,
NO. 143, DESI-1543

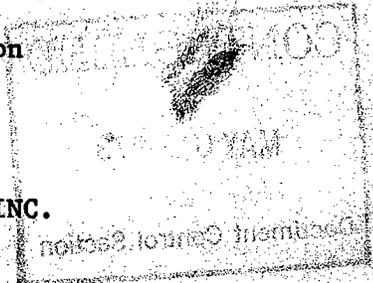
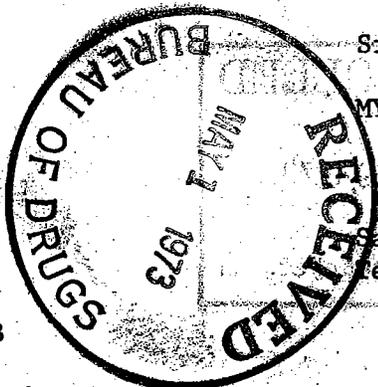
Dear Dr. Seife:

We are enclosing our Abbreviated New Drug Application
for _____, 40 mg./ml.

Sincerely yours,

MYERS-CARTER LABORATORIES, INC.

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



PB

Enclosure: Abb. NDA