CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040197

Trade Name : ESTRADIOL TABLETS USP

Generic Name: Estradiol Tablets USP 0.5mg, 1mg and 2mg

Sponsor : Barr Laboratories, Inc.

Approval Date: October 22, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040197

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Bioequivalence Review(s)	X			
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Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040197

APPROVAL LETTER

D, V

ANDA 40-197

OCT 22 1997

Barr Laboratories, Inc.
Attention: Christine A. Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Madam:

This is in reference to your abbreviated new drug application dated June 26, 1996, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Estradiol Tablets USP, 0.5 mg, 1 mg and 2 mg.

Reference is also made to your amendments dated October 4, and December 3, 1996; and January 21, July 10, July 31, and August 4, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Estradiol Tablets USP, 0.5 mg, 1 mg and 2 mg to be bioequivalent, and, therefore therapeutically equivalent to those of the listed drug (Estrace® Tablets 0.5 mg, 1 mg and 2 mg, respectively, of Bristol Myers Squibb Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040197

FINAL PRINTED LABELING

INFORMATION FOR PATIENTS

ESTRADIOL TABLETS, USP

1108860101

Three Patient Leaflets Attached

ESTRADIOL TABLETS, USP

INFORMATION FOR PATIENTS

INTRODUCTION:

This leaflet describes when and how to use estrogens, and the risks and benefits of estrogen treatment.

Estrogens have important benefits but also some risks. You must decide, with your doctor, whether the risks to you of estrogen use are acceptable because of their benefits. If you use estrogens, check with your doctor to be sure you are using the lowest possible dose that works, and that you don't use them longer than necessary. How long you need to use estrogens will depend on the reason for use.

WARNINGS:

ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE ("CHANGE OF LIFE").

If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.

USES OF ESTROGEN:

(Not every estrogen drug is approved for every use listed in this section. If you want to know which of these possible uses are approved for the medicine prescribed for you, ask your doctor or pharmacist to show you the professional labeling. You can also look up the specific estrogen product in a book called the "Physicians' Desk Reference", which is available in many book stores and public libraries. Generic drugs carry verbatim the same labeling information as their brand name versions.)

• **To reduce moderate or severe menopausal symptoms.** Estrogens are hormones made by the ovaries of normal women. Between the ages 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels which causes the "change of life" or menopause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden drop in estrogen levels causes "surgical menopause".

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. Most women have only mild menopausal symptoms or none at all and do not need to use estrogen drugs for these symptoms. Others may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. The majority of women do not need estrogen replacement for longer than six months for these symptoms.

• **To treat vulval and vaginal atrophy** (itching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause.

• **To treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.**

• **To treat certain types of abnormal vaginal bleeding due to hormonal imbalance when your doctor has found no serious cause of the bleeding.**

• **To treat certain cancers in special situations, in men and women.**

• **To prevent thinning of bones.**

Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists and hips break most often in osteoporosis. Both men and women start to lose bone mass after about age 40, but women lose bone mass faster after the menopause. Using estrogens after the menopause slows down bone thinning and may prevent bones from breaking. Lifelong adequate calcium intake, either in the diet (such as dairy products) or by calcium supplements (to reach a total daily intake of 1000 milligrams per day before menopause or 1500 milligrams per day after menopause), may help to prevent osteoporosis. Regular weight-bearing exercise (like walking and running for an hour, two or three times a week) may also help to prevent osteoporosis. Before you change your calcium intake or exercise habits, it is important to discuss these lifestyle changes with your doctor to find out if they are safe for you.

Since estrogen use has some risks, only women who are likely to develop osteoporosis should use estrogens for prevention. Women who are likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, sister, or aunt. Women who have relatively early menopause, often because their ovaries were removed during an operation ("surgical menopause"), are more likely to develop osteoporosis than women whose menopause happens at the average age.

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• **During pregnancy** (see boxed WARNINGS).

Regular weight-bearing exercise (like walking and running for an hour, two or three times a week) may also help to prevent osteoporosis. Before you change your calcium intake or exercise habits, it is important to discuss these lifestyle changes with your doctor to find out if they are safe for you.

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Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.

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Since estrogens increase the risk of certain types of cancer, you should not use estrogens if you have ever had cancer of the breast or uterus, unless your doctor recommends that the drug may help in the cancer treatment. (For certain patients with breast or prostate cancer, estrogens may help.)

• If you have any circulation problems.

Estrogen drugs should not be used except in unusually special situations in which your doctor judges that you need estrogen therapy so much that the risks are acceptable. Men and women with abnormal blood clotting conditions should avoid estrogen use (see **DANGERS OF ESTROGENS**, below).

• When they do not work.

During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims and such long-term estrogen use may have serious risks.

• After childbirth or when breastfeeding a baby:

Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born.

(Over)

ESTRADIOL TABLETS, USP

INFORMATION FOR PATIENTS

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• To treat vulval and vaginal atrophy (itching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause.

• To treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.

• To treat certain types of abnormal vaginal bleeding due to hormonal imbalance when your doctor has found no serious cause of the bleeding.

• To treat certain cancers in special situations, in men and women.

• To prevent thinning of bones.

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During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims and such long-term estrogen use may have serious risks.

- **After childbirth or when breastfeeding a baby:**

Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see **DANGERS OF ESTROGENS**, below).

If you are breastfeeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your health care provider.

DANGERS OF ESTROGENS:

- **Cancer of the uterus.**

Your risk of developing cancer of the uterus gets higher the longer you use estrogens and the larger doses you use. One study showed that after women stop taking estrogens, this higher cancer risk quickly returns to the usual level of risk (as if you had never used estrogen therapy). Three other studies showed that the cancer risk stayed high for 8 to more than 15 years after stopping estrogen treatment. Because of this risk, **IT IS IMPORTANT TO TAKE THE LOWEST DOSE THAT WORKS AND TO TAKE IT ONLY AS LONG AS YOU NEED IT.**

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• **After childbirth or when breastfeeding a baby:**

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(Over)

Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (but see **OTHER INFORMATION** below).

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

• **Cancer of the breast.**

Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used higher doses for shorter time periods.

Regular breast examinations by a health professional and monthly self-examination are recommended for all women.

• **Gallbladder disease.**

Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.

• **Abnormal blood clotting.**

Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), a pulmonary embolus (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long term disability. However, most studies of low dose estrogen usage by women do not show an increased risk of these complications.

SIDE EFFECTS:

In addition to the risks listed above, the following side effects have been reported with estrogen use:

Nausea and vomiting.

Breast tenderness or enlargement.

Enlargement of benign tumors ("fibroids") of the uterus.

Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.

A spotty darkening of the skin, particularly on the face.

REDUCING RISK OF ESTROGEN USE:

If you use estrogens, you can reduce your risks by doing these things:

• **See your doctor regularly.** While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.

• **Reassess your need for estrogens.** You and your doctor should reevaluate whether or not you still need estrogens at least every six months.

• **Be alert for signs of trouble.** If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:

Abnormal bleeding from the vagina (possible uterine cancer)

Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)

Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye)

Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly)

Yellowing of the skin or eyes (possible liver problem)

Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

OTHER INFORMATION:

Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctor may prescribe a progestin for you to take together with the estrogen.

You should know, however, that taking estrogens with progestins may have additional risks. These include:

- unhealthy effects on blood fats (especially the lowering of the HDL blood cholesterol, the "good" blood fat which protects against heart disease);
- unhealthy effects on blood sugar (which might make a diabetic condition worse); and
- a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

Some research has shown that estrogens taken without progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about how much to take.

Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.

This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physicians' Desk Reference," which is available in book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

HOW SUPPLIED:

Estradiol Tablets, USP are available as:

0.5 mg: White to off-white, oval, flat-faced, beveled-edge, scored tablet. Debossed with 899/½ on the scored side and ḇ on the other side. Available in bottles of:

100 NDC 0555-0899-02

1 mg: Light purple, oval, flat-faced, beveled-edge, scored tablet. Debossed with 886/1 on the scored side and ḇ on the other side. Available in bottles of:

90 NDC 0555-0886-14
100 NDC 0555-0886-02
500 NDC 0555-0886-04

2 mg: Green, oval, flat-faced, beveled-edge, scored tablet. Debossed with 887/2 on the scored side and ḇ on the other side. Available in bottles of:

90 NDC 0555-0887-14
100 NDC 0555-0887-02
500 NDC 0555-0887-04

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.

This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physicians Desk Reference," which is available in book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

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MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

PL-899, 886, 887

Revised JUNE 1997

Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (but see **OTHER INFORMATION** below).

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

• **Cancer of the breast.**

Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used higher doses for shorter time periods.

Regular breast examinations by a health professional and monthly self-examination are recommended for all women.

• **Gallbladder disease.**

Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.

• **Abnormal blood clotting.**

Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), a pulmonary embolus (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long term disability. However, most studies of low dose estrogen usage by women do not show an increased risk of these complications.

SIDE EFFECTS:

In addition to the risks listed above, the following side effects have been reported with estrogen use:

Nausea and vomiting.

Breast tenderness or enlargement.

Enlargement of benign tumors ("fibroids") of the uterus.

Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.

A spotty darkening of the skin, particularly on the face.

REDUCING RISK OF ESTROGEN USE:

If you use estrogens, you can reduce your risks by doing these things.

• **See your doctor regularly.** While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.

• **Reassess your need for estrogens.** You and your doctor should reevaluate whether or not you still need estrogens at least every six months.

• **Be alert for signs of trouble.** If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:

Abnormal bleeding from the vagina (possible uterine cancer).

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

Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye).

Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly).

Yellowing of the skin or eyes (possible liver problem).

Pain, swelling, or tenderness in the abdomen (possible gallbladder problem).

OTHER INFORMATION:

Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctor may prescribe a progestin for you to take together with the estrogen.

You should know, however, that taking estrogens <u>with</u> progestins may have additional risks. These include:

- unhealthy effects on blood fats (especially the lowering of the HDL blood cholesterol, the "good" blood fat which protects against heart disease);
- unhealthy effects on blood sugar (which might make a diabetic condition worse); and
- a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

Some research has shown that estrogens taken <u>without</u> progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused

your bloodstream: they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), a pulmonary embolus (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long term disability. However, most studies of low dose estrogen usage by women do not show an increased risk of these complications.

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In addition to the risks listed above, the following side effects have been reported with estrogen use:

Nausea and vomiting;

Breast tenderness or enlargement;

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A spotty darkening of the skin, particularly on the face.

REDUCING RISK OF ESTROGEN USE:

If you use estrogens, you can reduce your risks by doing these things:

- **See your doctor regularly.** While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.
- **Reassess your need for estrogens.** You and your doctor should reevaluate whether or not you still need estrogens at least every six months.
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Abnormal bleeding from the vagina (possible uterine cancer)

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Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye)

Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly)

Yellowing of the skin or eyes (possible liver problem)

Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

OTHER INFORMATION:

Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctor may prescribe a progestin for you to take together with the estrogen.

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- unhealthy effects on blood fats (especially the lowering of the HDL blood cholesterol, the "good" blood fat which protects against heart disease);
- unhealthy effects on blood sugar (which might make a diabetic condition worse); and
- a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

Some research has shown that estrogens taken without progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about how much to take.

Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.

This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physicians' Desk Reference," which is available in book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

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100	NDC 0555-0887-02
500	NDC 0555-0887-04

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MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

PL-899, 886, 887

Revised JUNE 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040197

CHEMISTRY REVIEW(S)

D N

1. *CHEMIST's REVIEW #3*

2. **ANDA 40-197**

3. APPLICANT, Name/Address/Telephone:
Barr Laboratories, Inc.
Attention: Christine A. Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519
tel. 914-362-1100

4. LEGAL BASIS FOR ANDA SUBMISSION: 505(j)

5. Supplement: n/a

6. Proprietary Name: none

7. Non-PROPRIETARY NAME: **Estradiol Tablets USP**

Innovator's Product Name: *Estrace® Tablets*
(*Mead Johnson Labs*) (same 3 strengths)

8. Supplement Provides For: n/a

9. AMENDMENTS & Other DATES.

A. **FIRM:**

06-26-96	date of application
*07-10-97	Fax amendment
*07-25-97	Telecon
*07-28-97	Telecon
*07-31-97	Fax amendment
*08-01-97	Telecon re wording of "tentative"
*08-04-97	Fax amendment

B. **FDA:**

06-24-97	NA letter/Fax
07-24-97	Telecon re remaining deficiencies.
07-31-97	Telecon re fax amendment concerning "tentative" and spec for the

10. PHARMACOLOGICAL CATEGORY: Estrogen replacement

11. Rx or OTC: R_x

12. RELATED ANDAs:

13. DOSAGE FORM: tablets

14. POTENCY: 0.5, 1, and 2 mg.

15. CHEMICAL NAME: Estra-1,3,5(10)-triene-3,17 β-diol. $C_{18}H_{24}O_2$

16. Records & Reports: n/a

17. COMMENTS.

A. General Comments:
USP drug substance and drug product.
All 3 strengths of the tablets are reported scored.

B. Comments to the Firm's Amendment of July 10th 1997:

1. Request:
Please justify the large limit of for the impurity when actural values observed were significantly less. We would suggest a value more like in your release specifications.
COMMENT: sat.
The firm provided revised impurity limits for

2. Request:
Please provide the COA to this application on their batch FD&C Yellow #5
COMMENT: sat.
The applicant submitted the COA on their batch FD&C Yellow #5 in Exhibit #1 on page 193.

18. CONCLUSIONS & RECOMMENDATIONS:
For Approval awaiting results of a positive CGMP.

19. Reviewer/Branch Chief:
Robert W. Trimmer
BRANCH II, DIV. OF CHEMISTRY I, OGD

Michael J. Smela, Jr.
TEAM LEADER

Date Started: 07-18-97
Date Completed: 07-21-97
revised 08-04-97

cc: ANDA 40-197
Division File
Field Copy

Endorsements:

HFD-625/RTrimmer/8/4/97
HFD-625/SSherken for MSmela/8/14/97
file #X:\new\firmsam\Barr\ltrs&rev\40197r3.bRT
F/t by: gp/8/15/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040197

BIOEQUIVALENCE REVIEW(S)

ANDA 40-197

JUN 25 1997

Barr Laboratories. Inc.
Attention: Claire M. Lathers, Ph.D.
2 Quaker Road
P.O. BOX 2900
Pomona NY 10970-0519

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/s/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 20 1997

Estradiol
0.5 mg, 1 mg, & 2 mg tablet
NDA #40-197
Reviewer: J. Lee
40197SA.197

Barr Laboratories. Inc.
Pomona. New York
Submission date:
January 21, 1997

Review of a Study Amendment

This submission provides the responses to the deficiencies cited in the review of the original bio-study (rev. 12/12/96).

Analytical Methodology:

The company was requested to submit the complete analytical methodology, including the sample, standard and QC preparation and processing procedures.

The company has now submitted the detailed, analytical procedures that were omitted in the original bio-study report.

In-process Stability Data:

Batch Size:

The batch size of the test bio-batch was not stated in the original bio-submission.

It is reported to be

Dissolution:

The analytical methodology used in the dissolution testing was

Comment:

1. The sponsor has adequately responded to the deficiencies.

Recommendation:

1. The bioequivalence study conducted by on its estradiol 2 mg tablet, batch #6R88701, comparing it to Estrace® 2 mg tablet, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Barr's test product is bioequivalent to the reference product, Estrace® 2 mg tablet manufactured by Bristol-Myers Squibb.

2. The in-vitro dissolution testing data using the USP method is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 ml of 0.3% sodium lauryl sulfate in H_2O, at 37°C using USP XXIII apparatus II (paddle) at 100 rpm. The test product should meet the following specification:

   Not less thar of the labeled amount of the drug in the tablet is dissolved in 60 minutes.

3. The in-vitro dissolution testing data on the 1 mg and 0.5 mg tablets is also acceptable. The formulation for the 1 mg and 0.5 mg tablets are proportionally similar to the 2 mg tablet, which underwent bioequivalence testing. The waivers of in-vivo study requirements for the 1 mg and 0.5 mg tablets are granted. Barr's estradiol 1 mg and 0.5 mg tablets are deemed bioequivalent to the like strengths of Estrace® tablets.

4. From the bioequivalence viewpoint the firm has met the requirements of in-vivo bioavailability and in-vitro dissolution testing and the application is acceptable.

6/11/97

J. Lee

DEC 1 2 1996

Estradiol
0.5 mg, 1 mg & 2 mg tablet
NDA #: 40-197
Reviewer: J. Lee
40197SDW.696

Barr Laboratories, Inc.
Pomona, New York
Submission date:
June 26, 1996
October 4, 1996

Review of an in-vivo Bioavailability Study, Dissolution Testing Data, and 2 Requests for Waiver

Background:

17-beta-Estradiol is the most potent physiologic estrogen and is the principal endogenous estrogen. Estradiol is used in women for the management of moderate to severe vasomotor symptoms associated with menopause, the treatment of vulval and vaginal atrophy, the treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure, the treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease, the treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only) and the prevention of osteoporosis.

Estradiol and estrone are interconvertible, and estriol is the predominant urinary end product of estrogen metabolism. Estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor. Estrone and estradiol both circulate predominantly in the conjugated (primarily sulfated) form. Unconjugated estrone represents only 5-10% of total endogenous plasma estrone in pre-and postmenopausal women. Estrone sulfate is biologically inactive and serves as a reservoir for formation of estrone. Unconjugated estradiol represents about 43% of total endogenous estradiol. The oral route leads to a predominance of estrone over estradiol. As a result of massive estradiol first-pass metabolism, ratios of estrone (unconjugated) to estradiol (unconjugated) are the same regardless of whether estrone sulfate, micronized estradiol or the ester estradiol valerate is dosed. The result is an overall increase in plasma estrogen levels, although the estradiol/estrone ratio is less than unity and not restored to the desired premenopausal range. Estrogens are distributed throughout most body tissues with the greatest concentrations of estrogens may occur in the fat deposits of the body. Estrogens are 50-80% bound to plasma proteins. Estriol is bound less to plasma proteins than is estrone or estradiol but all 3 estrogens are bound to approximately the same extent by erythrocytes. Conjugation of estrogens increases water solubility and facilitates excretion in urine. Large amounts of free estrogens are also distributed into the bile, reabsorbed from the GI tract, and recirculated through the liver where further degradation occurs. Estrogens and their metabolites are excreted mainly in urine.

For the management of moderate to severe vasomotor symptoms associated with menopause, the usual initial oral dosage of estradiol is 1 or 2 mg daily in a cyclic regimen. Subsequent dosage should be adjusted according to the patient's therapeutic response, using the lowest possible effective maintenance dosage.

Adverse reactions associated with estrogen therapy include nausea, changes in appetite and in weight, elevated blood pressure, fluid retention and edema, breakthrough bleeding, mental depression, dizziness and headache.

Estradiol is available commercially as Estrace®, 0.5 mg, 1 mg and 2 mg, manufactured by Bristol Myers Squibb.

Objective:

To determine the relative bioavailability of 2 mg estradiol tablets after administration of single doses to healthy female subjects under fasted and conditions.

Study Design:

The clinical study (#EP413) was conducted at
in under the supervision of

Forty healthy, post-menopausal or surgically castrated, non-smoking female volunteers between the ages of 21-65 years and within 15% of ideal body weight for height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination and clinical laboratory tests [hematology, serum chemistry and urinalysis].

Subject inclusion criteria:

- absence of menses for at least 1 year (physiological) or 6 weeks (surgical)
- 17β-estradiol serum levels <20 pg/ml
- FSH serum levels >50 mUI/ml
- pelvic exam consistent with hypoestrogenism

Those with any of the following conditions were excluded:

History of:

- significant cardiovascular, hepatic, renal, CNS hematological or GI disease
- alcoholism or drug abuse within the last year
- thrombotic disorders
- coronary artery disease or cerebrovascular disease

- clinically significant gallbladder disorders or breast nodules on mammography
- diabetes or other endocrine disorder
- estrogen dependant neoplasia
- postmenopausal uterine bleeding or endometrial hyperplasia

Rx and OTC medications (including vitamins) were not allowed within 14 days of the first drug administration and throughout the study. There was to be no alcohol or xanthine-containing beverage and food consumption at least 72 hours prior to each drug administration until 72 hours post-dose.

Antibiotics and estrogens or other hormones (including progestins) were prohibited for at least 28 days prior to study start.

The study was designed as a randomized, open-label, two-way crossover study with a 14 day washout period between dosings. Treatments consisted of a single 2 mg dose of the following:

A. Estradiol
2 mg tablet, batch # 6R88701
Barr Laboratories, Inc.
mfg date: January 26, 1996

B. Estrace®
2 mg tablet, batch # MFJ26
Bristol-Myers Squibb
expiry date: July, 1, 1998

Twenty-eight subjects were dosed according to the following schedule:

	Period I 02/17/96	Period II 03/02/96
sequence I	A	B
sequence II	B	A

sequence I - subj. #2, 4, 5, 8, 11, 12, 13, 16, 18, 19, 22, 24, 26, 27, 31, 32, 34, 35, 37, 39
sequence II - subj. #1, 3, 6, 7, 9, 10, 14, 15, 17, 20, 21, 23, 25, 28, 29, 30, 33, 36, 38, 40

After an overnight fast, subjects were given a 2 mg dose of estradiol with 240 ml of water. Fasting continued for 4 hours post-dose. Blood samples (10 ml) were drawn in Vacutainers containing sodium heparin at -48, -24, within 1 hr before dosing (pre-dose), 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 14, 16, 24, 32, 40, 48, 60 and 72 hours. Samples were cooled in an ice bath and cold centrifuged soon after collection. Plasma samples were then stored at -70°C, pending shipment to the analytical lab. All blood draws were taken within 5% of scheduled times, except for one subject (#20, per II, test.

53 minutes late at 10.5 hr sampling). Her actual sampling time was used in AUC calculations.

Four subjects reported 5 adverse events that was possibly drug related and mild in severity. None required medication. The adverse events summary is attached.

Several deviations from protocol with respect to meals were reported. None were judged likely to affect bioavailability comparisons.

Analytical: [Not for release under FOI]

Data Analysis:

It was noted that the original data analysis was performed on datasets where AUC values were incorrectly calculated due to an error in data entry of one sampling time (10.5 hr). Although the ultimate difference in AUC values were small, the sponsor requested the statitician to correct all errors in the AUC calculations and redo the statistics (amendment submitted Oct. 4, 1996).

Data was analyzed by the GLM procedure of SAS to determine statistically signficant ($p<0.05$) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters and plasma level concentrations at each sampling time. All of the original forty subjects enrolled in the study completed the crossover; forty datasets were analyzed.

*Thirty-one subjects reached C_{max} at the first sampling time for total estrone. Their data was eliminated in the statistical analyses; Nine datasets were used in the analysis for C_{max} for total estrone.

Results:

No statistically significant differences or sequence effects were found in any of the pharmacokinetic indices, neither on the original nor on the ln-transformed scale for any of the three measured moieties (baseline corrected data). There was approximate 1% difference between the test and reference formulations for plasma levels of estradiol in AUC_{0-t} and AUC_{inf}.; there was no difference in plasma levels for C_{max}. For free estrone there was no difference in plasma levels for AUC_{0-t} and AUC_{inf} and a 2.2% difference in C_{max}. For total estrone there was a 1% difference in plasma levels for AUC_{0-t} and AUC_{inf} (40 subj.) and a 6% difference in C_{max} (9 subj.). The 90% shortest confidence intervals are presented below:

		90% CI (n=40)	
original scale	AUC_{0-t}	[93.9; 103]	***estradiol***
	AUC_{inf}	[93.8; 104]	
	C_{max}	[87.3; 113]	
ln-transformed scale	AUC_{0-t}	[93.8; 105]	
	AUC_{inf}	[93.1; 105]	
	C_{max}	[93.2; 110]	
original scale	AUC_{0-t}	[95.4; 105]	***free estrone***
	AUC_{inf}	[95.2; 106]	
	C_{max}	[92.3; 103]	
ln-transformed scale	AUC_{0-t}	[95.3; 105]	
	AUC_{inf}	[94.9; 105]	
	C_{max}	[91.6; 103]	
original scale	AUC_{0-t}	[96.8; 105]	***total estrone***
	AUC_{inf}	[96.7; 105]	
	C_{max} (n=9)	[94.7; 118]	
ln-transformed scale	AUC_{0-t}	[96.9; 104]	
	AUC_{inf}	[96.6; 104]	
	C_{max} (n=9)	[94.7; 118]	

Mean plasma level data and pharmacokinetic summaries are attached.

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study using the current USP method. The results are acceptable and the resultant summaries are attached.

Content Uniformity:

The assay for content uniformity for 10 dosage units of the Barr product was 99.0% of label claim; range = (0.9% CV). For the innovator product the CU assay was 100.1% of label claim; range = (2.6% CV).

Batch Size:

The batch size for the bio-batch of Barr's 2 mg estradiol tablet was not given.

Waiver Request:

The sponsor has submitted dissolution data comparing their 1 mg and 0.5 mg estradiol tablets vs the like strengths of Estrace® tablet and formulation comparisons of their 2 mg, 1 mg and 0.5 mg tablet in support of waiver requests.

Comment:

1. The company did not submit the sample, standard and QC preparation and processing procedure. The company should submit the complete analytical methodology to include all aspects of sample handling and processing, not just the description.

2. The company did not submit in-process stability data. The company should submit in-process stability data for estradiol, free estrone and total estrone.

3. Recovery data was not submitted for total estrone. The sponsor should submit the data.

   The sponsor should also explain their method of calculating recovery. Generally, the Division of Bioequivalence views recovery as the response (amount) of the unextracted moiety vs the response of the extracted moiety. The sponsor should comment on the purpose of the 'nominal concentrations' used as a reference in the recovery calculations. Both values (nominal and 'found') are values from extracted samples. The sponsor should also submit the SOP for the recovery procedure.

4. The company should state the batch size of the test bio-batch used in this study.

5. The company should supply the analytical methodology used in the dissolution testing.

Recommendation:

1. The bioequivalence study conducted by for Barr Laboratories, Inc. on its estradiol 2 mg tablet, batch #6R88701, comparing it to Estrace®

2 mg tablet has been found incomplete per comments #1 - 5.

All comments should be transmitted to the company.

12/12/96

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

Concur: _____ Date: 12/12/96

Rabi Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

JLee/jl/11-26-96

cc: NDA #40-197 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

USP XXIII Apparatus II Basket ____ Paddle X rpm 100

Medium: 0.3% Sodium Dodecyl (lauryl) Sulfate in H_2O @ 37°C Volume: 500 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Estrace® tablet USP METHOD

Assay Methodology: not given

2 mg tablet

Results

Time (min)	Test Product Lot # 6R88701 Mean % Dissolved	Range	(CV)	Reference Product Lot # MFJ26 Mean % Dissolved	Range	(CV)
15	81		(3.9)	74		(9.9)
30	92		(2.5)	88		(2.6)
45	94		(2.1)	94		(1.3)
60	95		(2.0)	96		(1.4)
			( )			( )
			( )			( )

1 mg tablet

	Lot # 6R88604			Lot # H5G09A		
15	92		(3.1)	92		(1.7)
30	98		(2.0)	98		(1.1)
45	100		(2.0)	100		(1.4)
60	101		(1.6)	100		(1.4)
			( )			( )
Q = NLT		IN 60 MINUTES	( )			( )

USP XXIII Apparatus II Basket ____ Paddle X rpm 100

Medium: 0.3% Sodium Dodecyl (lauryl) Sulfate in H_20 @ 37°C Volume: 500 ml

Number of Tabs/Caps Tested: 12

USP METHOD

Reference Drug: Estrace® tablet

Assay Methodology: not given

0.5 mg tablet

Results

Time (min)	Test Product Lot # 6R89903 Mean % Dissolved	Range	(CV)	Reference Product Lot # MEJ04 Mean % Dissolved	Range	(CV)
15	91		(3.7)	87		(1.9)
30	96		(2.9)	93		(1.3)
45	97		(2.7)	95		(1.3)
60	98		(2.5)	96		(1.3)
			( )			( )
			( )			( )

	Lot #			Lot #		
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )

ESTRADIOL FASTING STUDY
BARR EP413
ESTRADIOL DATA
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	1522.170	1542.892	98.7
AUCINF	1661.840	1677.011	99.1
CMAX	59.97825	59.96692	100
TMAX	8.200000	8.887500	92.3
KELM	0.043479	0.040307	108
THALF	17.37869	18.48212	94.0
AUCT_UC	1693.806	1705.716	99.3
CMAX_UC	62.37000	62.23250	100

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(93.9; 103)	0.99999	0.6377
AUCINF	(93.8; 104)	0.99994	0.7767
CMAX	(87.3; 113)	0.73053	0.9980
TMAX	(81.0; 104)	0.83144	0.2537
KELM	(98.9; 117)	0.95619	0.1454
THALF	(86.8; 101)	0.99446	0.1691
AUCT_UC	(95.6; 103)	>0.99999	0.7530
CMAX_UC	(88.1; 112)	0.77239	0.9757

Units AUC = (pg/ml) x hr
Cmax = (pg/ml)
Tmax = hr

ESTRADIOL FASTING STUDY
BARR EP413
ESTRADIOL DATA
SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	7.239098	7.247847	1392.84	1405.08
AUCINF	7.318261	7.327855	1507.58	1522.11
CMAX	3.992502	3.979434	54.19	53.49
AUCT_UC	7.362826	7.367840	1576.28	1584.21
CMAX_UC	4.039306	4.027915	56.79	56.14

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	99.1	(93.8; 105)	0.99987	0.7923
AUCINF	99.0	(93.1; 105)	0.99927	0.7950
CMAX	101	(93.2; 110)	0.97565	0.7922
AUCT_UC	99.5	(95.9; 103)	>0.99999	0.8179
CMAX_UC	101	(93.8; 109)	0.99009	0.8010

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

ESTRADIOL FASTING STUDY
BARR EP413
FREE ESTRONE DATA
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	9408.050	9382.195	100
AUCINF	9878.580	9841.837	100
CMAX	462.8432	473.2413	97.8
TMAX	6.922500	6.112500	113
KELM	0.052573	0.049722	106
THALF	13.95261	14.90544	93.6
AUCT_UC	10758.10	10778.02	99.8
CMAX_UC	481.6000	492.7750	97.7

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(95.4; 105)	0.99999	0.9244
AUCINF	(95.2; 106)	0.99997	0.9034
CMAX	(92.3; 103)	0.99988	0.5087
TMAX	(99.6; 127)	0.67175	0.1096
KELM	(99.6; 112)	0.99936	0.1231
THALF	(86.7; 100)	0.99666	0.1261
AUCT_UC	(95.7; 104)	>0.99999	0.9406
CMAX_UC	(92.4; 103)	0.99994	0.4775

Units AUC = (pg/ml) × hr
C_{max} = pg/ml
T_{max} = hr

ESTRADIOL FASTING STUDY
BARR EP413
FREE ESTRONE DATA
SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	9.057410	9.053599	8581.89	8549.25
AUCINF	9.098593	9.098428	8942.70	8941.22
CMAX	6.078226	6.106146	436.25	448.61
AUCT_UC	9.212280	9.218438	10019.42	10081.31
CMAX_UC	6.122832	6.151918	456.15	469.62

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	100	(95.3; 106)	0.99996	0.9028
AUCINF	100	(94.9; 105)	0.99995	0.9958
CMAX	97.2	(91.6; 103)	0.99958	0.4353
AUCT_UC	99.4	(95.3; 104)	>0.99999	0.8059
CMAX_UC	97.1	(91.7; 103)	0.99979	0.3967

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

ESTRADIOL FASTING STUDY
BARR EP413
- TOTAL ESTRONE DATA
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	444.7228	440.4814	101
AUCINF	463.0217	458.7334	101
CMAX	37.69008	39.70262	94.9
TMAX	2.737500	2.662500	103
KELM	0.044055	0.046102	95.6
THALF	17.27343	16.90532	102
AUCT_UC	450.9852	447.1217	101
CMAX_UC	37.77750	39.79500	94.9

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(96.8; 105)	>0.99999	0.6954
AUCINF	(96.7; 105)	>0.99999	0.7108
CMAX	(88.8; 101)	0.99942	0.1685
TMAX	(84.3; 121)	0.41975	0.7990
KELM	(90.9; 100)	>0.99999	0.1184
THALF	(95.0; 109)	0.99432	0.6130
AUCT_UC	(96.9; 105)	>0.99999	0.7175
CMAX_UC	(88.9; 101)	0.99947	0.1664

Units AUC = (ng/ml) x hr
Cmax = ng/ml
Tmax = hr

ESTRADIOL FASTING STUDY
BARR EP413
TOTAL ESTRONE DATA
SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	6.027507	6.022821	414.680	412.741
AUCINF	6.065705	6.063089	430.826	429.701
CMAX	3.587773	3.642928	36.153	38.204
AUCT_UC	6.038020	6.033334	419.062	417.103
CMAX_UC	3.589955	3.645007	36.232	38.283

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	100	(96.9; 104)	>0.99999	0.8296
AUCINF	100	(96.6; 104)	>0.99999	0.9064
CMAX	94.6	(88.9; 101)	0.99913	0.1451
AUCT_UC	100	(96.9; 104)	>0.99999	0.8264
CMAX_UC	94.6	(88.9; 101)	0.99921	0.1434

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

ESTADIOL TABLET FASTING STUDY
BARR EP413
ESTRADIOL DATA
ARITHMETIC MEANS BY PRODUCT
BASELINE CORRECTED

PRODUCT=A:TEST

pg/ml

Variable	Label	N	Mean	Std Dev	CV
AUCTLQC		40	1522.170	608.174	39.954
AUCINF		40	1661.840	713.249	42.919
CMAX		40	59.978	33.181	55.322
TMAX		40	8.200	4.000	48.777
KELM		40	0.043	0.014	31.447
THALF		40	17.379	5.020	28.888
LAUCTLQC		40	7.239	0.451	6.234
LAUCINF		40	7.318	0.470	6.425
LCMAX		40	3.993	0.432	10.813
BASELINE		40	2.392	2.186	91.389
C3	0.00 HR	40	0.245	0.561	229.136
C4	1.50 HR	40	22.302	14.179	63.578
C5	3.00 HR	40	28.216	11.278	39.972
C6	4.50 HR	40	37.671	13.583	36.058
C7	6.00 HR	40	47.738	21.664	45.381
C8	7.50 HR	40	46.908	16.755	35.718
C9	9.00 HR	40	44.933	16.443	36.594
C10	10.5 HR	40	47.108	20.653	43.842
C11	12.0 HR	40	43.706	16.008	36.626
C12	14.0 HR	40	40.041	13.996	34.954
C13	16.0 HR	40	43.634	31.828	72.945
C14	24.0 HR	40	28.412	12.023	42.319
C15	32.0 HR	40	20.335	10.376	51.024
C16	40.0 HR	40	15.192	9.017	59.353
C17	48.0 HR	40	10.698	6.777	63.344
C18	60.0 HR	40	7.668	5.975	77.923
C19	72.0 HR	40	4.408	4.046	91.789

ESTADIOL TABLET FASTING STUDY
BARR EP413
ESTRADIOL DATA
ARITHMETIC MEANS BY PRODUCT
BASELINE CORRECTED

PRODUCT=B:REFERENCE

pg/ml

Variable	Label	N	Mean	Std Dev	CV
AUCTLQC		40	1542.892	617.657	40.032
AUCINF		40	1677.011	692.030	41.266
CMAX		40	59.967	32.561	54.298
TMAX		40	8.888	4.192	47.164
KELM		40	0.040	0.011	27.506
THALF		40	18.482	5.217	28.226
LAUCTLQC		40	7.248	0.465	6.420
LAUCINF		40	7.328	0.471	6.425
LCMAX		40	3.979	0.471	11.847
BASELINE		40	2.266	2.280	100.643
C3	0.00 HR	40	0.270	0.585	216.550
C4	1.50 HR	40	23.713	12.338	52.032
C5	3.00 HR	40	30.654	13.006	42.427
C6	4.50 HR	40	38.059	16.483	43.308
C7	6.00 HR	40	51.477	29.558	57.420
C8	7.50 HR	40	48.509	28.386	58.516
C9	9.00 HR	40	46.282	22.067	47.680
C10	10.5 HR	40	47.139	24.391	51.742
C11	12.0 HR	40	47.239	23.938	50.673
C12	14.0 HR	40	41.409	17.393	42.002
C13	16.0 HR	40	39.099	16.305	41.702
C14	24.0 HR	40	28.959	13.446	46.430
C15	32.0 HR	40	20.594	9.888	48.014
C16	40.0 HR	40	15.092	7.557	50.072
C17	48.0 HR	40	10.826	6.010	55.516
C18	60.0 HR	40	8.444	6.050	71.646
C19	72.0 HR	40	4.457	3.097	69.476

ESTADIOL TABLET FASTING STUDY
BARR EP413
FREE ESTRONE DATA
ARITHMETIC MEANS BY PRODUCT
BASELINE CORRECTED

PRODUCT=A:TEST

pg/ml

Variable	Label	N	Mean	Std Dev	CV
AUCTLQC		40	9408.050	4024.536	42.778
AUCINF		40	9878.580	4515.161	45.707
CMAX		40	462.843	158.880	34.327
TMAX		40	6.923	2.574	37.181
KELM		40	0.053	0.012	23.443
THALF		40	13.953	3.527	25.279
LAUCTLQC		40	9.057	0.449	4.959
LAUCINF		40	9.099	0.463	5.092
LCMAX		40	6.078	0.353	5.813
BASELINE		40	18.757	6.383	34.030
C3	0.00 HR	40	1.644	3.382	205.738
C4	1.50 HR	40	141.443	68.721	48.585
C5	3.00 HR	40	298.318	122.695	41.129
C6	4.50 HR	40	419.243	154.356	36.818
C7	6.00 HR	40	406.418	151.383	37.248
C8	7.50 HR	40	359.043	125.893	35.064
C9	9.00 HR	40	363.543	132.773	36.522
C10	10.5 HR	40	350.558	142.595	40.677
C11	12.0 HR	40	308.151	122.310	39.692
C12	14.0 HR	40	266.043	115.012	43.231
C13	16.0 HR	40	240.051	108.389	45.153
C14	24.0 HR	40	158.403	87.854	55.462
C15	32.0 HR	40	103.276	63.332	61.323
C16	40.0 HR	40	72.081	51.347	71.235
C17	48.0 HR	40	50.493	37.595	74.456
C18	60.0 HR	40	28.083	27.461	97.786
C19	72.0 HR	40	19.311	20.153	104.359

ESTADIOL TABLET FASTING STUDY
BARR EP413
FREE ESTRONE DATA
ARITHMETIC MEANS BY PRODUCT
BASELINE CORRECTED

PRODUCT=B:REFERENCE

pg/ml

Variable	Label	N	Mean	Std Dev	CV
AUCTLQC		40	9382.195	3774.702	40.233
AUCINF		40	9841.837	4090.502	41.562
CMAX		40	473.241	156.517	33.073
TMAX		40	6.113	2.132	34.877
KELM		40	0.050	0.013	25.613
THALF		40	14.905	4.121	27.646
LAUCTLQC		40	9.054	0.461	5.097
LAUCINF		40	9.098	0.466	5.117
LCMAX		40	6.106	0.335	5.481
BASELINE		40	19.534	10.019	51.291
C3	0.00 HR	40	1.755	2.793	159.156
C4	1.50 HR	40	165.476	81.686	49.364
C5	3.00 HR	40	304.474	113.692	37.341
C6	4.50 HR	40	430.091	147.477	34.290
C7	6.00 HR	40	417.566	161.357	38.642
C8	7.50 HR	40	376.341	133.596	35.499
C9	9.00 HR	40	360.366	130.045	36.087
C10	10.5 HR	40	347.341	130.265	37.503
C11	12.0 HR	40	303.506	129.306	42.604
C12	14.0 HR	40	259.431	111.999	43.171
C13	16.0 HR	40	237.421	100.111	42.166
C14	24.0 HR	40	152.440	79.186	51.946
C15	32.0 HR	40	101.484	58.882	58.021
C16	40.0 HR	40	69.251	42.014	60.669
C17	48.0 HR	40	48.895	32.345	66.152
C18	60.0 HR	40	30.182	26.595	88.114
C19	72.0 HR	40	18.165	15.638	86.090

ESTADIOL TABLET FASTING STUDY
BARR EP413
TOTAL ESTRONE DATA
ARITHMETIC MEANS BY PRODUCT
BASELINE CORRECTED

PRODUCT=A:TEST

ng/ml

Variable	Label	N	Mean	Std Dev	CV
AUCTLQC		40	444.723	189.412	42.591
AUCINF		40	463.022	204.061	44.072
CMAX		40	37.690	10.599	28.122
TMAX		40	2.738	1.515	55.336
KELM		40	0.044	0.013	29.006
THALF		40	17.273	5.907	34.195
LAUCTLQC		40	6.028	0.362	6.003
LAUCINF		40	6.066	0.364	6.002
LCMAX		40	3.588	0.299	8.330
BASELINE		40	0.087	0.163	186.769
C3	0.00 HR	40	0.016	0.049	312.523
C4	1.50 HR	40	32.470	10.687	32.913
C5	3.00 HR	40	28.108	9.756	34.710
C6	4.50 HR	40	30.068	10.763	35.797
C7	6.00 HR	40	21.846	7.012	32.096
C8	7.50 HR	40	17.966	6.653	37.030
C9	9.00 HR	40	16.368	6.595	40.291
C10	10.5 HR	40	15.074	6.841	45.382
C11	12.0 HR	40	12.084	5.918	48.971
C12	14.0 HR	40	9.880	5.210	52.731
C13	16.0 HR	40	8.395	4.831	57.548
C14	24.0 HR	40	5.588	3.837	68.666
C15	32.0 HR	40	3.329	2.666	80.080
C16	40.0 HR	40	2.143	1.812	84.543
C17	48.0 HR	40	1.661	1.602	96.409
C18	60.0 HR	40	0.854	0.799	93.613
C19	72.0 HR	40	0.648	0.703	108.463

ESTADIOL TABLET FASTING STUDY
BARR EP413
TOTAL ESTRONE DATA
ARITHMETIC MEANS BY PRODUCT
BASELINE CORRECTED

PRODUCT=B:REFERENCE

pg/ml

Variable	Label	N	Mean	Std Dev	CV
AUCTLQC		40	440.481	171.757	38.993
AUCINF		40	458.733	181.710	39.611
CMAX		40	39.703	10.885	27.418
TMAX		40	2.663	1.461	54.856
KELM		40	0.046	0.014	31.045
THALF		40	16.905	7.214	42.674
LAUCTLQC		40	6.023	0.357	5.926
LAUCINF		40	6.063	0.356	5.868
LCMAX		40	3.643	0.286	7.856
BASELINE		40	0.092	0.207	223.861
C3	0.00 HR	40	0.042	0.177	419.154
C4	1.50 HR	40	35.683	13.216	37.037
C5	3.00 HR	40	26.053	8.201	31.477
C6	4.50 HR	40	31.858	10.597	33.265
C7	6.00 HR	40	21.858	8.268	37.825
C8	7.50 HR	40	18.294	7.708	42.131
C9	9.00 HR	40	16.368	6.983	42.662
C10	10.5 HR	40	14.655	7.254	49.499
C11	12.0 HR	40	11.771	5.834	49.563
C12	14.0 HR	40	9.680	5.376	55.535
C13	16.0 HR	40	8.067	4.388	54.398
C14	24.0 HR	40	5.532	3.139	56.746
C15	32.0 HR	40	3.175	2.097	66.031
C16	40.0 HR	40	1.943	1.235	63.578
C17	48.0 HR	40	1.476	1.024	69.385
C18	60.0 HR	40	0.822	0.746	90.667
C19	72.0 HR	40	0.592	0.544	91.813

ESTRADIOL FASTING STUDY
BARR EP413
TOTAL ESTRONE DATA
DATA FROM SUBJECTS WITH TMAX LATER THAN 1.5 HOURS
SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

n= 9

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	6.171476	6.107385	478.893	449.162
AUCINF	6.215341	6.148392	500.366	467.964
CMAX	3.626994	3.569742	37.600	35.507
AUCT_UC	6.185008	6.124535	485.417	456.932
CMAX_UC	3.629582	3.573562	37.697	35.643

n=9

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	107	(97.1; 117)	0.93423	0.2332
AUCINF	107	(98.6; 116)	0.97243	0.1625
CMAX	106	(94.7; 118)	0.83093	0.3638
AUCT_UC	106	(96.6; 117)	0.92456	0.2682
CMAX_UC	106	(94.7; 118)	0.83955	0.3683

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

ESTRADIOL FASTING STUDY
BARR EP413
TOTAL ESTRONE DATA
DATA FROM SUBJECTS WITH TMAX LATER THAN 1.5 HOURS
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

	TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
	AUCTLQC	507.8873	485.2514	105
	AUCINF	530.4162	505.4109	105
n=9	CMAX	38.86106	36.54225	106
	TMAX	4.375	4.375	100
	KELM	0.041913	0.048351	86.7
	THALF	18.7556	15.97583	117
	AUCT_UC	515.9093	495.995	104
	CMAX_UC	38.975	36.69167	106

	TITLE	90% CI	POWER OF ANOVA	P VALUE
	AUCTLQC	(98.8; 111)	0.99766	0.1764
	AUCINF	(99.7; 110)	0.99907	0.1174
n=9	CMAX	(94.7; 118)	0.80088	0.3348
	TMAX	(87.7; 112)	0.75317	1.0000
	KELM	(72.5; 101)	0.61737	0.1181
	THALF	(97.9; 137)	0.34455	0.1340
	AUCT_UC	(98.3; 110)	0.99812	0.2254
	CMAX_UC	(94.8; 118)	0.81496	0.3356

TABLE C1
SUBJECT DEMOGRAPHICS AND RANDOMIZATION SCHEME

Subject No.	Formulation Code*		At Screening			Frame
	Period		Age (yrs)	Height (cm)	Weight (kg)	
	1	2				
1	B	A	54	162	62.3	Medium
2	A	B	56	155	63.3	Large
3	B	A	61	157	67.7	Medium
4	A	B	59	155	63.4	Medium
5	A	B	64	158	45.1	Medium
6	B	A	65	152	56.6	Medium
7	B	A	55	171	69.0	Small
8	A	B	51	159	55.5	Medium
9	B	A	55	164	72.6	Medium
10	B	A	63	162	67.2	Medium
11	A	B	60	163	55.4	Medium
12	A	B	53	158	63.7	Medium
13	A	B	64	153	65.9	Medium
14	B	A	55	148	61.5	Medium
15	B	A	47	157	64.8	Large
16	A	B	54	157	70.0	Large
17	B	A	58	167	73.4	Medium
18	A	B	52	166	71.5	Medium
19	A	B	58	156	52.3	Medium
20	B	A	57	165	65.9	Medium
21	B	A	61	159	76.0	Large
22	A	B	56	164	78.2	Large
23	B	A	57	154	70.2	Large

All subjects were caucasian.

* A: 1 x 2 mg Barr 17-β-estradiol tablets
B: 1 x 2 mg Bristol-Myers Squibb (Estrace®) 17-β-estradiol tablets

TABLE C1
SUBJECT DEMOGRAPHICS AND RANDOMIZATION SCHEME

Subject No.	Formulation Code*		At Screening			Frame
	Period		Age (yrs)	Height (cm)	Weight (kg)	
	1	2				
24	A	B	60	162	66.3	Medium
25	B	A	47	162	68.6	Medium
26	A	B	51	158	54.6	Small
27	A	B	63	160	58.0	Medium
28	B	A	57	160	72.0	Large
29	B	A	52	159	63.4	Small
30	B	A	61	160	64.5	Medium
31	A	B	55	159	63.0	Medium
32	A	B	63	146	59.9	Medium
33	B	A	47	160	67.0	Medium
34	A	B	53	163	66.7	Medium
35	A	B	53	169	58.5	Large
36	B	A	56	160	63.3	Medium
37	A	B	60	155	67.0	Medium
38	B	A	65	161	76.7	Large
39	A	B	54	154	57.9	Medium
40	B	A	60	147	55.5	Medium
	n		40	40	40	
	Mean		57	159	64.4	
	C.V.%		8.6	3.4	11.00	

All subjects were caucasian.

* A: 1 x 2 mg Barr 17-β-estradiol tablets
B: 1 x 2 mg Bristol-Myers Squibb (Estrace®) 17-β-estradiol tablets

TABLE C2
CLINICAL COMPLAINTS

Subject No.	Period/ Treatment*	Complaint	Onset**	Relationship
4	1/A	Difficulty digesting	02:15:24	Remote
23	1/B	Hot flash	01:09:06	Possible
23	1/B	Weakness	00:10:16	Possible
32	1/A	Headache	02:20:28	Possible
17	2/A	Rash	00:23:28	Possible

* A: 1 x 2 mg Barr 17-β-estradiol tablets
B: 1 x 2 mg Bristol-Myers Squibb (Estrace®) 17-β-estradiol tablets

** Days:hours:minutes after last dose

Following is a full statement of the composition of the dosage formulation:

Estradiol Tablets, USP

Ingredients	0.5 mg/Dose	1 mg/Dose	2 mg/Dose
Estradiol, USP	0.5(A)	1(A)	2(A)
Lactose Monohydrate, NF			
Lactose Monohydrate, NF			
Sodium Starch Glycolate, NF			
FD&C Blue #1			
D&C Red #27			
FD&C Yellow #5			
Starch, NF			
Dibasic Calcium Phosphate, USP			
Magnesium Stearate, NF			
Colloidal Silicon Dioxide, NF			
Total Tablet Weight (mg)	100.00	100.00	100.00

(A) Actual weight adjusted according to the assay value (as is basis).

(B) To be adjusted for total weight.