CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-312

Approval Letter

ANDA 40-312

NOV 19 '99

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
100 Overlook Center, Suite 200
Princeton, NJ 08540-7810

Dear Sir:

This is in reference to your abbreviated new drug application dated April 30, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Innofem® Tablets (Estradiol Tablets, USP), 0.5 mg, 1 mg, and 2 mg.

Reference is also made to your amendments dated November 17 and December 22, 1998; and April 27, May 12, May 28, June 1, August 12, August 19, August 25, September 21, October 22, November 3, and November 5, 1999.

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 Innofem® Tablets (Estradiol Tablets, USP), 0.5 mg, 1 mg, and 2 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Estrace® Tablets, 0.5 mg, 1mg, and 2 mg, respectively, of Bristol Myers Squibb Co. Pharmaceutical Research Institute). 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 and 314.98. 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-40). 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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 11/19/99

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

(Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

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

cc: ANDA 40-312

Endorsements:

.ap

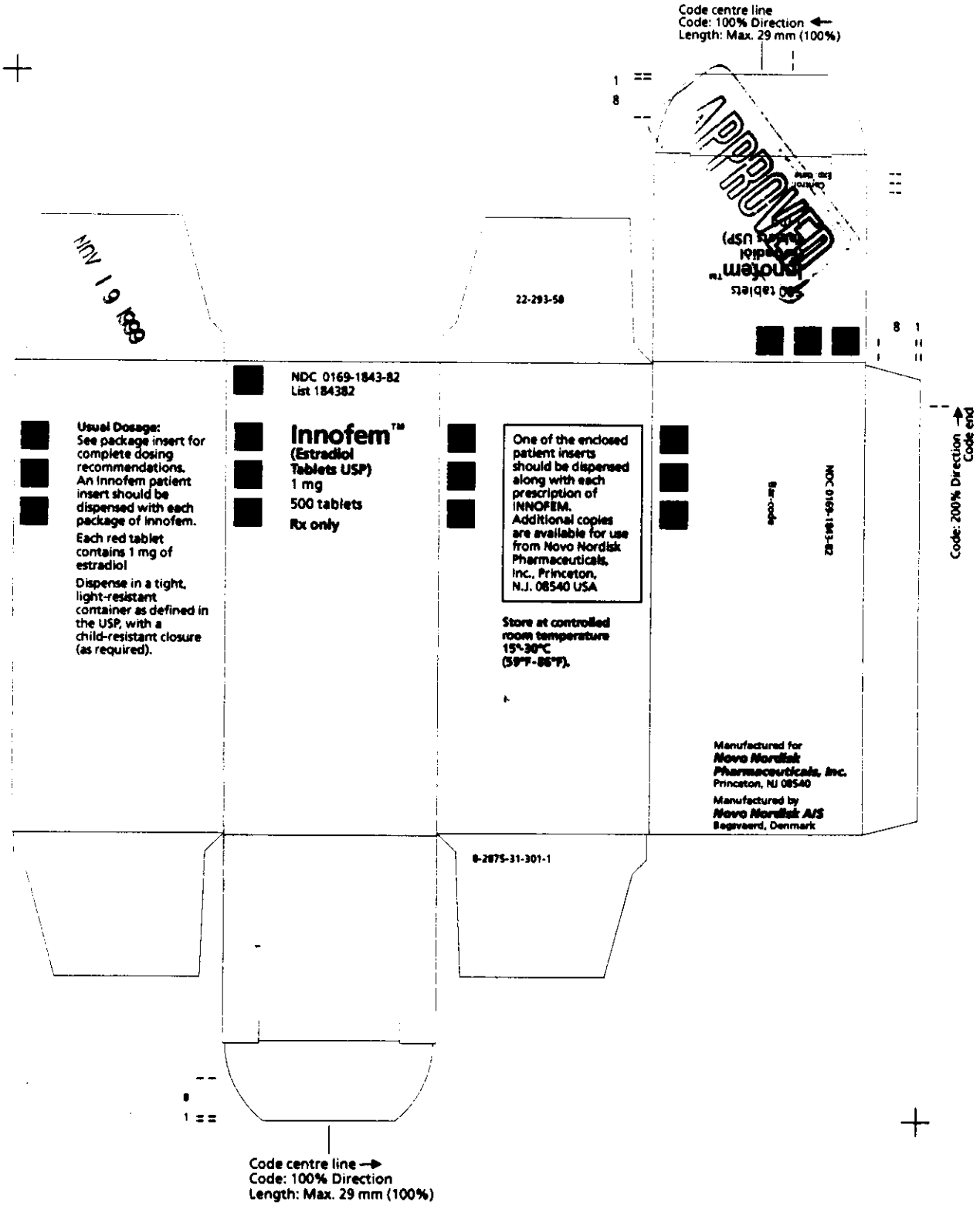
APPROVAL

Rec'd
11/5/99

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-312

FINAL PRINTED LABELING



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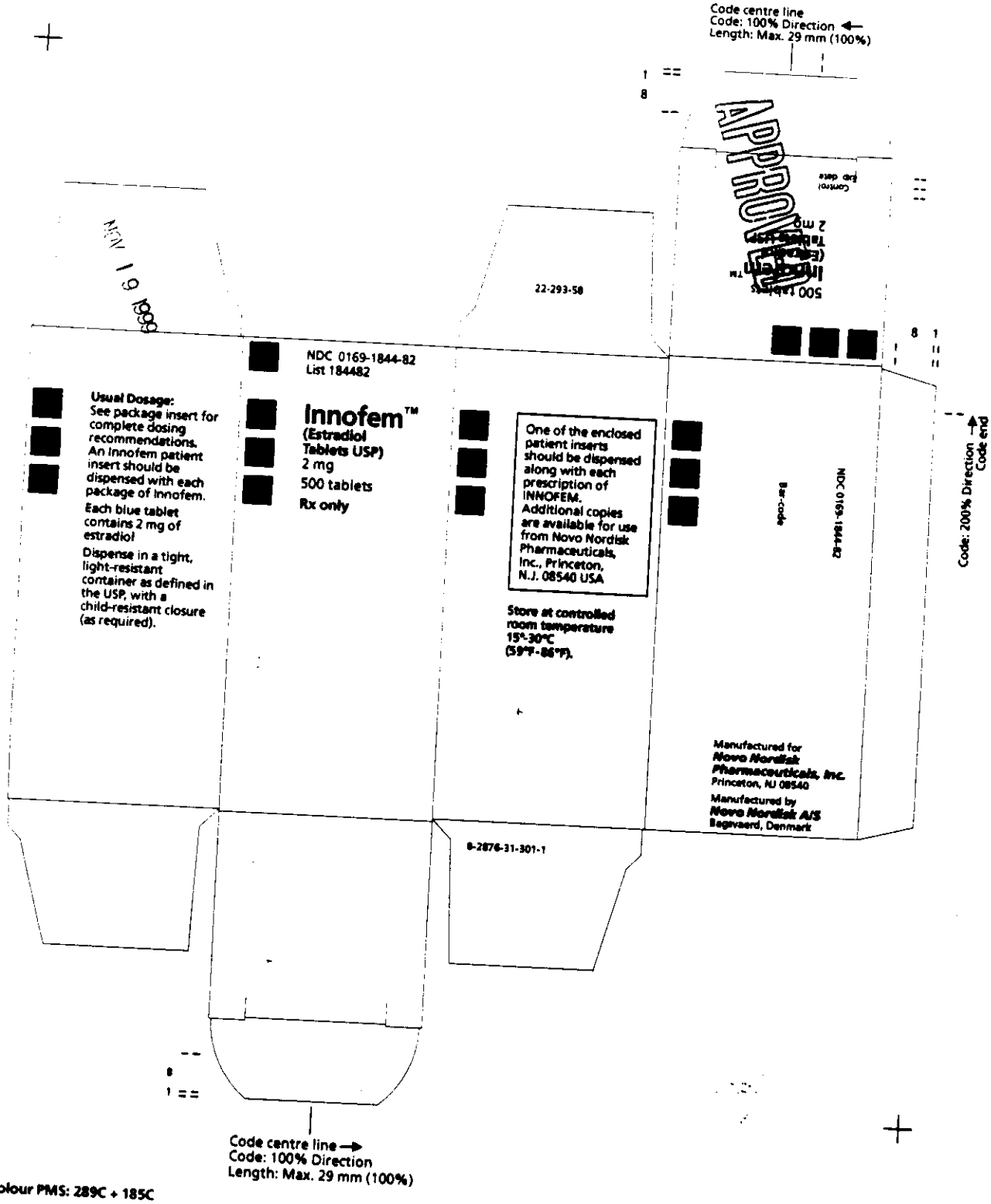
Edition: 09.97-3xx-1

50 ml

Property of:
Novo Nordisk A/S
PrePress Service Centre



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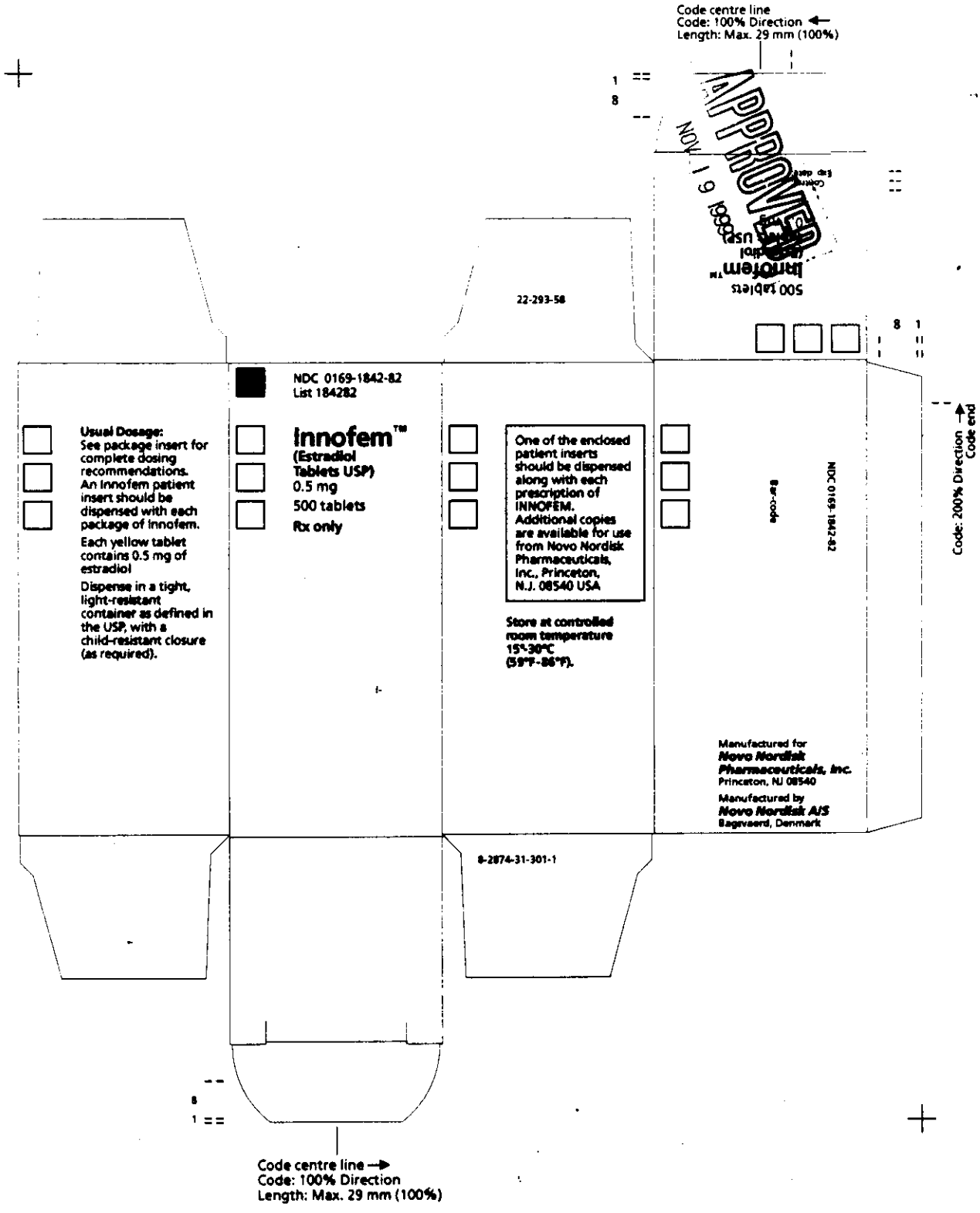

Colour PMS: 289C + Outline

Carton size: 22-293-58
Edition: 09.97-3xx-1

50 ml

Property of:
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PrePress Service Centre

Novo Nordisk

Rx only

Innofem™

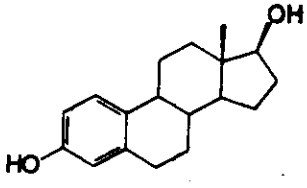
(Estradiol Tablets, USP)

WARNINGS

1. **ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.** Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.
2. **ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.** There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement. Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

DESCRIPTION

Innofem™ (Estradiol Tablets, USP) for oral administration contains 0.5, 1 or 2 mg of micronized estradiol per tablet. Estradiol (17β-estradiol) is a white, crystalline solid, chemically described as estra-1,3,5,(10)-triene-3, 17β-diol. It has a molecular formula of $C_{18}H_{24}O_2$ and molecular weight of 272.39. The structural formula is:



Innofem™, 0.5 mg, contains the following inactive ingredients: lactose monohydrate, starch (corn), gelatin, talc, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, yellow iron oxide and propylene glycol. Innofem™, 1 mg, contains the following inactive ingredients: lactose monohydrate, starch (corn), gelatin, talc, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, red iron oxide and propylene glycol. Innofem™, 2 mg, contains the following inactive ingredients: lactose monohydrate, starch (corn), gelatin, talc, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, indigo carmine and polyethylene glycol 400.

CLINICAL PHARMACOLOGY

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse throughout cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fats. Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. They also 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, and pigmentation of the nipples and genitalia.

Estrogens occur naturally in several forms. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estriol. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone - especially in its sulfate ester form - is the most abundant circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor. Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

Administered estrogens and their esters are handled within the body essentially the same as the endogenous hormones. Metabolic conversion of the estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms which are continually interconverted, especially between estrone and estradiol and between esterified and unesterified forms. Although naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin, only unbound estrogens enter target tissue cells. A significant proportion of the circulating estrogen exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogenic species. A certain proportion of the estrogen is excreted into the bile and then reabsorbed from the intestine. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine). When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. By contrast synthetic estrogens such as ethinyl estradiol and the nonsteroidal estrogens are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency.

Estrogen drug products administered by non-oral routes are not subject to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and enterohepatic recycling.

INDICATIONS AND USAGE

Innofem™ (Estradiol Tablets, USP) is indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. There is no adequate 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. Treatment of vulval and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).
6. Prevention of osteoporosis.

Since estrogen administration is associated with risk, selection of patients should ideally be based on prospective identification of risk factors for developing osteoporosis. Unfortunately, there is no certain way to identify those women who will develop osteoporotic fractures. Most prospective studies of efficacy for this indication have been carried out in white menopausal women, without stratification by other risk factors, and tend to show a universally salutary effect on bone. Thus, patient selection must be individualized based on the balance of risks and benefits. A more favorable risk/benefit ratio exists in a hysterectomized woman because she has no risk of endometrial cancer (see BOXED WARNING 1).

Estrogen replacement therapy reduces bone resorption and retards or halts post menopausal bone loss. Case-control studies have shown an approximately 60 percent reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen prevents further loss of bone mass for as long as the treatment is continued. The results of a two-year, randomized, placebo-controlled, double-blind, dose-ranging study have shown that treatment with 0.5 mg estradiol daily for 23 days (of a 28 day cycle) prevents vertebral bone mass loss in postmenopausal women. When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period. There is no evidence that estrogen replacement therapy restores bone mass to premenopausal levels.

At skeletal maturity there are sex and race differences in both the total amount of bone present and its density, in favor of men and blacks. Thus, women are at higher risk than men because they start with less bone mass and, for several years following natural or induced menopause, the rate of bone mass decline is accelerated. White and Asian women are at higher risk than blacks.

Early menopause is one of the strongest predictors for the development of osteoporosis. In addition, other factors affecting the skeleton which are associated with osteoporosis include genetic factors (small build, family history), and endocrine factors (nulliparity, thyrotoxicosis, hypogonadism/castration, Cushing's syndrome, hyperprolactinemia, Type I diabetes), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight, dietary calcium intake).

The mainstays of prevention and management of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. By comparison, premenopausal women require about 1000 mg/day and the average of calcium intake in the USA is 400-800 mg/day, therefore, when not contraindicated, calcium supplementation may be helpful.

Weight-bearing exercise and nutrition may be important adjuncts to the prevention and management of osteoporosis. Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown both to reduce bone loss and to increase bone mass. The optimal type and amount of physical activity that would prevent osteoporosis have not been established, however in two studies an hour of walking and running exercise twice or three times weekly significantly increased lumbar spine bone mass.

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy (see BOXED WARNING 2). Estrogens may cause fetal harm when administered to a pregnant woman.
2. Undiagnosed abnormal genital bleeding.
3. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
4. Known or suspected estrogen-dependent neoplasia.
5. Active thrombophlebitis or thromboembolic disorders.

WARNINGS

1. **Induction of malignant neoplasms.**

Endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use - with increased risks of 15 to 24-fold for five to ten years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study a significant decrease in the incidence of endometrial cancer occurred six months after estrogen withdrawal. Concurrent progestin therapy may offset this risk but the overall health impact on postmenopausal women is not know (see PRECAUTIONS).

Breast Cancer. While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3-2.0) in those taking higher dose or those taking lower doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.

Congenital lesions with malignant potential. Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who received DES during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

2. **Gallbladder disease.** Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens.
3. **Cardiovascular disease.** Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.
4. **Elevated blood pressure.** Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.
5. **Hypercalcemia.** 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

1. **Addition of a progestin.** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia which would otherwise be induced by estrogen treatment. Morphological and biochemical studies of endometrium suggest that 10-14 days of progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. There are, however, possible additional risks which may be associated with the inclusion of progestins in estrogen replacement regimens. These include: (1) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL) which may diminish the possible cardioprotective effect of estrogen therapy (see PRECAUTIONS); (2) impairment of glucose tolerance; and (3) possible enhancement of mitotic activity in breast epithelial tissue although few epidemiological data are available to address this point (see PRECAUTIONS). Indeed, The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues remain to be clarified.
2. **Cardiovascular risk.** A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known. In recent years many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy without added progestins and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed the statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports: (1) Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit. (2) Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see PRECAUTIONS and WARNINGS). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels. (3) While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see WARNINGS above). Because relatively long-term use of estrogens by a women with a uterus has been shown to induce endometrial cancer, physicians often recommend that women who are deemed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.
3. **Physical examination.** A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without reexamining the patient.
4. **Hypercoagulability.** Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (all primarily conjugated estrogen users) report no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.
5. **Familial hypertriglyceridemia.** Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in individuals with familial defects of lipoprotein metabolism.
6. **Fluid retention.** Because estrogens may cause some degree of fluid retention, conditions which might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.
7. **Uterine bleeding and mastodynia.** Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.
8. **Impaired liver function.** Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.
9. **Information for the Patient.** See text of Patient Package Insert below.
C. **Laboratory Tests.** Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable. For prevention and treatment of osteoporosis, however, see DOSAGE AND ADMINISTRATION section.

D. **Drug/Laboratory Test Interactions.**

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VII antigen, VII coagulant activity; IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.
3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.
7. Reduced serum folate concentration.

E. Carcinogenesis, Mutagenesis, and Impairment of Fertility. Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. See CONTRAINDICATIONS and WARNINGS.

F. Pregnancy Category X. Estrogens should not be used during pregnancy. See CONTRAINDICATIONS and BOXED WARNINGS.

G. 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. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

H. Pediatric Use. Safety and effectiveness in pediatric patients have not been established.
Large and repeated doses of estrogen over an extended period of time have been shown to accelerate epiphyseal closure, resulting in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. In patients in whom bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended. Estrogen treatment of prepubertal children also induces premature breast development and vaginal cornification, and may potentially induce vaginal bleeding in girls. In boys, estrogen treatment may modify the normal pubertal process. All other physiological and adverse reactions shown to be associated with estrogen treatment of adults could potentially occur in the pediatric population, including thromboembolic disorders and growth stimulation of certain tumors. Therefore, estrogens should only be administered to pediatric patients when clearly indicated and the lowest effective dose should always be utilized.

ADVERSE REACTIONS

The following additional adverse reactions have been reported with estrogen therapy (see WARNINGS regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia):

1. Genitourinary system.
Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting.
Increase in size of uterine leiomyomata.
Vaginal candidiasis.
Change in amount of cervical secretion.
2. Breast.
Tenderness, enlargement.
3. Gastrointestinal.
Nausea, vomiting.
Abdominal cramps, bloating.
Cholestatic jaundice.
Increased incidence of gallbladder disease.
4. Skin.
Chloasma or melasma which may persist when drug is discontinued.
Erythema multiforme.
Erythema nodosum.
Hemorrhagic eruption.
Loss of scalp hair.
Hirsutism.
5. Eyes.
Steepening of corneal curvature.
Intolerance to contact lenses.
6. Central Nervous System.
Headache, migraine, dizziness.
Mental depression.
Chorea.
7. Miscellaneous.
Increase or decrease in weight.
Reduced carbohydrate tolerance.
Aggravation of porphyria.
Edema.
Changes in libido.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

1. For treatment of moderate to severe vasomotor symptoms, vulval and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.
The usual initial dosage range is 1 or 2 mg daily of estradiol adjusted as necessary to control presenting symptoms. The minimal effective dose for maintenance therapy should be determined by titration. Administration should be cyclic (e.g., 3 weeks on and 1 week off).
2. For treatment of female hypogonadism due to hypogonadism, castration, or primary ovarian failure.
Treatment is usually initiated with a dose of 1 or 2 mg daily of estradiol, adjusted as necessary to control presenting symptoms; the minimal effective dose for maintenance therapy should be determined by titration.
3. For treatment of breast cancer, for palliation only, in appropriately selected women and men with metastatic disease.
Suggested dosage is 10 mg three times daily for a period of at least three months.
4. For treatment of advanced androgen-dependent carcinoma of the prostate, for palliation only.
Suggested dosage is 1 to 2 mg three times daily. The effectiveness of therapy can be judged by phosphatase determinations as well as by symptomatic improvement of the patient.
5. For prevention of osteoporosis.
Therapy with Innofem™ (Estradiol Tablets, USP) to prevent postmenopausal bone loss should be initiated as soon as possible after menopause. A daily dosage of 0.5 mg should be administered cyclically (e.g., 25 days on and 5 days off). The dosage may be adjusted if necessary to control concurrent menopausal symptoms. Discontinuation of estrogen replacement therapy may re-establish the natural rate of bone loss.

HOW SUPPLIED

Innofem™ (Estradiol Tablets, USP) 0.5 mg yellow round tablets debossed with "Novo 293" and a dividing score

NDC 0169-1842-81 Bottles of 100
NDC 0169-1842-82 Bottles of 500

Innofem™ (Estradiol Tablets, USP) 1 mg; red round tablets debossed with "Novo 282" and a dividing score

NDC 0169-1843-81 Bottles of 100
NDC 0169-1843-82 Bottles of 500

Innofem™ (Estradiol Tablets, USP) 2 mg; blue round tablets debossed with "Novo 280" and a dividing score

NDC 0169-1844-81 Bottles of 100
NDC 0169-1844-82 Bottles of 500

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

INFORMATION FOR THE PATIENT

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

1. **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.
2. **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 ESTROGENS

(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 virtually 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 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. Utilizing 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.

WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:

- During pregnancy (see Boxed Warnings).
If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.
- If you have unusual vaginal bleeding which has not been evaluated by your doctor (see Boxed Warnings).
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.
- If you have had cancer.
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. 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.**
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 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 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 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.

NOVO NORDISK PHARMACEUTICALS, INC.
Princeton, New Jersey 08540

Revised November 1998 Rev 02

APPROVED

Novo Nordisk A/S
2880 Bagsvaerd, Denmark

Novo Nordisk

Colour PMS: 289C

Novo Nordisk

Rx Only

Innofem™

(Estradiol Tablets, USP)

INFORMATION FOR THE PATIENT

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

1. **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.
2. **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 virtually 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 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.

WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:

- **During pregnancy (see Boxed Warnings).**
  If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.
- **If you have unusual vaginal bleeding which has not been evaluated by your doctor (see Boxed Warnings).**
  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.
- **If you have had cancer.**
  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. 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 advise 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.**
  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 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 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 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.

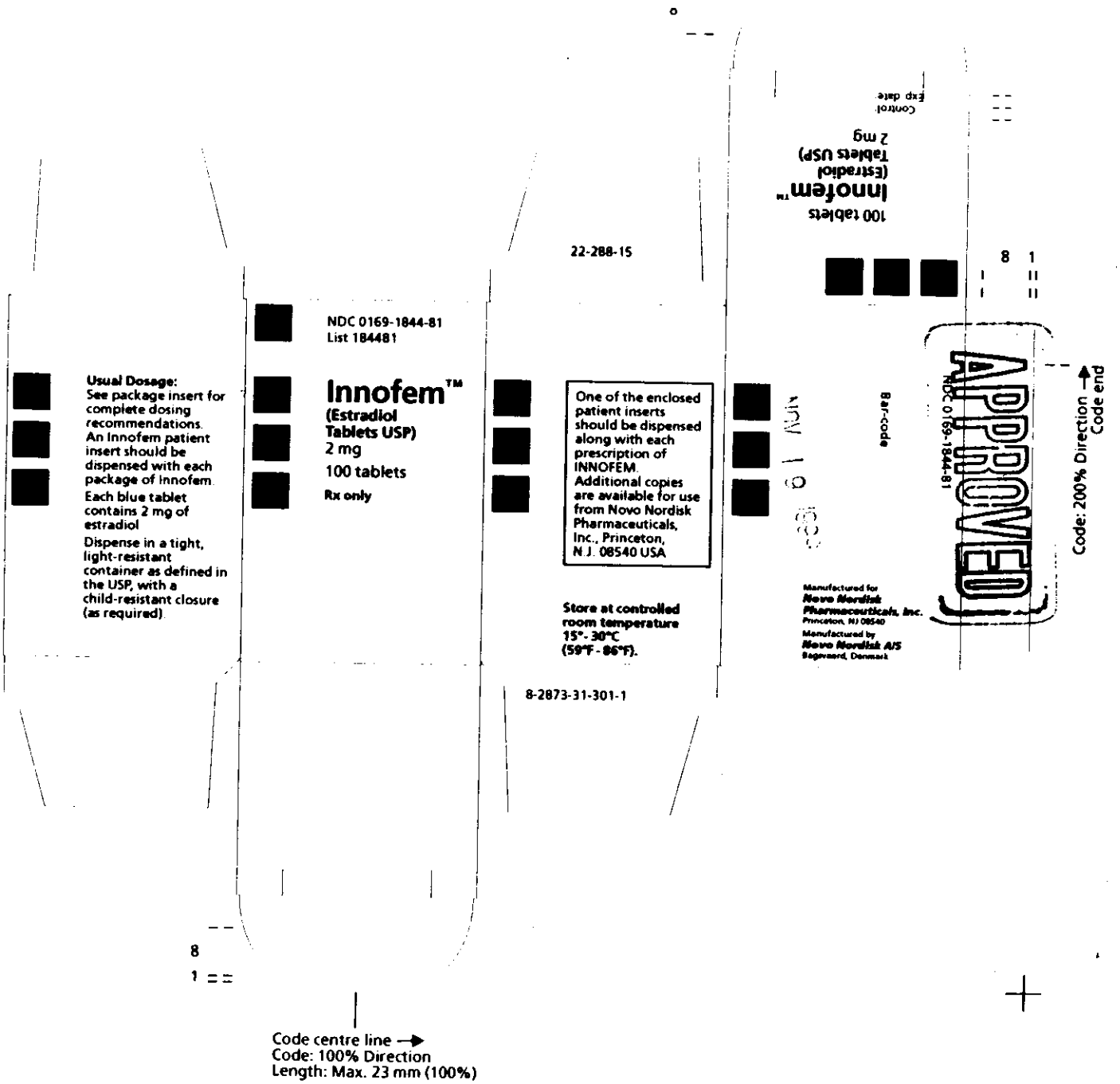
This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physicians' Desk Reference", which is available in book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

NOVO NORDISK
PHARMACEUTICALS, INC.
Princeton, New Jersey 08640

APPROVED
— 9 1989

Novo Nordisk A/S
2880 Bagsværd, Denmark

Novo Nordisk



Colour PMS: 289C + 185C

Carton size: 22-288-15
Edition: 09.97-3xx-1

15 ml

Property of:
Novo Nordisk A/S

1 mg 500 Tablets

Novo Nordisk

Innofem™

(Estradiol Tablets USP)

Each red tablet contains
1 mg estradiol.

Dispense in a tight, light resistant container as defined in the USP

Usual Dosage: See package insert for complete dosage recommendations.

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

NDC 0169-1843-82
NSN xxxx-xx-xxx-xxxx

List 184382
Rx only

An Innofem patient insert should be dispensed with each prescription of Innofem.

Manufactured by:
Novo Nordisk A/S
Bagsvaerd, Denmark

For:
Novo Nordisk Pharmaceuticals Inc.
Princeton, N.J. 08540

APPROVED
6/9/99

Lot No./
Exp. Date:

8-2875-31-201-1

Colour PMS: 289C +

Colour: PMS: 289C + 185C

2 mg 500 Tablets

Novo Nordisk

Innofem™

(Estradiol Tablets USP)

Each blue tablet contains
2 mg estradiol.

Dispense in a tight, light resistant container as defined in the USP

Usual Dosage: See package insert for complete dosage recommendations.

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

NDC 0169-1844-82 List 184482

NSN 6505-xx-xxx-xxxx **Rx only**

A Novo Nordisk patient insert should be dispensed with each prescription of

Manufactured for
Novo Nordisk A/S
Bagsværd Denmark
For
Novo Nordisk
Pharmaceuticals, Inc.
Princeton, N.J. 08540

APPROVED
NOV 19 1986

Lot No./
Exp. Date:

8-2876-31-201-1

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-312

CHEMISTRY REVIEW(S)

JUL 13 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-312 APPLICANT: Novo Nordisk Pharmaceuticals, Inc.

DRUG PRODUCT: Innofem™ (Estradiol Tablets USP), 0.5 mg, 1 mg and 2 mg

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. When you submit a long series of attachments or appendices, tabbing, as you have done, is very helpful. An index would also be appreciated by the reviewer.

2. Many of the figures in the appendices in the revised version of the validation report, in Appendix 13, are smaller than the same figures in the original ANDA. In the future, please make figures as large as is practical, for greater ease of review.

3. Presentation of updated stability data in the same order as in the preceding version of the report would facilitate review. Names of identified individual impurities should be used in the stability report, rather than relative retention times, for easier comparison with stability specifications. Please provide all available long term data in the format.

4. During laboratory verification of your drug product, an FDA analyst found pieces of a small winged insect, possibly *Drosophila melanogaster*, in the sample container you provided. Please comment.

5. Your response must also address the labeling deficiencies.

6. A satisfactory compliance evaluation is necessary for approval. We have requested an evaluation from the Office of Compliance.

7. Your bioequivalence information is pending review.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

URGENT
CONFIDENTIAL
FACSIMILE

NEW CORRESP
NC

DATE: May 28, 1999

TO: Lt. Denise Huie
FAX No.: (301) 594-0180

FROM: Michael Barbush MB
PHONE No.: (609) 987-5973
FAX No.: (609) 987-3916

No. PAGES: 3 (including cover sheet)

MESSAGE:

Dear Denise:

Per our telephone conversation on May 27th , attached to this cover sheet please find a copy of the approved, revised specifications for the estradiol hemihydrate Ph.Eur./USP. Please provide a copy for the Chemistry reviewer for review.

A hard copy will follow and will be submitted as a "New Correspondence" to the ANDA.

If there are any questions, please contact me at the number provided above.

Thank you.

Health Care Quality
QA Solid Dosage Forms
Dept. 242
97-030/JaHi

Date:	21-May-99
Version No.:	12
Status:	Final
Page:	1 of 2

Novo Nordisk

SPECIFICATION

Estradiol hemihydrate Ph.Eur./USP[1]
Novo Nordisk Item No.: 101-4862

Test Item	Method	Limits
	USP	%
	Ph.Eur.	%

Health Care Quality QA Solid Dosage Forms Dept. 242 97-030/JaHi		Date: Version No.: Status: Page:	21-May-1999 12 Final 2 of 2

Novo Nordisk

Test Item	Method	Limits
Particle size distribution[7]:		

1
2
3
4
5
6)
7)

STPe 21. MAY 1999

Søren Thuesen Pedersen, Specialist, QA Solid Dosage Forms

AUG 99 05 27

Niels Ulrik Daugbjerg, Chemist, SDF Product Support

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-312 APPLICANT: Novo Nordisk Pharmaceuticals, Inc.

DRUG PRODUCT: Innofem™ (Estradiol Tablets USP), 0.5 mg, 1 mg and 2 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. In Section VII, Components and Composition:

Page(s) 7

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Review

11/2/98

#38

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Information on manufacturing facilities and outside contractors need not be duplicated in Sections IX and X. For example, all of the information for Novo Nordisk A/S could have been put into Section IX, and all the information for Unipack Limited could have been put into Section X.

   Since the information in Sections IX and X is used as a basis for planning pre-approval inspections, it would be more convenient for us to have a table such as that on pages 5/4-6 arranged by address, with all of the activities at that address listed in one place in the table.

2. The time limit from granulation to compression begins on the day the drug substance is mixed with an excipient, and the time limit from compression to coating starts on the day the first tablets are

compressed.

3. Please acknowledge that the expiration dating period for the drug product begins on the day the drug substance is mixed with an excipient.

4. Please acknowledge that when a Novo Nordisk analytical method is different from a USP/NF method, the USP/NF method will be the regulatory method and will prevail in case of a dispute, and the Novo Nordisk method will be the alternate method.

5. Please provide any additional stability data that may be available for the exhibit batches.

6. Your response must also address the labeling deficiencies.

7. A satisfactory establishment evaluation is necessary for approval. We have requested an evaluation from the Office of Compliance.

8. Your bioequivalence information is pending review.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-312

BIOEQUIVALENCE REVIEW(S)

(2)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-312 SPONSOR : Novo Nordisk Pharmaceuticals, Inc.

DRUG AND DOSAGE FORM : Estradiol Tablets

STRENGTH(S) : 0.5, 1, 2 mg Strengths

TYPES OF STUDIES : Fasting Study

CLINICAL STUDY SITE(S) Clinical: Harris Labs., Lincoln NE

ANALYTICAL SITE(S) : Analytical: Corning Nicholes Institute, Princeton, NJ

STUDY SUMMARY : Single-dose fasting is acceptable.
DISSOLUTION : Dissolution study is acceptable

DSI INSPECTION STATUS

Inspection needed: ~~YES~~ NO	Inspection status:	Inspection results:
First Generic __No__	Inspection requested: (date)	
New facility __No_	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : S. P. Shrivastava, Ph.D. BRANCH : II

INITIAL : /S/ DATE : 6/17/99

TEAM LEADER : S. Nerurkar, Ph.D. /S/ BRANCH :

INITIAL : DATE : 6/22/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ **DATE :** 6/25/99

1. CHEMISTRY REVIEW NO. 3 Cycle Number: 2

2. ANDA # 40-312

ADDENDUM

3. NAME AND ADDRESS OF APPLICANT

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

6. PROPRIETARY NAME

INNOFEM™

7. NONPROPRIETARY NAME

Estradiol

13. DOSAGE FORM

Tablets, USP

14. STRENGTH

0.5, 1, and 2 mg

4. LEGAL BASIS FOR SUBMISSION

The RLD is Estrace® Tablets, Bristol Myers Squibb, NDA 84-500. The applicant knows of no patent or exclusivity.

9. AMENDMENTS AND OTHER DATES:

Vol. A4.1:

07/13/99	NA fax - chemistry and labeling
08/10/99	Telecon re submission of FAX amendment
08/12/99	Fax copy of FAX amendment - chem & labeling *
08/19/99	Hard copy of FAX amendment - chem&labeling *
09/14/99	Telecon re updating DS specs to USP 23 Supplement 10 *
09/21/99	Fax copy of telephone amendment *

*** (The subjects of Chemistry Review #3 for Cycle #2)**

09/23/99 Chemistry Close pending labeling and two Type II DMFs

Vol. A5.1:

08/20/99	NC - Labeling
08/25/99	FAX amendment - Labeling in response to telecon on 8/24/99
08/30/99	Telecon re tightening dissolution limit
08/31/99	Telecon re tightening dissolution limit
09/21/99	Hard copy of telephone amendment

Vol. A6.1:

10/22/99	FAX amendment - Labeling in response to telecon on 8/30/99

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

17. COMMENTS

The following Review Point is **incomplete**:

22. Synthesis

One of the two Type II DMFs will probably be found adequate by another reviewer, but documentation has not been completed, as of 10/27/99.

The other Type II DMF was found adequate 9/13/99.

All other chemistry issues have been completed.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

This is not a sterile product.

31. SAMPLES AND RESULTS

The drug substance and drug product are **in USP 23**.

32. LABELING

Ms. Teresa Watkins informed me by E-mails on September 22 and 23, 1999 that she was waiting for another amendment. This was the basis for the CHEMISTRY CLOSE of this review.

She found the labeling **satisfactory** 10/27/99.

33. ESTABLISHMENT INSPECTION

All facilities were found **acceptable** 6/25/99.

34. BIOEQUIVALENCE STATUS

"No further questions" 7/13/99.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 40-312 can be **APPROVED**, pending acceptability of the remaining Type II DMF.

19. REVIEWER:	ADDENDUM COMPLETED:
Eugene L. Schaefer, Ph.D.	10/27/99

Page(s) 2

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Chemistry Review #3

FINAL ~~DRAFT~~ ECCKD

1. CHEMISTRY REVIEW NO. 3 Cycle Number: 2

2. ANDA # 40-312

CHEMISTRY CLOSE

3. NAME AND ADDRESS OF APPLICANT

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

6. PROPRIETARY NAME
INNOFEM™

7. NONPROPRIETARY NAME
Estradiol

13. DOSAGE FORM
Tablets, USP

14. STRENGTH
0.5, 1, and 2 mg

10. PHARMACOLOGICAL CATEGORY
Female hormone

11. Rx or OTC
Rx

4. LEGAL BASIS FOR SUBMISSION

The RLD is Estrace® Tablets, Bristol Myers Squibb, NDA 84-500.

The applicant knows of no patent or exclusivity restriction.

5. SUPPLEMENT(s)
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1	:	Chemistry
A1.2	:	Bioequivalence
A1.3	:	Bioequivalence and Chemistry
A1.4 to A1.12	:	Chemistry

04/30/98 Original submission.

Vol. A1.1:

05/13/98 Acceptable for filing
11/02/98 Chem NA Major fax
11/02/98 Bio deficiency fax

Vol. A2.1:

11/17/98 Bio amendment

Vol. A3.1:

12/22/98	Chem Major amendment
05/24/99	Fax from Novo Nordisk re laser diffraction method
05/28/99	Fax of NC - Revised specs for the DS
06/10/99	Minutes of Meeting re Possible Violation of OGD Franchising Policy
01/27/99	MV report from Philadelphia District Laboratory

Vol. A4.1:

04/27/99	Bio amendment
05/12/99	Labeling amendment
06/01/99	Hard copy of NC - Revised specs for the DS
06/28/99	Bio "no further questions"
07/13/99	NA fax - chem and labeling
08/10/99	Telecon re submission of facsimile amendment
08/12/99	Fax copy of facsimile amendment - C&L *
08/19/99	Hard copy of facsimile amendment - C&L *
09/14/99	Telecon re updating DS specs to USP 23 Supplement 10 *
09/21/99	Telephone amendment *

*** (The subjects of this review)**

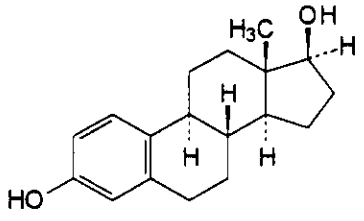
Vol. A5.1:

08/20/99	NC - Labeling
08/26/99	NC - Labeling

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

15. CHEMICAL NAME AND STRUCTURE

Generic name: Estradiol
Chemical name: Estra-1,3,5-(10)-triene-3,17-diol, (17b)-
Formula: $C_{18}H_{24}O_2$
Molecular weight: 272.39
CAS registry number(s): 50-28-2
Pharmacologic and/or therapeutic category: Estrogen
Reference: USP 23, page 622
Chemical structure:



16. RECORDS AND REPORTS N/A

17. COMMENTS

The following Review Point is **incomplete:**

22. Synthesis

The two Type II DMFs will probably be found **adequate** by other reviewers, but documentation has not been completed, as of 9/22/99.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

This is not a sterile product.

31. SAMPLES AND RESULTS

The drug substance and drug product are **in USP 23.**

32. LABELING

Ms. Teresa Watkins informed me by E-mails 22- and 23-Sep-1999 that **she is waiting for another amendment,** and she might not receive it until October. This is the basis for the CHEMISTRY CLOSE of this review.

33. ESTABLISHMENT INSPECTION

A corrected EER was submitted 6/24/99. It included the Unipack packaging site at Westhoughton. All facilities were found **acceptable** 6/25/99.

34. BIOEQUIVALENCE STATUS

"No further questions" 7/13/99.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 40-312 can be **APPROVED**. However, documentation is needed for the acceptability of the labeling, and the two Type II DMFs, as of 9/23/99. Therefore, a CHEMISTRY CLOSE is being performed.

19. REVIEWER:	DATE COMPLETED:	REVISED:
Eugene L. Schaefer, Ph.D.	9/10/99	9/23/99

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Information and are not

releasable.

Chemistry Review

#3

BIOEQUIVALENCY - Acceptable

ANDA: 40-312 APPLICANT: Novo Nordisk Pharmaceuticals, Inc.

DRUG PRODUCT: Estradiol Tablets, 0.5, 1, 2 mg

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

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 provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

(2)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-312 SPONSOR : Novo Nordisk Pharmaceuticals, Inc.

DRUG AND DOSAGE FORM : Estradiol Tablets

STRENGTH(S) : 0.5, 1, 2 mg Strengths

TYPES OF STUDIES : Fasting Study

CLINICAL STUDY SITE(S) Clinical: Harris Labs., Lincoln NE

ANALYTICAL SITE(S) : Analytical: Corning Nicholes Institute, ~~Princeton, NJ~~ SAN JUAN, CAPISTRANO, CA

STUDY SUMMARY : Single-dose fasting is acceptable.
DISSOLUTION : Dissolution study is acceptable

DSI INSPECTION STATUS

Inspection needed: ~~YES~~ NO	Inspection status:	Inspection results:
First Generic __No__	Inspection requested: (date)	
New facility __No_	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : S. P. Shrivastava, Ph.D. BRANCH : II

INITIAL : /S/ DATE : 6/17/99

TEAM LEADER : S. Nerurkar, Ph.D. BRANCH :

INITIAL : /S/ DATE : 6/22/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAI /S/ **DATE :** 6/28/99

Estradiol Tablet (Innofem^{R})
0.5, 1, and 2 mg
ANDA# 40-312
Reviewer : S.P. Shrivastava
V:\firmsnz\novonord\ltrs&rev\40312SA.N98

Novo Nordisk Pharm., Inc.
Princeton, NJ
Submission Dates:
November 17, 1998
April 27, 1999

REVIEW OF A BIOEQUIVALENCE STUDY AMENDMENT

I. BACKGROUND

The firm had submitted ANDA for 2 mg, 1 mg and 0.5 mg estradiol tablets on April 30, 1998. In support of this, it had conducted a bioequivalence study on 2 mg tablet and requested waivers of bioequivalence study for 1 mg and 0.5 mg tablets. While dissolution data for the products were acceptable, certain deficiencies were cited in biostudies (see review by SShrivastava, 10/7/98).

In this submission, the firm has responded to the deficiencies (11/17/98). Since the data provided on diskette were not "SAS Ready", and were full of unnecessary text, missing codes, different codes for one item in two tables, two types of data (baseline-adjusted and baseline non-adjusted) in one table, etc., the firm was requested to send another set of diskettes. Revised diskettes were mailed on 4/27/99.

II. RESPONSE TO DEFICIENCIES

Deficiency 1. *The firm has not provided drug concentration and PK data on diskette. The firm should submit data on a diskette in ASCII format containing two separate files as follows for estradiol, estrone, and estrone sulfate:*

A. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX THALF KEL

B. SUBJ SEQ PER TRT C1 C2 C3 ..... Cn

The fields should be delimited by one blank space, and missing values should be indicated by a period (.).

Response: The firm has submitted data on diskette. However, it was not 'SAS-Ready', and reviewer had to clean up the unnecessary text, etc. prior to running SAS program.

Conclusion: PK parameters for all three components, estradiol, estrone and estrone sulfate, meet the 90% CI criterion, with or without the respective baseline corrections (see Tables 1-6).

The response is acceptable.

TABLE 1. Estradiol: Baseline Adjusted PK Parameters.
General Linear Models Procedure
Least Squares Means

TRT	AUC LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	90% CI
Estrace	1611.77557	61.42944	0.0001	0.0878	- - - -
Estrofem	1767.31913	61.42944	0.0001		

TRT	AUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	1811.70136	101.83659	0.0001	0.2736	- - - -
Estrofem	1973.61110	101.83659	0.0001		

TRT	CMAX LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	60.1174242	1.6972968	0.0001	0.0092	- - - -
Estrofem	66.9981061	1.6972968	0.0001		

TRT	LAUC LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	7.32024621	0.03697289	0.0001	0.1024	99.9-119.6
Estrofem	7.40954545	0.03697289	0.0001		

TRT	LAUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	7.44329167	0.04044146	0.0001	0.3423	95.8-116.6
Estrofem	7.49885606	0.04044146	0.0001		

TRT	LCMAX LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	4.03457576	0.03074276	0.0001	0.0124	104.5-121.4
Estrofem	4.15346970	0.03074276	0.0001		

Table 2. Estradiol: Non-Adjusted Baseline PK Data

General Linear Models Procedure

Least Squares Means

TRT	AUC LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2	90% CI
Estrace	2286.89583	89.47689	0.0001	0.5904	- - - -
Estrofem	2217.73201	89.47689	0.0001		

TRT	AUCI LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2	
Estrace	3912.69178	708.69291	0.0001	0.2802	- - - -
Estrofem	2801.68758	708.69291	0.0007		

TRT	CMAX LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2	
Estrace	69.4090909	2.3679300	0.0001	0.2736	- - - -
Estrofem	73.1742424	2.3679300	0.0001		

TRT	LAUC LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2	
Estrace	7.63393561	0.02485953	0.0001	0.8995	94.6-106.7
Estrofem	7.63843182	0.02485953	0.0001		

TRT	LAUCI LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2	
Estrace	7.90580682	0.04221177	0.0001	0.1990	83.4-102.4
Estrofem	7.82662879	0.04221177	0.0001		

TRT	LCMAX LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2	
Estrace	4.16622727	0.03297385	0.0001	0.1061	99.9-117.2
Estrofem	4.24496212	0.03297385	0.0001		

Table 3. Estrone: Baseline Adjusted PK Parameter
General Linear Models Procedure
Least Squares Means

TRT	AUC LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	90% CI
Estrace	8938.03220	187.42071	0.0001	0.0097	- - - -
Estrofem	9691.71678	187.42071	0.0001		

TRT	AUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	9424.2140	204.7301	0.0001	0.0194	- - - -
Estrofem	10157.5108	204.7301	0.0001		

TRT	CMAX LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO LSMEAN1=LSMEAN2	
Estrace	453.895833	12.607641	0.0001	0.0612	- - - -
Estrofem	489.162879	12.607641	0.0001		

TRT	LAUC LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	9.00588258	0.02903088	0.0001	0.0234	103..0-118.6
Estrofem	9.10621970	0.02903088	0.0001		

TRT	LAUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	9.05706818	0.03043019	0.0001	0.0410	102.0-118.3
Estrofem	9.15078030	0.03043019	0.0001		

TRT	LCMAX LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1 = LSMEAN2	
Estrace	6.04265909	0.03356557	0.0001	0.0520	101.6-119.7
Estrofem	6.14046970	0.03356557	0.0001		

Table 4. Estrone: Baseline non-Adjusted PK Data

General Linear Models Procedure

Least Squares Means

TRT	AUC LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2	90% CI
Estrace	10503.4309	184.5856	0.0001	0.0215	- - - -
Estrofem	11151.9110	184.5856	0.0001		

TRT	AUCI LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2	
Estrace	11740.8080	201.3561	0.0001	0.0878	- - - -
Estrofem	12250.6538	201.3561	0.0001		

TRT	CMAX LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2	
Estrace	475.488636	12.589352	0.0001	0.0714	- - - -
Estrofem	509.303030	12.589352	0.0001		

TRT	LAUC LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2	
Estrace	9.18673485	0.02221591	0.0001	0.0317	101.8-113.5
Estrofem	9.25902652	0.02221591	0.0001		

TRT	LAUCI LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2	
Estrace	9.30066288	0.02070807	0.0001	0.0883	100.2-110.8
Estrofem	9.35300758	0.02070807	0.0001		

TRT	LCMAX LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2	
Estrace	6.09465530	0.03155336	0.0001	0.0599	101.2-118.0
Estrofem	6.18342424	0.03155336	0.0001		

Table 5. Estrone Sulfate: Baseline Adjusted PK Parameters

General Linear Models Procedure

Least Squares Means

TRT	AUC LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	90% CI
Estrace	284319.936	10015.414	0.0001	0.2040	- - - -
Estrofem	302890.805	10015.414	0.0001		

TRT	AUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	292853.602	10475.057	0.0001	0.2529	- - - -
Estrofem	310267.967	10475.057	0.0001		

TRT	CMAX LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	21342.8011	728.7444	0.0001	0.0859	- - - -
Estrofem	23200.3617	728.7444	0.0001		

TRT	LAUC LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	12.4631705	0.0318054	0.0001	0.0770	100.6 - 117.5
Estrofem	12.5468220	0.0318054	0.0001		

TRT	LAUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	12.4910530	0.0316335	0.0001	0.0968	100.1 - 116.7
Estrofem	12.5688182	0.0316335	0.0001		

TRT	LCMAX LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	9.86424621	0.03396783	0.0001	0.0292	103.0 - 121.5
Estrofem	9.97670455	0.03396783	0.0001		

Table 6. Estrone Sulfate: Baseline Non-Adjusted PK Data

General Linear Models Procedure

Least Squares Means

TRT	AUC LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	90% CI
Estrace	303783.632	9011.827	0.0001	0.2386	- - - -
Estrofem	319243.535	9011.827	0.0001		

TRT	AUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	319119.850	9032.161	0.0001	0.3387	- - - -
Estrofem	331626.329	9032.161	0.0001		

TRT	CMAX LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	21611.3712	726.0888	0.0001	0.0917	- - - -
Estrofem	23426.1515	726.0888	0.0001		

TRT	LAUC LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	12.5250227	0.0302221	0.0001	0.0996	100.0-115.9
Estrofem	12.5986515	0.0302221	0.0001		

TRT	LAUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	12.5701402	0.0294010	0.0001	0.1385	99.3-114.5
Estrofem	12.6341629	0.0294010	0.0001		

TRT	LCMAX LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0	Pr > |T| HO: LSMEAN1=LSMEAN2	
Estrace	9.87620833	0.03390751	0.0001	0.0317	102.8-121.3
Estrofem	9.98658712	0.03390751	0.0001		

Deficiency 2. *The firm has provided partial pharmacokinetic data on estradiol, estrone and estrone sulfate including mean and individual subject data for AUC_{0-t}, C_{max} and T_{max}, and mean data for AUC_{0-inf}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}. However, individual subject data for AUC_{0-inf}, $LAUC_{0-inf}$, T_{half}, and K_{el} were not available for review. The firm should provide individual data and statistics in a tabular form for the test and reference products separately.*

Response: The firm has submitted data as requested.

Conclusion: The response is acceptable.

Deficiency 3. *The firm should provide table of data points included in calculating K_{el} values and regression coefficients for each drug/metabolite concentration-time curve.*

Response: The firm did not submit data as requested. Tables of PK data for components are copied and reattached.

Conclusion: The response is acceptable. The reviewer has examined the individual drug concentration time curves. They are acceptable.

Deficiency 4. *The 90% CI for $LAUC_{0-inf}$ for estradiol, estrone and estrone sulfate should be calculated and provided for review.*

Response: The firm has submitted data as requested.

Conclusion: The response is acceptable.

III. RECOMMENDATIONS

1. The bioequivalence study submitted by Novo Nordisk Pharmaceuticals on its estradiol tablets, 2 mg, Lot #EK5A404 comparing it with Mead-Johnson's Estrace^R, 2 mg tablets, Lot # MCD67, is acceptable to the Division of Bioequivalence. The study demonstrates that Novo Nordisk's estradiol 2 mg tablets are bioequivalent to the reference product Estrace^R, 2 mg tablets, manufactured by Mead-Johnson.

2. The dissolution testing conducted by Novo Nordisk Pharmaceuticals, on its estradiol 2, 1 and 0.5 mg tablets, Lot #EK5A404, FK5H413 and FK5G401, respectively are acceptable. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing, and the application is acceptable.

3. The formulation for 0.5 and 1 mg strength test tablets is similar to the 2 mg strength of the test product, which underwent bioequivalency testing. The waiver of the in vivo bioequivalence study requirements for 0.5 and 1 mg tablets of the test product is granted. The 0.5, 1 and 2 mg test tablets are, therefore, deemed bioequivalent to Estrace®, 0.5, 1 and 2 mg tablets, manufactured by Mead-Johnson.

4. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 500 mL of sodium lauryl sulfate at 37°C using apparatus II (paddle) at 100 rpm. The test product should meet the following specifications:

   Not less than (Q) of the labeled amount of estradiol in the dosage form is dissolved in 60 minutes.

The firm should be informed of the recommendations.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNerurkar
FT INITIALED SNerurkar /S/ for VMT Date 6/22/99

Concur: /S/ Date: 6/28/99

Dale Conner, Pharm.D.
Director
Division of Bioequivalence

SPS/sps/5-20-99/40312SA.N98

cc
Fi...

BIOEQUIVALENCY - Acceptable

ANDA: 40-312 APPLICANT: Novo Nordisk Pharmaceuticals, Inc.

DRUG PRODUCT: Estradiol Tablets, 0.5, 1, 2 mg

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

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 provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC:

Endorsements: (Final with Dates)

/S/ 6/22/99

BIOEQUIVALENCY - ACCEPTABLE

Study Amendment

1. ~~FASTING STUDY~~ (STA/OT)

submission date: 11/17/98
Strengths: 0.5, 1, 2 mg
Outcome: **AC**

2. OTHER ~~(STA/OT)~~ (OTH) (diskettes)

submission date: 4/27/99
Strengths: 2 mg
Outcome Decisions: AC

Outcome Decisions: AC

AC = Acceptable
WINBIO COMMENTS: The application is acceptable

BIOAVAILABILITY

ORIG AMENDMENT

N/AB

November 17, 1998

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research (HFD-650)
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: ANDA No. 40-312 INNOFEM® (estradiol tablets USP)
BIOEQUIVALENCY AMENDMENT

Dear Dr. Conner:

Reference is made to Novo Nordisk Pharmaceuticals, Inc.'s pending Abbreviated New Drug Application for Innofem® (estradiol tablets USP), 0.5 mg, 1 mg and 2 mg, submitted on April 30, 1998. Reference is also made to your facsimile of November 2, 1998 detailing deficiencies in this application with regard to the bioequivalence section. As requested, a copy of the facsimile in included with this response.

Accordingly, we are herewith providing our official written response to the November 2, 1998 facsimile. For ease of review, we have organized the information in a comment-response format, i.e., FDA comment followed by Novo Nordisk's written reply for each question.

This amendment to ANDA 40-312 is being provided in duplicate: one Archival copy (blue jacket) and one Review copy (orange jacket).

We trust that this response satisfactorily addresses all of your comments expressed in your facsimile and look forward to the acceptance and eventual approval of this application. Should you have any questions concerning this submission, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

RECEIVED
NOV 18 1998

NOV 2 1993

BIOEQUIVALENCY DEFICIENCIES

ANDA: 40-312 APPLICANT: Novo Nordisk Pharmaceuticals, Inc.

DRUG PRODUCT: Estradiol Tablets, 0.5, 1, 2 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have not provided drug concentration and PK data on diskette. You should submit data on a diskette in ASCII format containing two separate files as follows for estradiol, estrone, and estrone sulfate:

   A. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX THALF KEL

   B. SUBJ SEQ PER TRT C1 C2 C3 ..... Cn

   The fields should be delimited by one blank space, and missing values should be indicated by a period (.).

2. You have provided partial pharmacokinetic data on estradiol, estrone and estrone sulfate including mean and individual subject data for AUC_{0-t}, C_{max} and T_{max}, and mean data for AUC_{0-inf}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}. However, individual subject data for AUC_{0-inf}, $LAUC_{0-inf}$, T_{half}, and K_{el} were not available for review. You should provide individual data and statistics in a tabular form for the test and reference products separately.

3. You should provide table of data points included in calculating K_{el} values and regression coefficients for each drug/metabolite concentration-time curve.

4. The 90% CI for $LAUC_{0-inf}$ for estradiol, estrone and estrone sulfate should be calculated and provided for review.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 2

BIOEQUIVALENCY DEFICIENCIES

ANDA: 40-312 APPLICANT: Novo Nordisk Pharmaceuticals, Inc.

DRUG PRODUCT: Estradiol Tablets, 0.5, 1, 2 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have not provided drug concentration and PK data on diskette. You should submit data on a diskette in ASCII format containing two separate files as follows for estradiol, estrone, and estrone sulfate:

   A. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX THALF KEL

   B. SUBJ SEQ PER TRT C1 C2 C3 ..... Cn

   The fields should be delimited by one blank space, and missing values should be indicated by a period (.).

2. You have provided partial pharmacokinetic data on estradiol, estrone and estrone sulfate including mean and individual subject data for AUC_{0-t}, C_{max} and T_{max}, and mean data for AUC_{0-inf}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}. However, individual subject data for AUC_{0-inf}, $LAUC_{0-inf}$, T_{half}, and K_{ei} were not available for review. You should provide individual data and statistics in a tabular form for the test and reference products separately.

3. You should provide table of data points included in calculating K_{el} values and regression coefficients for each drug/metabolite concentration-time curve.

4. The 90% CI for $LAUC_{0-inf}$ for estradiol, estrone and estrone sulfate should be calculated and provided for review.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY DEFICIENCIES

ANDA: 40-312 APPLICANT: Novo Nordisk Pharmaceuticals, Inc.

DRUG PRODUCT: Estradiol Tablets, 0.5, 1, 2 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have not provided drug concentration and PK data on diskette. You should submit data on a diskette in ASCII format containing two separate files as follows for estradiol, estrone, and estrone sulfate:

   A. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX THALF KEL

   B. SUBJ SEQ PER TRT C1 C2 C3 ..... Cn

   The fields should be delimited by one blank space, and missing values should be indicated by a period (.).

2. You have provided partial pharmacokinetic data on estradiol, estrone and estrone sulfate including mean and individual subject data for AUC_{0-t}, C_{max} and T_{max}, and mean data for AUC_{0-inf}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}. However, individual subject data for AUC_{0-inf}, $LAUC_{0-inf}$, T_{half}, and K_{el} were not available for review. You should provide individual data and statistics in a tabular form for the test and reference products separately.

3. You should provide table of data points included in calculating K_{el} values and regression coefficients for each drug/metabolite concentration-time curve.

4. The 90% CI for $LAUC_{0-inf}$ for estradiol, estrone and estrone sulfate should be calculated and provided for review.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Estradiol Tablet (Innofem^{R})
0.5, 1, and 2 mg
ANDA# : 40-312
Reviewer : S.P. Shrivastava
40312SDW.498

Novo Nordisk Pharmaceuticals, Inc.
Princeton, NJ
Submission Dates:
April 30, 1998

REVIEW OF ONE BIOSTUDY, FIVE SETS OF DISSOLUTION DATA AND THREE WAIVER REQUESTS

I. BACKGROUND

17β-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. The exclusivity of the prevention of osteoporosis indication will not expire until September 8, 1995.

In vivo, estradiol is readily oxidized to estrone by 17-oxidase activity in the small intestinal mucosa and liver. 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 oral tablets, Estrace[R], 0.5 mg, 1 mg and 2 mg, manufactured by Mead Johnson.

In this submission, the firm has submitted ANDA for 2 mg, 1 mg and 0.5 mg estradiol tablets. It has conducted a bioequivalence study on 2 mg tablet and requested waivers of bioequivalence study for 1 mg and 0.5 mg tablets.

II. PROTOCOL FOR *IN VIVO* BIOEQUIVALENCE STUDY: #EST/PD/21/USA

Objective: To establish equivalence between the test and reference drug products on the basis of human blood data obtained after the oral administration of the drug products.

Investigators

Study Design: Randomized, single dose, fasting, crossover design with 10 days washout period.

Randomization Scheme: See Attachment #1.

Study Dates: Clinical May 15, 1995 to June 21, 1995
Analytical June 25, 1995 to July 28, 1995
Total Storage Time: 74 Days

Subject Selection

Twenty-three (23) post-menopausal (spontaneous or induced), non-smoking females between the ages of 30-60 years and body weight within ± 20% of the ideal body weight were selected. Good health of these subjects were checked by medical history, blood chemistry, hematology, urinalysis, ECG, pap smear and vital signs. They did not: **i)** have hypersensitivity towards study drug, **ii)** have history of drug and alcohol abuse, **iii)** use hormonal products within two months of the study including vaginal or topical estrogens, **iv)** smoke, **v)** use any prescription medicine within 14 days of the study, and **vi)** have baseline serum estradiol level more than 20 pg/mL. All 23 subjects completed the study.

Drug Administration

Following an overnight fast of 10 hours, every subject will be administered 1x2 mg tablets with 200 ml of water according to computer generated sequence.

Blood Drawing

Ten mL blood samples were collected at 0.5 and 0.0 hour pre-dose, and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 36, 48, 60 and 72 hours post-dose. Each specimen was allowed to clot for 10 minutes and then the serum was separated by disposable pipette. Serum samples were stored frozen at -15°C. The collected samples were shipped to Corning Nichols Institute, San Juan, CA. The assay method involved extraction, column chromatography, and radioimmunoassay.

Treatment:

Test Drug (Innofem/Estrofem):	A: Lot # EK5A404, Lot Size: (Exhibit or Production Batch size) Date of Manuf.: 3/6/95 Potency - 100.0%
Reference Drug: (Estrace®):	Lot #MCD67 (Mead-Johnson); Date of expiry: April 1, 1997; Potency - 97.0%

III. ASSAY METHODOLOGY

Serum samples were subjected to two procedures, one to quantitate free (unconjugated) 17β-estradiol and free estrone, and another to quantitate estrone sulfate. The unconjugated components were analyzed by double antibody radioimmunoassay (RIA) procedure following sample extraction, and column chromatography. The amount of estrone sulfate was determined by double antibody RIA procedure following enzyme hydrolysis, extraction, and column chromatography.

1. Pre-study Validation

A. Estradiol:

Specificity:

Limit of Quantitation: 2 pg/mL

Recovery: 64-97%, with average recovery of 80% by

Internal Standard: ual

Linearity: Range: 0.5-50 pg/RIA Tube; r = 0.999

Sensitivity and Precision:

Inter-day: Estradiol

	Conc., pg/RIA Tube	CV, %	Accuracy, %
Std. Curve	0.5	6.1	96
(n=6)	1.0	5.3	97
	2.5	5.6	105
	5.0	3.6	103
	10.0	2.1	104
	25.0	4.9	101
	50.0	3.1	94

Intra-day: Estradiol

	Conc., pg/RIA Tube	CV, %	Accuracy, %
Std. Curve	0.5	7.4	94
(n=4)	1.0	5.0	102
	2.5	3.8	100
	5.0	4.3	104
	10.0	4.9	100
	25.0	9.2	100
	50.0	12.4	97

Stability: Stability was checked under various conditions, including refrigeration at 4 °C, at room temperature, during three freeze-thaw cycles, and long-term stability at -20 °C for six months. Plasma samples were stable under the study conditions.

Storage	Test Conc. pg/mL	Storage Period	Temperature	% Diff.
Three Freeze-Thaw	6.4	3 Cycles	Room/-20 °C	- 2
Cycles (n=3)	16.4			-10
	121.0			3
Bench-Top	6.4	48 Hours	Room	14
(n=3)	16.4			18
	121.0			9
Refrigerator	6.4	7 Days	4 °C	12
(n=3)	16.4			12
	121.0			8

Long-Term Stab.	6.4	6 months	-20 °C	-5
(n=3)	16.4			14
	121.0			5

B. Free Estrone

Specificity: Method is highly specific for a given analyte.

Recovery: 65-101%, with average recovery of 80% by

Internal Standard:
samples.

Linearity: Range: RIA Tube; r = 0.999

Sensitivity and Precision:

Inter-day: Free Estrone

	Conc., pg/RIA Tube	CV, %	Accuracy, %
Std. Curve	2.5	3.8	104
(n=6)	5.0	3.1	98
	10.0	5.6	102
	20.0	3.2	94
	40.0	4.3	100
	80.0	2.0	100
	160.0	2.1	102

Intra-day: Estrone

Std. Curve	2.5	3.1	104
(n=4)	5.0	4.3	96
	10.0	1.8	104
	20.0	3.2	96
	40.0	2.6	95
	80.0	4.3	102
	160.0	6.5	102

Stability: Stability was checked under various conditions, including refrigeration at 4 °C, at room temperature, during three freeze-thaw cycles, and long-term stability at -20 °C for six months. Plasma samples were stable under the study conditions.

Storage	Test Conc. pg/mL	Storage Period	Temperature	% Diff.
Three Freeze-Thaw Cycles (n=3)	25	3 Cycles	Room/-20 °C	4
	55			7
	405			-2
Bench-Top (n=3)	25	48 Hours	Room	11
	55			7
	405			8
Refrigerator (n=3)	25	7 Days	4 °C	- 7
	55			- 7
	405			-14
Long-Term Stab. (n=3)	25	6 months	-20 °C	4
	55			-7
	405			-1

C. Estrone Sulfate:

Specificity: Method is very specific for a given analyte.

Recovery: 39-65%, with average recovery of 55% by

Internal Standard: iated estrone were used to correct recovery.

Linearity: g/RIA Tube; r = 0.999

Sensitivity and Precision:

Inter-day

	Conc., pg/RIA Tube	CV, %	Accuracy, %
Std. Curve (n=6)	2.5	3.8	104
	5.0	3.1	98
	10.0	5.6	102
	20.0	3.2	94
	40.0	4.3	100
	80.0	2.0	100
	160.0	2.1	102

Intra-day

Std. Curve	2.5	3.1	104
(n=4)	5.0	4.3	96
	10.0	1.8	104
	20.0	3.2	96
	40.0	2.6	95
	80.0	4.3	102
	160.0	6.5	102

Stability: Stability was checked under various conditions, including refrigeration at 4 ^{0}C, at room temperature, during four freeze-thaw cycles, and long-term stability at -20 ^{0}C for six months. Plasma samples were stable under the study conditions.

Storage	**Test Conc. pg/mL**	**Storage Period**	**Temperature**	**% Diff.**
Three Freeze-Thaw	924	4 Cycles	Room/-20 °C	- 14
Cycles (n=3)	1609			- 15
	2294			- 15
	5034			- 2
Bench-Top	924	48 Hours	Room	-18
(n=3)	1609			-24
	2294			-19
	5034			-14
Refrigerator	924	5 Days	4 °C	1
(n=3)	1609			-13
	2294			5
	5034			-1
Long-Term Stab.	1609	6 months	-20 °C	5
(n=3)	2294			- 4
	5034			11

2. Within Study Validation

A. Estradiol:

Specificity: RIA Method is very specific for a given analyte.

Internal Standard:

Linearity: Range: 0.25-25 pg/RIA Tube; r = 0.999

Sensitivity and Precision:

Inter-day: Estradiol

	Conc., pg/RIA Tube	CV, %	Accuracy, %
Std. Curve	0.25	10.5	107.0
(n=17)	0.5	8.7	102.1
	1.0	5.5	96.7
	2.5	6.4	95.1
	5.0	5.9	93.8
	10.0	4.1	101.9
	25.0	5.8	106.2
	Conc., pg/mL	**CV, %**	**Accuracy, %**
QC Samples	7.3	12.8	92.8
(n=24-51)	63.0	9.8	95.4
	202.0	9.3	102.1
	180.0	12.8	91.3

B. Free Estrone

Internal standard:

Specificity: Method is very specific for a given analyte.

Linearity: Range: pg/RIA Tube; r = 0.999

Sensitivity and Precision:

Inter-day: Free Estrone

	Conc., pg/RIA Tube	CV, %	Accuracy, %
Std. Curve	1.25	8.5	99.7
(n=20)	2.5	8.9	102.3
	5.0	7.3	104.2
	10.0	4.4	97.5
	20.0	4.3	95.5
	40.0	3.1	99.4
	80.0	4.4	103.2

	Conc., pg/mL	CV, %	Accuracy, %
QC Samples	12.5	15.3	96.3
(n=55-60)	53.0	9.9	99.2
	490.0	9.2	99.6

C. Estrone Sulfate:

Internal standard:

Specificity: Method is very specific for a given analyte.

Linearity: Range: g/RIA Tube; r = 0.999

Sensitivity and Precision:

Inter-day: Free Estrone

	Conc., pg/RIA Tube	CV, %	Accuracy, %
Std. Curve	1.25	7.5	103.9
(n=23)	2.5	7.0	101.1
	5.0	7.2	100.2
	10.0	3.6	95.6
	20.0	3.2	95.6
	40.0	2.8	99.5
	80.0	4.1	105.7
	Conc., pg/mL	**CV, %**	**Accuracy, %**
QC Samples	285	9.1	90.6
(n=38-46)	811	11.0	91.5
	4489	8.7	86.3
	4022	12.2	87.9

IV. RESULTS

1. Drug/Metabolite Concentration in Blood Serum and Pharmacokinetic Parameters

Partial drug/metabolite concentration and PK data on estradiol, estrone, and estrone sulfate provided by the firm are given in Attachments 2-8.

2. Adverse Reactions: Table below gives the list of probable or possible drug related

adverse reactions. No significant differences between test and reference were observed.

Adverse Events	Number of Subjects	
	Test	Reference
Myalgia	0	1
Cramps legs	1	0
Dizziness	0	1
Headache	4	4
Hyperkinesia	0	1
Conjunctivitis	1	0
Depression, psychotic	1	0
Somnolence	1	0
Constipation	2	0
Dysphagia	1	0
Nausea	1	0
Vomiting	2	0
Rhinitis	1	0
Leukorrhea (Vag. discharge)	0	1
Fatigue	1	0
Hot flushes	0	2
Rigors	0	1

V. FORMULATION

Comparative formulation data are given in Tables 1 and 2. The listed inactive ingredients are within the IIG limits.

VI. *IN VITRO* RESULTS (DISSOLUTION)

Comparative dissolution is given in Table 3. The firm has conducted dissolution testing in water containing 0.3% sodium lauryl sulfate (SLS) according to USP procedure. The test products meets the *in vitro* dissolution specifications of NLT in 60 minutes.

[NOT FOR RELEASE UNDER F.O.I.]

TABLE 1. Comparison of Reference and Test Product Formulations, 2 mg Tablets

Ingredients	**Test**	**Reference**
Estradiol	2.07[1]	2.0
Lactose monohydrate		
Corn Starch		
Gelatin		
Talc		
Magnesium Stearate		
Calcium Phosphate, dibasic	----	

	--	

Film Coating Ingredients for Test Product:		
Total Weight	**81.8**	**83.0**

1

2

TABLE 2. Comparison of Test Dosage Strength Formulations

Ingredients	**2 mg**	**1 mg**	**0.5 mg**
Estradiol[3]	2.07	1.03	0.517
Lactose monohydrate			
Corn Starch			
Gelatin, NF/Ph. Eur.			
Talc, USP/Ph.Eur.			
Magnesium Stearate			
Subtotal	**80.00**	**80.00**	**80.00**
Film Coating Ingredients for Test Products:			
Film Coat Total Wt.	**1.80**	**1.40**	**1.40**
Total Weight	**81.80**	**81.40**	**81.40**

3

4

5

TABLE 3. *In Vitro* Dissolution Testing of Estradiol Biobatches

Conditions

Method **USP XXIII** **Apparatus: II (Paddle) at 100 RPM**
Medium: **0.3% SLS** **Volume: 500 mL No. of Units: 12**
Reference Drug: **Estrace[R]** **Manufacturer: Mead-Johnson**
Assay Methods:

Time Min.	Strength, 2 MG					
	Test Lot #EK5A404			Reference Lot #MCD67		
	Mean %	Range	SD	Mean	%Range	SD
15	96.8		2.1	88.9	3	4.4
30	98.2		1.9	93.4	7	5.1
60	98.5		1.1	95.3	01	5.1
	Test Lot # EK5A404 Stored for 18 months					
	500 x 2 mg (BX)			100 x 2 mg (BW)		
15	91.8		3.6	90.8		4.4
30	98.1		2.0	97.4		2.3
60	98.7		1.4	97.7		1.8
	Scored Tablets: 2 mg					
	Test Lot # FK5J422			Reference Lot # F6J053A		
15	88.8		4.8	73.3		3.4
30	98.2		1.4	87.7		3.0
60	100.0		2.0	95.7		3.0

Scored Tablets: 1 mg					
	Test Lot #FK5H413			**Ref. C6K05A**	
15	94.1		2.7	79.7	3.3
30	99.3		2.4	92.7	2.1
60	100.3		2.0	97.7	1.8
Scored Tablets: 0.5 mg					
	Test Lot #FK5G401			**Ref. M5K13A**	
15	92.2		3.0	90.7	2.0
30	98.3		1.7	96.8	1.8
60	98.8		1.6	97.6	1.7

VII. DEFICIENCIES

1. The firm has not provided drug concentration and PK data on diskette. The firm should submit data on a diskette in ASCII format containing two separate files as follows for estradiol, estrone, and estrone sulfate:

   A. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX THALF KEL

   B. SUBJ SEQ PER TRT C1 C2 C3 ..... Cn

   The fields should be delimited by one blank space, and missing values should be indicated by a period (.).

2. The firm has provided partial pharmacokinetic data on estradiol, estrone and estrone sulfate including mean and individual subject data for AUC_{0-t}, C_{max} and T_{max}, and mean data for AUC_{0-inf}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}. However, individual subject data for AUC_{0-inf}, $LAUC_{0-inf}$, T_{half}, and K_{el} were not available for review. The firm should provide individual data and statistics in a tabular form for the test and reference products separately.

3. The firm should provide table of data points included in calculating K_{el} values and regression coefficients for each drug/metabolite concentration-time curve.

4. The 90% CI for $LAUC_{0-inf}$ for estradiol, estrone and estrone sulfate should be calculated and provided for review.

VIII. RECOMMENDATIONS

1. The single dose fasting study conducted by Novo Nordisk Pharmaceuticals on its estradiol tablets, 2 mg, Lot # comparing it with Mead-Johnson's Estrace®, 2 mg tablets, Lot # MCD67, has been found incomplete due to deficiencies #1-4 cited above.

2. The dissolution testing data conducted by Novo Nordisk Pharmaceuticals, on its estradiol 2, 1 and 0.5 mg tablets, Lot #EK5A404, FK5H413 and FK5G401, respectively are acceptable. The firm, however, has not conducted an acceptable *in vivo* bioequivalency study. From the bioequivalence point of view, the application is incomplete.

3. From the bioequivalence point of view, the firm has not met the *in vivo* bioavailability requirements for its estradiol 2 mg tablets, and in the absence of an acceptable *in vivo* biostudy, the request for waiver of its estradiol 0.5 and 1 mg tablets cannot be granted. The waiver request is denied. The firm should submit additional data.

The firm should be informed of the deficiencies #1-4 and recommendations.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

/S/

RD INITIALED SNerurkar
FT INITIALED SNerurkar Date 10/1/98

Concur: /S/ Date: 10/7/98

Dale Conner, Pharm.D.
Director
Division of Bioequivalence

Attachments-8

2SW.498

CC:

Endorsements: (Final with Dates)

10/1/98

.498

BIOEQUIVALENCY - DEFICIENCIES submission date: 4/30/98

1. **FASTING STUDY** (STF)
   Clinical: Harris Labs
   Analytical: Corning Nicholes Institute, Princeton, NJ
   Strengths: 2mg
   Outcome: UN

3. **DISSOLUTION DATA** (DIS)
   0.5, 1, 2 mg
   Outcome: **AC**

4. **DISSOLUTION WAIVER** (DIW)
   Strengths: 0.5 and 1 mg
   Outcome: UN

Outcome Decisions:
UN - Acceptable

WINBIO COMMENTS:

Attachment - 1

FFL-NR : 95103
STUDIENR : 5997

LÆGE :

A = Estrofem / Estrace
B = Estrace / Estrofem
C =
D =
E =

ANTAL PATIENTER : 28
ANTAL MEDIKAMENTER : 2
BLOKNING : J
BLOK STØRRELSE : 4
LIGELIG FORDELING : J
FORDELING : 1,00 1,00 0,00 0,00 0,00

P.NR.	MEDIKAMENT
1	A
2	B
3	B
4	A
5	B
6	B
7	A
8	A
9	B
10	B
11	A
12	A
13	A
14	A
15	B
16	B
17	B
18	A
19	A
20	B
21	B
22	A
23	B
24	A
25	A
26	A
27	B
28	B

KOPI
SIGN. MLa DATE: 24-95

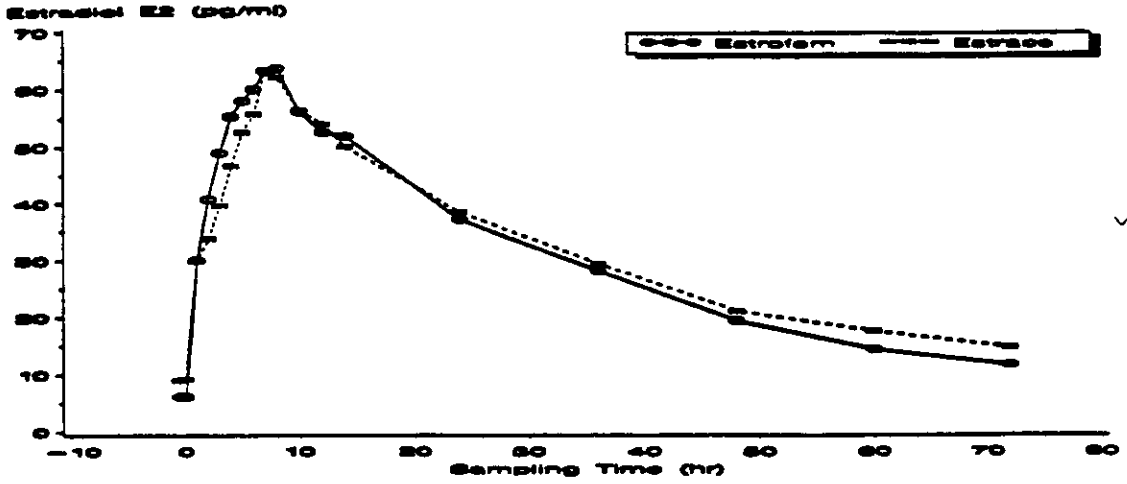
ORIGINAL
GODKENDT / APPROVED
Sign. Date: 24/4-95

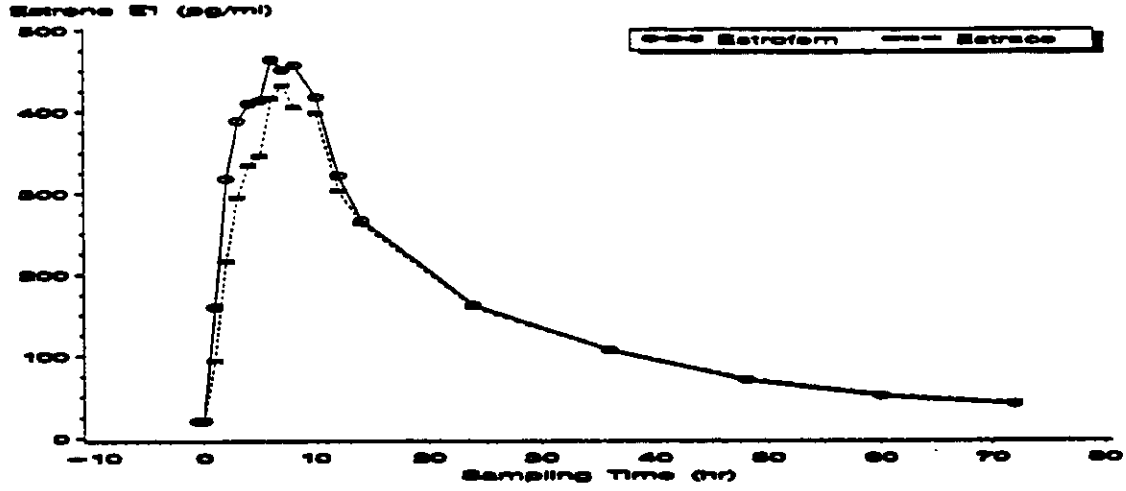
Attachment - 2

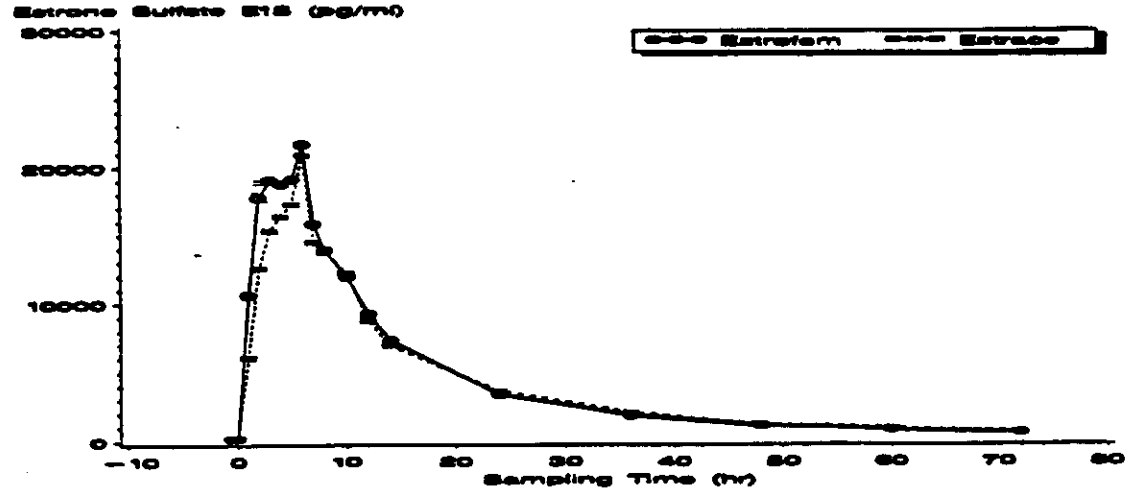
EST/PD/21

FIGURE 1

Mean Concentration Over Time







Attachment- 3

EST/PD/21

Table 8

Estradiol (E2) - Mean Concentration (pg/mL)

	Estrofem Mean (SD)	Estrace Mean (SD)
Sample Size	23	23
Time		
-30 min	6.17(5.29)	9.04(16.47)
0 hr	6.13(4.40)	9.26(17.71)
1 hr	30.13(9.05)	30.04(23.61)
2 hr	40.78(11.37)	33.78(18.47)
3 hr	48.96(16.79)	39.70(19.06)
4 hr	55.22(19.21)	46.61(21.84)
5 hr	57.87(18.98)	52.57(24.83)
6 hr	59.96(20.23)	55.65(25.99)
7 hr	63.04(19.83)	63.26(25.34)
8 hr	63.52(20.75)	62.00(21.02)
10 hr	56.04(19.08)	56.30(22.07)
12 hr	52.57(16.83)	53.91(21.97)
14 hr	51.83(18.52)	50.00(19.53)
24 hr	37.13(16.85)	38.48(18.35)
36 hr	28.30(12.14)	29.57(17.13)
48 hr	19.52(10.68)	21.22(18.74)
60 hr	14.48(9.10)	17.70(17.43)
72 hr	11.70(9.30)	14.78(18.54)

Attachment - 4

Table 7

Estradiol (E2) (pg/mL) - AUC, Cmax, Tmax

	Estrofem Mean (SD)	Estrace Mean (SD)	P-value
Sample Size	23	23	
Analysis not Adjusted for Baseline			
AUC 0-72 (pg/ml*hr)	2211.82(819.87)	2277.95(1239.11)	0.5904
Log AUC 0-72	7.64(0.37)	7.63(0.43)	0.8974
AUC 0-infinity (pg/ml*hr)	2787.61(1681.69)	3856.87(6324.89)	0.2802
Log AUC 0-infinity	7.82(0.44)	7.90(0.64)	0.1990
Cmax (pg/ml)	73.09(21.36)	69.22(27.26)	0.2736
Log Cmax	4.24(0.33)	4.16(0.40)	0.1062
Tmax (hr)	6.87(3.14)	6.87(2.47)	0.9474
90% CI for ratio of AUC 0-72 :	(0.9459, 1.0673)		
90% CI for ratio of Cmax 0-72 :	(1.0002, 1.1740)		
Analysis Adjusted for Baseline			
AUC 0-72 (pg/ml*hr)	1763.05(622.89)	1612.92(534.99)	0.0878
Log AUC 0-72	7.41(0.39)	7.32(0.39)	0.1024
AUC 0-infinity (pg/ml*hr)	1966.53(867.42)	1813.15(593.06)	0.2736
Log AUC 0-infinity	7.50(0.43)	7.44(0.37)	0.3413
Cmax (pg/ml)	66.93(20.24)	60.07(20.33)	0.0092*
Log Cmax	4.15(0.34)	4.03(0.38)	0.0123*
Tmax (hr)	6.87(3.14)	6.87(2.47)	0.9474
90% CI for ratio of AUC 0-72 :	(0.9963, 1.1926)		
90% CI for ratio of Cmax 0-72 :	(1.0457, 1.2143)		

E2 adjusted for baseline defined as 0 if E2 - baseline <= 2pg/ml.
Confidence Interval for ratios back transformed from difference of Logs.
P-value for AUC, Log AUC, Cmax, and Log Cmax based on ANOVA with sequence, subject(sequence), treatment, and period in model.
P-value for Tmax based on Wilcoxon signed rank test.
* Denotes p-value <= 0.05

Table 10

Estrone (E1) - Mean Concentration (pg/mL)

	Estrofem Mean (SD)	Estrace Mean (SD)
Sample Size	23	23
Time		
-30 min	20.09(7.49)	20.87(9.79)
0 hr	20.26(8.02)	22.26(10.31)
1 hr	160.04(71.38)	94.61(47.38)
2 hr	318.30(130.87)	216.39(118.32)
3 hr	388.57(126.79)	294.65(130.44)
4 hr	409.65(126.67)	334.61(133.37)
5 hr	413.26(127.69)	346.17(114.69)
6 hr	463.43(144.89)	415.52(160.59)
7 hr	450.61(161.26)	432.00(164.57)
8 hr	456.39(167.90)	405.43(140.77)
10 hr	417.57(144.48)	397.57(143.55)
12 hr	321.91(124.59)	303.04(122.60)
14 hr	266.52(100.98)	262.43(104.35)
24 hr	162.30(66.68)	160.26(64.43)
36 hr	106.74(44.34)	106.26(46.16)
48 hr	70.09(28.42)	71.74(32.58)
60 hr	50.57(21.71)	52.35(24.70)
72 hr	40.39(18.92)	42.22(18.78)

Attachment 6

Table 9

Estrone (E1) (pg/mL) - AUC, Cmax, Tmax

	Estrofem Mean (SD)	Estrace Mean (SD)	P-value
Sample Size	23	23	
Analysis not Adjusted for Baseline			
AUC 0-72 (pg/ml*hr)	11143.15(3614.93)	10520.20(3500.31)	0.0215*
Log AUC 0-72	9.26(0.37)	9.19(0.43)	0.0318*
AUC 0-infinity (pg/ml*hr)	12246.55(4058.60)	11761.26(3979.71)	0.0878
Log AUC 0-infinity	9.35(0.37)	9.30(0.42)	0.0881
Cmax (pg/ml)	508.22(153.55)	475.74(166.06)	0.0714
Log Cmax	6.18(0.33)	6.09(0.41)	0.0599
Tmax (hr)	6.61(2.15)	7.00(1.68)	0.5426
90% CI for ratio of AUC 0-72 :	(1.0166, 1.1326)		
90% CI for ratio of Cmax 0-72 :	(1.0104, 1.1778)		
Analysis Adjusted for Baseline			
AUC 0-72 (pg/ml*hr)	9680.48(3410.97)	8956.79(3196.87)	0.0097*
Log AUC 0-72	9.11(0.41)	9.01(0.50)	0.0234*
AUC 0-infinity (pg/ml*hr)	10148.77(3676.41)	9446.39(3434.78)	0.0194*
Log AUC 0-infinity	9.15(0.42)	9.06(0.51)	0.0409*
Cmax (pg/ml)	488.04(151.55)	454.17(164.62)	0.0612
Log Cmax	6.14(0.34)	6.04(0.43)	0.0518
Tmax (hr)	6.61(2.15)	7.00(1.68)	0.5426
90% CI for ratio of AUC 0-72 :	(1.0276, 1.1832)		
90% CI for ratio of Cmax 0-72 :	(1.0145, 1.1944)		

E1 adjusted for baseline defined as 0 if E1 - baseline <= 2pg/ml.
Confidence Interval for ratios back transformed from difference of Logs.
P-value for AUC, Log AUC, Cmax, and Log Cmax based on ANOVA with sequence, subject(sequence), treatment, and period in model.
P-value for Tmax based on Wilcoxon signed rank test.
* Denotes p-value <= 0.05

Table 12

Estrone Sulfate (E1S) - Mean Concentration (pg/mL)

	Estrofem Mean (SD)	Estrace Mean (SD)
Sample Size	23	23
Time		
-30 min	225.2(149.6)	250.6(308.1)
0 hr	224.3(159.6)	281.5(368.0)
1 hr	10633.7(5691.3)	6119.3(3964.1)
2 hr	17803.6(7107.8)	12597.7(6307.2)
3 hr	19093.3(7368.4)	15342.5(7149.9)
4 hr	18796.7(7289.5)	16430.0(6653.3)
5 hr	19142.7(8620.9)	17301.1(7535.5)
6 hr	21711.5(9448.9)	20943.4(10349.8)
7 hr	15864.0(5955.5)	14511.9(5844.7)
8 hr	13930.6(4938.2)	13824.8(5535.8)
10 hr	11994.1(4959.7)	12257.6(5563.8)
12 hr	9263.0(5083.8)	8799.7(4369.9)
14 hr	7339.4(3798.6)	6950.1(3584.0)
24 hr	3393.5(1965.4)	3644.2(1881.7)
36 hr	1874.7(1081.2)	2075.0(1277.4)
48 hr	1132.0(623.4)	1202.1(733.0)
60 hr	854.7(610.5)	977.7(706.3)
72 hr	619.9(457.7)	709.3(523.2)

Table 11

Estrone Sulfate (E1S) (pg/mL) - AUC, Cmax, Tmax

	Estrofem Mean (SD)	Estrace Mean (SD)	P-value
Sample Size	23	23	
Analysis not Adjusted for Baseline			
AUC 0-72 (pg/ml*hr)	318101.25(130215.32)	303471.99(128813.88)	0.2386
Log AUC 0-72	12.60(0.39)	12.52(0.47)	0.0992
AUC 0-infinity (pg/ml*hr)	330562.55(138224.55)	318809.22(139254.40)	0.3387
Log AUC 0-infinity	12.63(0.40)	12.57(0.48)	0.1386
Cmax (pg/ml)	23279.70(9294.68)	21572.13(10171.67)	0.0917
Log Cmax	9.98(0.40)	9.87(0.47)	0.0316*
Tmax (hr)	4.74(1.63)	5.74(1.05)	0.0300*
90% CI for ratio of AUC 0-72 :	(0.9982, 1.1561)		
90% CI for ratio of Cmax 0-72 :	(1.0240, 1.2076)		
Analysis Adjusted for Baseline			
AUC 0-72 (pg/ml*hr)	301822.76(122041.63)	284193.07(116199.54)	0.2040
Log AUC 0-72	12.54(0.39)	12.46(0.47)	0.0774
AUC 0-infinity (pg/ml*hr)	309283.20(126872.50)	292795.52(120940.95)	0.2529
Log AUC 0-infinity	12.57(0.40)	12.49(0.47)	0.0965
Cmax (pg/ml)	23054.93(9202.06)	21306.11(10011.67)	0.0859
Log Cmax	9.97(0.40)	9.86(0.47)	0.0292*
Tmax (hr)	4.74(1.63)	5.74(1.05)	0.0300*
90% CI for ratio of AUC 0-72 :	(1.0037, 1.1717)		
90% CI for ratio of Cmax 0-72 :	(1.0257, 1.2100)		

E1S adjusted for baseline defined as 0 if E1S - baseline <= 2pg/ml.
Confidence Interval for ratios back transformed from difference of Logs.
P-value for AUC, Log AUC, Cmax, and Log Cmax based on ANOVA with sequence, subject(sequence), treatment, and period in model.
P-value for Tmax based on Wilcoxon signed rank test.
* Denotes p-value <= 0.05

BIOEQUIVALENCY DEFICIENCIES

ANDA: 40-312 APPLICANT: Novo Nordisk Pharmaceuticals, Inc.

DRUG PRODUCT: Estradiol Tablets, 0.5, 1, 2 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have not provided drug concentration and PK data on diskette. You should submit data on a diskette in ASCII format containing two separate files as follows for estradiol, estrone, and estrone sulfate:

   A. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX THALF KEL

   B. SUBJ SEQ PER TRT C1 C2 C3 ..... Cn

   The fields should be delimited by one blank space, and missing values should be indicated by a period (.).

2. You have provided partial pharmacokinetic data on estradiol, estrone and estrone sulfate including mean and individual subject data for AUC_{0-t}, C_{max} and T_{max}, and mean data for AUC_{0-inf}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}. However, individual subject data for AUC_{0-inf}, $LAUC_{0-inf}$, T_{half}, and K_{el} were not available for review. You should provide individual data and statistics in a tabular form for the test and reference products separately.

3. You should provide table of data points included in calculating K_{el} values and regression coefficients for each drug/metabolite concentration-time curve.

4. The 90% CI for $LAUC_{0-inf}$ for estradiol, estrone and estrone sulfate should be calculated and provided for review.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 40-312
ANDA DUPLICATE

Endorsements: (Final with Dates)

BIOEQUIVALENCY - DEFICIENCIES submission date: 4/30/98

1. **FASTING STUDY** (STF)
Clinical:
Analytic

Strengths: 2mg
Outcome: UN

3. **DISSOLUTION DATA** (DIS)

0.5, 1, 2 mg
Outcome: **AC**

4. **DISSOLUTION WAIVER** (DIW)

Strengths: 0.5 and 1 mg
Outcome: UN

Outcome Decisions:
UN - Acceptable

WINBIO COMMENTS:

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-312

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 40-312	CHEMIST: Eugene L. Schaefer, Ph.D.	DATE: October 27, 1999
DRUG PRODUCT: Estradiol Tablets USP (INNOFEM®)		
FIRM: Novo Nordisk		
DOSAGE FORM: Film-coated Tablets	STRENGTH: 0.5 mg, 1 mg, 2 mg	
cGMP: The facilities were found acceptable on 6/25/99.		
BIO: A "No further questions" fax was issued 7/13/99.		
VALIDATION - (Description of dosage form received by FDA lab same as in firm's ANDA?): Yes DS and DP in USP - MV not needed.		
STABILITY: The containers in the stability studies are identical to those in the container section.		
LABELING: Container, carton, and insert labeling were found satisfactory by Ms. Teresa Watkins on 10/27/99.		
STERILIZATION VALIDATION (If applicable): Not a sterile product.		
SIZE OF BIO BATCH (Firm's source of NDS ok?): DMFs are adequate, as of 10/27/99. See Addendum to Chemistry Review #3. tablets		
SIZE OF STABILITY BATCHES (If different from bio batch, were they manufactured via the same process?): The stability batches were tablets each.		
PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?: The maximum size of production batches will be tablets. The manufacturing process is essentially the same as the exhibit batches.		
Signature of chemist: /S/	Signature of supervisor: /S/	
Eugene L. Schaefer, Ph.D. /7/9	Michael Smela	

\\CDV008\WP51F99\FIRMSNZ\NOVONORD\LTRS&REV\40312AP.SUM

Printed by Pat Beers-Block

Electronic Mail Message

Date: 15-Nov-1999 08:54am
From: DSI Bioequivalence
DSIBE
Dept: HFD-340 MPN1 115
Tel No: 301-827-5460

Subject: RE: Request for Inspection History

Our only inspection at the site in the last 5 years was in September 1997, regarding ANDA 40-114; classified NAI.

There are many other labs throughout the US and in other countries. Since they operate with different SOPs, methodologies, management, etc., we regard them as separate entities.

>Hello. I was wondering if the analytical site (now
>) is the same as
>)?
>
>If not, can you please tell me if there is an inspectional history on
t?

>Thank you,
>
>Jen

Printed by Pat Beers-Block

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 05-Aug-1999 05:57pm
From: Elaine Hu
HUE
Dept: HFD-615 MPN2 118
Tel No: 301-827-5862 FAX 301-594-0181

TO: See Below
Subject: Re: Audits at 7 sites

Good Afternoon,

It was concluded after the Bio Division Directors Meeting held on 8/3/99 with Doug Sporn and Dale Conner, to cancel DSI inspections that have not been started at the following study sites:

-
-
-
-
-

Dr. Skelly provided a list of ANDAs that utilized clinical/analytical sites mentioned above and that are pending DSI audits (please see below). The Division of Bioequivalence reviewed this list, and is authorizing the cancellation of all inspection requests listed below.

Pl e feel free to contact me if you have any further questions.

Th. . you very much for your help,
Elaine
(7-5721)

> Elaine:
>
> The requests for ANDA audit/inspection for which the inspections at
> the seven sites have not yet begun involve these ANDAs:
>
> ion at
>
> [illegible]
>
> [illegible] the audit of the

Distribution:

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RECORD OF TELEPHONE CONVERSATION

Mr. Barbush has a question regarding his pending ANDA 40-312, which is being reviewed as a response to a fax amendment.
Mr. Barbush wishes to change the time point in their dissolution method. Currently they have not less than of the labeled amount is dissolved in 60 min. He wants to change to not less than of the labeled amount to be dissolved in 30 min. Mr. Barbush wants to know how he should submit this information.

I informed Mike Smela and Eugene Schaefer of the above question.
I was instructed to call Mr. Barbush with the following response;

- The USP method is regulatory
- The tightening of the time limit for the dissolution method can be done in an annual report.

DATE
August 30, 1999

ANDA NUMBER
40-312

IND NUMBER

TELECON

INITIATED BY

X **SPONSOR**

FDA

PRODUCT NAME
Estradiol Tablets USP, 0.5, 1, 2 mg

FIRM NAME
Novo Nordisk Pharm

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Michael Barbush
Regulatory Affairs

TELEPHONE NUMBER
(609) 987-5973

SIGNATURE
M.Dillahunt
M. Dillahunt 8/31/99

CC: ANDA 40-312

RECORD OF TELEPHONE CONVERSATION

Mr. Barbush called again on August 31, 1999 and wanted to know what type of data would be necessary to include in the annual report to tighten the limit.

I informed Mr. Barbush, per Mike Smela, he does not need to include any data. He needs to include a notification in the annual report that they are using a tighter in house spec than required by USP.

Mr. Barbush agreed.

DATE
August 30, 1999

ANDA NUMBER
40-312

IND NUMBER

TELECON

INITIATED BY

X **SPONSOR**

FDA

PRODUCT NAME
Estradiol Tablets USP, 0.5, 1, 2 mg

FIRM NAME
Novo Nordisk Pharm

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Michael Barbush
Regulatory Affairs

TELEPHONE NUMBER
(609) 987-5973

SIGNATURE
M.Dillahunt
M Dillahunt 8/31/99

CC: ANDA 40-312

RECORD OF TELEPHONE CONVERSATION

On July 13, 1999, a facsimile amendment was issued to Novo Nordisk Pharmaceuticals, Inc.for ANDA 40-312, **Innofem®**(Estradiol Tablets USP)

On August 9, 1999, Mr.Barbush called requesting clarification on the procedure for submitting a response to a facsimile amendment. Mr. Barbush said he was told by labeling that he could submit the labeling response after the 30 day period without it changing the status of the amendment. I spoke with Pat Beers-Block who consulted with John Grace. They both agreed that a complete response including chemistry and labeling must be submitted to OGD within 30 calendar days from July 13, 1999. Also, the chemistry deficiency that went out on July 13, 1999, clearly states that the response must also address labeling deficiencies.

I returned the call to Mr. Barbush and informed him that a complete response including labeling and chemistry must be submitted within 30 calendar days from July 13, 1999. If a complete response is not received within 30 days, the application will be closed as a minor amendment.

V:\FIRMSNZ\NOVONORD\TELECONS\40312.doc

DATE
August 10, 1999

ANDA NUMBER
40-312

IND NUMBER

TELECON

INITIATED BY

X **SPONSOR**

FDA

PRODUCT NAME

Innofem®(Estradiol Tablets USP) 0.5, 1, 2 mg

FIRM NAME
Novo Nordisk Pharmaceuticals, Inc

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Michael Barbush, Regulatory Affairs

TELEPHONE NUMBER
(609) 987-5973

SIGNATURE
Michelle Dillard 8/11/99

CC

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **40-312** Date of Submission: **May 12, 1999**

Applicant's Name: **Novo Nordisk Pharmaceuticals, Inc.**

Proprietary Name: **Innofem**

Established Name: **Estradiol Tablets USP, 0.5 mg, 1 mg and 2 mg**

Labeling Deficiencies:

1. CONTAINER (100s and 500s)

   a. Satisfactory in draft.

2. CARTON (1 x 100 and 1 x 500)

   a. Please ensure that the NDC numbers are complete in all places in which it appears on the carton when you submit final print labeling.

   b. We acknowledge your statement that one patient package insert will accompany each package size. However, the reference listed drug, ESTRACE®, includes two patient package inserts in its 100 count package size and 10 patient package inserts in its 500 count package size. We request you do the same.

3. PHYSICIAN INSERT

   a. Satisfactory in draft.

4. PATIENT INFORMATION INSERT

   a. Satisfactory in draft.

Please revise your carton labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of final printed carton, physician's insert and patient information insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

40-312

STATUS REPORT FOR CHEMISTRY DOCUMENTS INTENDED TO BE FAXED

Imiquimod Gel-radial Tab. USP

Please check appropriate boxes to indicate the status of other application features when preparing a fax/minor/major def. Fax:

Feature	Pending	Acceptable /Comments Attached	Not Accept/ Comments Attached	Other (i.e. not needed, already sent)
BIO	✓ VK			
LABELING			✓	
METHODS VAL. SPL.		List		
EIR	✓	in Lavender Jacket		
MICRO		N/A		

ANDA #:

DATE: 6/20/07

Project Manager:

Bonnie McNeal _____
Denise Huie _____
Joe Buccine _____
Mark Anderson _____
Kassandra Sherrod _____
Tim Ames _____

RECORD OF TELEPHONE CONVERSATION/MEETING

Mr. Smela and I asked Dr. Barbush to have the specs for the DS updated to comply with the 10th Supplement to USP 23 by adding the new USP test and limits for chromatographic purity.

We also asked for CoAs from each of the DS suppliers, : and showing their materials meet the new requirements, or commitments that future lots of DS will meet the requirements.

We reminded Dr. Barbush how to submit a telephone amendment, and that it needs to be submitted within 10 days.

He said he would communicate our request to Novo Nordisk in Denmark, and he does not anticipate a problem.

\ \TEL
E

MSmela 9/14/99

ELS 9/14/99

DATE
9/14/99

ANDA NUMBER
40-312

TELECON

INITIATED BY _ **APPLICANT/ SPONSOR** **MADE BY** X **TELE.**

X **FDA** _ **IN PERSON**

PRODUCT NAME
Estradiol Tablets

FIRM NAME
Novo Nordisk

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Dr. Michael Barbush

TELEPHONE NUMBER
609-987-5800

SIGNATURE
ELSchaefer, Chemist, Br II
MSmela, TL, Br II

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

PHILADELPHIA DISTRICT
SCIENCE BRANCH

MEMORANDUM

DATE: January 27, 1999

FROM: Director, Science Branch
Philadelphia District, HFR-CE160

SUBJECT: ANDA 40-312: Estradiol Tablets USP, 0.5mg
Novo Nordisk Pharmaceuticals
RE: 13833

TO: Peter Rickman, Review Chemist,
ANDA Review Branch/OGD

The Philadelphia District Laboratory performed the analysis of Estradiol Tablets USP, using the USP method and samples provided. Attached are the summary of results, worksheets, and comments for the subject ANDA.

No problems were encountered with the methodology, and the product met USP specifications.

Based on the analytical results, the ANDA method appears to be suitable for regulatory control of this product.

for Richard E Becoat

W. Charles Becoat

cc

ITS

Summary of Results:

Identification: The principal spot obtained from the test solution corresponds to that of the standard solution

Dissolution:

(6) Tablets tested:
Range:
Requirements: Not less Q + dissolved in 60 minutes.

Assay: Declared 0.5mg Estradiol/tab

#1: 99.2% of declared
#2: 100.6% of declared

Requirements: Between 90.0% - 110.0% of declared

Content Uniformity:

(10) Tablets tested:
Range: %RSD- 1.27

Requirements: 85.0 –115.0% of Declared. RSD< 6.0%

For all tests…Meets USP requirements

M E M O R A N D U M DHHS/PHS/FDA/CDER/OPS/OGD/DCI

DATE: June 10, 1999 ELS 6/10/99

FROM: Eugene L. Schaefer

THROUGH: Mike Smela MSmela 6/11/99

TO: ANDA 40-312, Estradiol Tablets USP, Novo Nordisk

SUBJECT: Minutes of Meeting re Possible Violation of OGD Franchising Policy

PARTICIPANTS: Cecelia Parise, Don Hare, Frank Holcombe, Rashmikant M. Patel, Mike Smela, and Gene Schaefer

Novo Nordisk manufactured four exhibit batches of tablets each, and had more than ablets of each batch packaged by contract packaging companies. Our fax of November 2, 1998 included the following Deficiency #22:

> "Please state the disposition of the remaining bulk coated tablets from each exhibit batch that were not packaged into market containers in support of ANDA 40-312. Also, please acknowledge that exhibit batches may not be marketed until the ANDA has been approved. These batches must be utilized strictly to support the approval of your application."

In their amendment of December 22, 1998, Novo Nordisk responded that tablets from the three non-biobatch exhibit batches were used for stability testing and validation, and the remaining tablets will not be marketed until the ANDA has been approved.

However, for the biobatch, approximately tablets were used for clinical supply and stability testing, and the remaining tablets were sold in countries outside the USA.

The participants discussed the information in the original ANDA and in the amendment, in light of previous situations. They interpreted the franchising policy as intended to prevent firms from using data from the same batch to support more than one marketing application. In the present case, there is no evidence that Novo Nordisk will be using data from the bio-batch to support any application other than ANDA 40-312, and therefore the firm did not violate our franchising policy.

\\

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **40-312** Date of Submission: **April 30, 1998**

Applicant's Name: **Novo Nordisk Pharmaceuticals, Inc.**

Proprietary Name: **Innofem**

Established Name: **Estradiol Tablets USP, 0.5 mg, 1 mg and 2 mg**

Labeling Deficiencies:

1. CONTAINER (100s and 500s)

   a. 100s

      i. We encourage you to differentiate your product strengths with the use of boxing, contrasting colors or some other means.

      ii. Include "Usual Dosage" and "Each tablet contains..." statements.

      iii. Include "Dispense in..." statement.

      iv. Include "An Innofem patient insert..." statement.

   b. 100s and 500s

      Include "Rx only" or "℞ only" statement.

2. CARTON (1 x 100 and 1 x 500)

   a. See comment a. i. and b. i. under CONTAINER.

   b. How many patient package inserts will accompany each package size?

3. INSERT

   I. PHYSICIAN INSERT

      a. TITLE

See comment b.i. under CONTAINER.

b. DESCRIPTION

i. Revise to read "molecular formula" rather than "empirical formula".

ii. To be in accord with USP 23, revise the molecular weight to read "272.39" rather than "272.37".

iii. Inactive Ingredients - Revise to read "lactose monohydrate" rather than "lactose".

c. CLINICAL PHARMACOLOGY

Paragraph one, third sentence - Revise to read "transcription" rather than "transaction".

d. WARNINGS

Induction of malignant neoplasms, Breast Cancer - Revise to read "1.3" rather than "t.3".

e. PRECAUTIONS

i. General

A) Addition of a progestin - Revise this subsection to read as follows:

...progestin for 10 or more days of a cycle...There are, however, possible additional risks...cardioprotective effect of estrogen therapy (see PRECAUTIONS); ...(3) possible enhancement of...tissue although few...point (see PRECAUTIONS below).

B) Insert the following text to appear as the second subsection. In addition, renumber the remaining subsections accordingly:

Cardiovascular risk. A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this

putative benefit is not yet known.

In recent years many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy without added progestins and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports:

(1) Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socio-economic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.

(2) Current medical practice often

includes the use of concomitant progestin therapy in women with intact uteri (see PRECAUTIONS and WARNINGS). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels.

(3) While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see WARNINGS above).

Because relatively long-term use of estrogens by a woman with a uterus has been shown to induce endometrial cancer, physicians often recommend that women who are deemed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

ii. Information for the Patient - Relabel to read "B" rather than "A". In addition, relabel the remaining subsections accordingly.

iii. Insert the following text as the last subsection:

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Large and repeated doses of estrogen over an extended period of time have been shown to accelerate epiphyseal closure, resulting in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. In patients in whom bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended.

Estrogen treatment of prepubertal children also induces premature breast development and vaginal cornification, and may potentially induce vaginal bleeding in girls. In boys, estrogen treatment may modify the normal pubertal process. All other physiological and adverse reactions shown to be associated with estrogen treatment of adults could potentially occur in the pediatric population, including thromboembolic disorders and growth stimulation of certain tumors. Therefore, estrogens should only be administered to pediatric patients when clearly indicated and the lowest effective dose should always be utilized.

f. INFORMATION FOR THE PATIENT

i. USES OF ESTROGEN, fourth bullet - Revise to read "hormonal" rather than "hormone".

ii. WHO SHOULD NOT USE ESTROGENS, Fourth bullet - Delete "had" from the title.

iii. REDUCING THE RISK OF ESTROGEN USE

A) Delete "THE" from the section heading.

B) Third bullet - Insert "any" following "or" in the first sentence of paragraph one.

g. OTHER INFORMATION - Revise paragraph 1 to read as follows:

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 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 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...

II. PATIENT INFORMATION INSERT

a. TITLE - See comment bi under CONTAINER.

b. OTHER INFORMATION - See comment g under PHYSICIAN INSERT.

Please revise your container labels, carton and insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40-312

CORRESPONDENCE

ANDA Facsimile Amendment

Novo Nordisk
Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

October 22, 1999

Office of Generic Drugs
HFD-630, Document Control Room, 150
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/FA

Re: INNOFEM® (estradiol tablets USP)
ANDA No. 40-312
Facsimile Amendment: Labeling

Dear Sir:

Reference is made to the Novo Nordisk Pharmaceuticals, Inc. pending Abbreviated New Drug Application for Innofem® (estradiol tablets USP), 0.5 mg, 1 mg and 2 mg, submitted on April 30, 1998. Reference is also made to our August 12, 1999 facsimile response to OGD's chemistry and labeling review comments contained in your July 13, 1999 facsimile and an August 30, 1999 telephone conversation between Theresa Watkins and Novo Nordisk requesting that we submit the final printed labeling for each tablet strength of the 100 tablet-size container labels as they would appear on the container (i.e., folded label).

We are hereby submitting twelve (12) copies of the requested final printed labeling, with some of the container labels adhered to the containers for reference.

We trust that this response satisfactorily addresses your request and look forward to the acceptance and eventual approval of this application. Should you have any questions concerning this submission, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973.

Sincerely,
Novo Nordisk Pharmaceuticals, Inc.

Michael Barbush (for)

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

OCT [illegible]

ANDA Telephone Amendment

September 21, 1999

NDA ORIG AMENDMENT

Office of Generic Drugs
HFD-630, Document Control Room, 150
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Novo Nordisk

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: INNOFEM® (estradiol tablets USP)
ANDA No. 40-312
Telephone Amendment: Chemistry

Dear Sir:

Reference is made to the Novo Nordisk Pharmaceuticals, Inc. pending Abbreviated New Drug Application for Innofem® (estradiol tablets USP), 0.5 mg, 1 mg and 2 mg, submitted on April 30, 1998, and more recently to our August 12, 1999 facsimile amendment. Reference is also made to a September 14 telephone conversation between your Office and Novo Nordisk to request information in order to comply with recent revisions to the USP monograph for Estradiol.

In response to this request, we have provided the following documentation for your review:

- Revised specification for Estradiol (version 13, dated 08-Sep-1999)
- Certificate of Analysis for one batch of Estradiol from ot No. L00015178)
- Certificates of Analysis for two batches of Estradiol from 3atch Nos. 48052798 and 29052972)

In addition, Novo Nordisk commits to only receive batches from that comply with current USP monograph.

Pursuant to 21 CFR 314.96(b) a field copy is also being forwarded to the FDA District Office

We trust that this response satisfactorily addresses all of your comments expressed during the September 14 telephone conversation and look forward to the acceptance and eventual approval of this application. Should you have any questions concerning this submission, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973.

Sincerely,
Novo Nordisk Pharmaceuticals, Inc.

SEP

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cc: FDA Field Office (Field Copy Certification)

ANDA Facsimile Amendment

Novo Nordisk

August 25, 1999

Office of Generic Drugs
HFD-630, Document Control Room, 150
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

FDC
ORIG AMENDMENT
FA

Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: INNOFEM® (estradiol tablets USP)
ANDA No. 40-312
Facsimile Amendment: Labeling

Dear Sir:

Reference is made to the Novo Nordisk Pharmaceuticals, Inc. pending Abbreviated New Drug Application for Innofem® (estradiol tablets USP), 0.5 mg, 1 mg and 2 mg, submitted on April 30, 1998. Reference is also made to our August 12, 1999 facsimile response to OGD's chemistry and labeling review comments contained in your July 13, 1999 facsimile and an August 24, 1999 telephone conversation between Theresa Watkins and Novo Nordisk requesting that we re-submit the final printed labeling for the professional package and patient information inserts for the drug product.

We are hereby submitting twelve (12) copies of the requested final printed labeling.

We trust that this response satisfactorily addresses your request and look forward to the acceptance and eventual approval of this application. Should you have any questions concerning this submission, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973.

Sincerely,
Novo Nordisk Pharmaceuticals, Inc.

Michael Barbush (for)

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

CENTER FOR DRUGS
REC'D
AUG 26 1999
OGD
EVALUATION AND RESEARCH

ANDA Facsimile Amendment

August 19, 1999

ORIG AMEND.

FA

Office of Generic Drugs
HFD-630, Document Control Room, 150
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Novo Nordisk
Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: INNOFEM® (estradiol tablets USP)
ANDA No. 40-312
Facsimile Amendment: Chemistry and Labeling

Dear Sir:

Reference is made to the Novo Nordisk Pharmaceuticals, Inc. pending Abbreviated New Drug Application for Innofem® (estradiol tablets USP), 0.5 mg, 1 mg and 2 mg, submitted on April 30, 1998 and to our August 12, 1999 facsimile response to OGD's chemistry and labeling review comments contained in your July 13, 1999 facsimile.

We are hereby submitting the hard copy version of the August 12 facsimile amendment. This submission is being provided in duplicate: one Archival copy and one Review copy.

Reviewer Please Note: The twelve copies of final printed labeling will be provided to the agency by special overseas courier directly from Novo Nordisk A/S, Denmark.

We trust that this response satisfactorily addresses all of your comments expressed in your facsimile and look forward to the acceptance and eventual approval of this application. Should you have any questions concerning this submission, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973.

Sincerely,
Novo Nordisk Pharmaceuticals, Inc.

Barry Rein, Ph.D.
Vice President, Regulatory Affairs

ANDA Facsimile Amendment

August 12, 1999

Office of Generic Drugs
HFD-630, Document Control Room, 150
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Novo Nordisk

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: INNOFEM® (estradiol tablets USP)
ANDA No. 40-312
Facsimile Amendment: Chemistry and Labeling

Dear Sir:

Reference is made to the Novo Nordisk Pharmaceuticals, Inc. pending Abbreviated New Drug Application for Innofem® (estradiol tablets USP), 0.5 mg, 1 mg and 2 mg, submitted on April 30, 1998.

We are submitting by facsimile our response to OGD's chemistry and labeling review comments contained in your July 13, 1999 facsimile (Please refer to Attachments 1 and 2). For ease of review, we have organized our response in a comment-response format, i.e., the FDA comment followed by Novo Nordisk's reply.

Pursuant to 21 CFR 314.96(b) a field copy is also being forwarded to the FDA District Office

We trust that this response satisfactorily addresses all of your comments expressed in your facsimile and look forward to the acceptance and eventual approval of this application. Should you have any questions concerning this submission, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cc: FDA Field Office (Field Copy Certification)

NEW CORRESP
NC

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

20 August 1999
MMPe

99-312

Novo Nordisk A/S

Niels Steensens Vej 1
2820 Gentofte
Denmark

Tel. +45 4444 8888
Fax. +45 3968 3568
Telex 37173

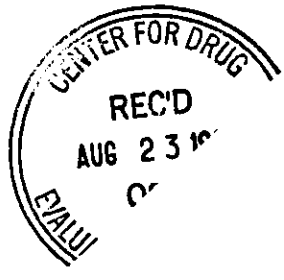
A/S Reg. No. 16201

This package contains the 12 copies of final printed labelling for Innofem (estradiol tablets USP) as requested in your July 13, 1999 facsimile and referred to in our August 12, 1999 facsimile amendment. A copy of the cover letter accompanying the August 12 facsimile amendment is provided.

Yours sincerely,

Mette Pedersen

Meite Meyer Pedersen
Labelling
HC RBS



ANDA Facsimile Amendment

t 25, 1999

of Generic Drugs
30, Document Control Room, 150
for Drug Evaluation and Research
nd Drug Administration
Park North II
tandish Place
lle, MD 20855

FPL
ORIG AMENDMENT
FA

Novo Nordisk
Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

INNOFEM® (estradiol tablets USP)
ANDA No. 40-312
Facsimile Amendment: Labeling

ir:

ıce is made to the Novo Nordisk Pharmaceuticals, Inc. pending Abbreviated New Drug Application ofem® (estradiol tablets USP), 0.5 mg, 1 mg and 2 mg, submitted on April 30, 1998. Reference is ıde to our August 12, 1999 facsimile response to OGD's chemistry and labeling review comments ed in your July 13, 1999 facsimile and an August 24, 1999 telephone conversation between Theresa s and Novo Nordisk requesting that we re-submit the final printed labeling for the professional package ient information inserts for the drug product.

hereby submitting twelve (12) copies of the requested final printed labeling.

st that this response satisfactorily addresses your request and look forward to the acceptance and ıl approval of this application. Should you have any questions concerning this submission, please Michael Barbush, Regulatory Affairs, at 609-987-5973.

ly,
Jordisk Pharmaceuticals, Inc.

(for)

Reit, Ph.D.
esident, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 26 1999
OGD

New Correspondence

NEW CORRESP

NC

1999

ikant M. Patel, Ph.D.
ector, Division of Chemistry I
ffice of Generic Drugs
DER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Novo Nordisk
Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: ANDA No. 40-312 INNOFEM® (estradiol tablets USP)

Dear Dr. Patel:

Reference is made to Novo Nordisk Pharmaceuticals, Inc.'s pending Abbreviated New Drug Application for Innofem® (estradiol tablets USP), 0.5 mg, 1 mg and 2 mg, submitted on April 30, 1998 and to all subsequent amendments to the subject ANDA. Reference is also made to correspondences between the Division and Novo Nordisk on May 10, 24, and 27, 1999, to discuss modifications to the drug substance specifications and guidance regarding submission of the revised specifications. The modification involved deleting the primary test method for particle size determination, "Determination of Particle Size Distribution in Suspensions performed by (", and replacing it with the current alternate method, "Particle size distribution of suspensions of estradiol and norethisterone acetate determined by laser diffraction, A3520a", which would then become the preferred regulatory method.

Data demonstrating the suitability and validation of the , method compared to the method was provided in our December 22, 1998 major CMC amendment to ANDA 40-312, under Attachment 2/Appendix 3, pages 414 - 476. The data clearly demonstrates that the , method is superior to the nethod, and supports the decision to employ the n method as the preferred regulatory method.

During the May 27 correspondence, it was agreed that we could submit the revised specifications to the application at this time without affecting the current review process. In addition, the Division requested that we submit the revised specifications for the drug substance as a "New Correspondence" submission to the application. Therefore, a copy of the revised specifications is enclosed with this letter.

We trust that this information satisfactorily addresses your request and we look forward to the acceptance and eventual approval of this application. Should you have any questions concerning this submission, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Karen O'Hopkins for

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

CENTER FOR DRUG
REC'D
JUN 02 1999
OGD
EVALUATION AND RESEARCH

NDA ORIG AMENDMENT

N/AF

May 12, 1999

Mr. Jerry Phillips
Director, Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research (HFD-650)
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

Novo Nordisk
Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: ANDA No. 40-312 INNOFEM™ (estradiol tablets USP)
LABELING AMENDMENT

Dear Mr. Phillips:

Reference is made to Novo Nordisk Pharmaceuticals, Inc.'s pending Abbreviated New Drug Application for Innofem™ (estradiol tablets USP), 0.5 mg, 1 mg and 2 mg, submitted on April 30, 1998. Reference is also made to your facsimile of November 2, 1998 detailing deficiencies in this application with regard to the container labels, carton, and insert labeling. As requested, a copy of the facsimile in included with this response.

Accordingly, we are herewith providing our official response to the November 2, 1998 facsimile. All comments made by the labeling reviewer requesting revisions to the container labels, professional package insert, and free-standing patient package information insert for Innofem™ (Estradiol Tablets, USP) have been addressed; Four copies of the revised labels and labeling for Innofem™ (Estradiol Tablets, USP) are provided. In addition, to facilitate review of the revised labels and labeling in this amendment, we have provided a side-by-side comparison of the revised proposed labeling with the proposed labeling from the April 30, 1998 submission with all differences annotated and explained.

This amendment to ANDA 40-312 is being provided in duplicate: one Archival copy (blue jacket) and one Review copy (red jacket).

We trust that this response satisfactorily addresses all of your comments expressed in your facsimile and look forward to the acceptance and eventual approval of this application. Should you have any questions concerning this submission, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973.

Sincerely,
Novo Nordisk Pharmaceuticals, Inc.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosures

BIOEQUIVALENCE
TELEPHONE AMENDMENT

April 27, 1999

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research (HFD-650)
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

Novo Nordisk

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: ANDA No. 40-312 INNOFEM™ (estradiol tablets, USP)

Dear Dr. Conner:

Reference is made to Novo Nordisk Pharmaceuticals, Inc.'s pending Abbreviated New Drug Application for Innofem™ (estradiol tablets, USP), 0.5 mg, 1 mg and 2 mg, submitted on April 30, 1998 and to our November 17, 1998 amendment to address bioequivalency deficiencies in the application. Reference is also made to an April 16, 1999 teleconference between your Division and Novo Nordisk to discuss: (1) the bioequivalency reviewer's difficulty in accessing the drug concentration and PK data provided on diskette as part of our response to your comment #1 in the November 17, 1998 amendment, and (2) his request for another diskette with corrected sequence and period fields for the drug concentration and PK data.

In response to this last mentioned request, we are providing a new diskette (in SAS transport file format) which addresses the bioequivalency reviewer's comments. In addition, we are also providing the SAS codes which can assist the reviewer to read in data for the ASCII files of the same datasets provided on diskette in the November 17th amendment.

This amendment to ANDA 40-312 is being provided in duplicate: one Archival copy (blue jacket) and one Review copy (orange jacket).

We trust that this response satisfactorily addresses all comments expressed during the April 16th teleconference and look forward to the acceptance and eventual approval of this application. Should you have any questions concerning this submission, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973.

Sincerely,
Novo Nordisk Pharmaceuticals, Inc.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosures

RECEIVED
APR 2 1999
GENERIC DRUGS

Eugene

May 24, 1999

RE: ANDA 40-312

Dear Denise:

Novo Nordisk has decided to modify the testing specifications for the estradiol drug substance with regard to the method for determination of particle size distribution of estradiol during the pre-approval review process. During a telephone conversation on May 10th , you indicated to me that such a change could take place during the review process without affecting the 180-day review clock for the ANDA.

The modified specifications for the drug substance will indicate that the current primary method for determining particle size distribution, "Determination of Particle Size Distribution in Suspensions performed by , will be designated as "alternate method", and the current alternate method, "Particle size distribution of suspensions of estradiol and determined by , A3520a", will become the preferred regulatory method.

Data demonstrating the suitability and validation of the method compared to the method was provided in our December 22, 1998 major CMC amendment to ANDA 40-312, under Attachment 2/Appendix 3, pages 414 - 476. The data clearly demonstrates that the method is superior to the r method, and supports the decision to employ the method as the preferred regulatory method. The counter method will remain in the specifications as the designated alternate method.

See also attachment 1, appendix 10, and appendix 3, 15

Based on the current 180-day review clock for the ANDA, the review is scheduled to end on June 30, 1999. If this re-designation of the preferred method for particle size determination is acceptable to the Office of Generic Drugs, Novo Nordisk proposes to provide the modified specifications in the annual report for the ANDA.

If you have any questions, please contact me at the number provided on the cover sheet.

Sincerely,

Denise, Please ask Mr. Barbush to provide the modified specifications now, rather than in annual report. I will review them with the major amendment. The modified specs could be NC, but send fax to our branch.

Thank you. Gene 5/24/99

Michael Barbush
Regulatory Affairs

ANDA Amendment

December 22, 1998

NDA ORIG AMENDMENT
N/Ac

Office of Generic Drugs
HFD-630, Document Control Room, 150
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: INNOFEM® (estradiol tablets USP)
ANDA No. 40-312
Major Amendment--CMC: Response to CMC Review

Dear Sir:

Reference is made to the Novo Nordisk Pharmaceuticals, Inc. pending Abbreviated New Drug Application for Innofem® (estradiol tablets USP), 0.5 mg 1 mg and 2 mg, submitted on April 30, 1998.

We are submitting in duplicate, in one volume, our response to the CMC Review comments of November 2, 1998 (Please refer to Attachment 1). Pursuant to 21 CFR 314.96(b) a field copy is also being forwarded to the FDA District Office. Please note the requested labeling changes will be submitted at a later date as discussed with the OGD.

For ease of review, we have organized our response in a comment-response format, i.e., the FDA comment followed by Novo Nordisk's reply for each question of section A and question 5 of section B.

Regarding Dr. Patel's comments in section B of the November 2 facsimile, Novo Nordisk acknowledges the following:

1. Information on manufacturing facilities and outside contractors need not be duplicated in Sections IX and X. Future submissions will have a listing of manufacturing activities/site address.
2. The time limit from granulation to compression begins on the day the drug substance is mixed with an excipient, and the time limit from compression to coating starts on the day the first tablets are compressed.
3. The expiration dating period for the drug product begins on the day the drug substance is mixed with an excipient.
4. When a Novo Nordisk analytical method is different from a USP/NF method, , the USP/NF method becomes the recognized regulatory method and the Novo Nordisk method becomes an alternate method in cases of a dispute.
5. Additional stability data for exhibit batches: see Attachment 1.
6. Labeling deficiencies: addressed above.
7. An evaluation has been requested from the Office of Compliance. The manufacturing site was inspected during the week of September 28, 1998. There were no 483 citations and the facility

8. The bioequivalence information is pending review. On November 17, 1998 a bioequivalency amendment was submitted to the ANDA which addressed the cited deficiencies (D.P. Connor facsimile of November 2).

Additionally, we are amending the CMC section regarding the specification for purified water, testing of nd an alternate method of particle size determination for the drug substance. Full descriptions of the changes along with supporting documentation have been provided in Attachment 2.

We trust that this response satisfactorily addresses all of your comments expressed in your facsimile and look forward to the acceptance and eventual approval of this application. Should you have any questions concerning this submission, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Karen A. Hopkins

for Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cc: FDA Field Office (Field Copy Certification)

ANDA 40-312

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
100 Overlook Center, Suite 300
Princeton, NJ 08540-7810

Dear Sir:

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

NAME OF DRUG: Estradiol Tablets USP, 0.5 mg, 1 mg and 2 mg

DATE OF APPLICATION: April 30, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 1, 1998

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

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

Should you have questions concerning this application, contact:

Sheila O'Keefe
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

505(j)(2)(A) CK
5/11/98

April 30, 1998

Novo Nordisk
Novo Nordisk Pharmaceuticals Inc.
Suite 200
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Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Office of Generic Drugs
HFD-630, Document Control Room, 150
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

SUBJECT: INNOFEM™ (estradiol tablets USP) 0.5 mg, 1 mg, and 2 mg

Dear Sir:

Novo Nordisk Pharmaceuticals, Inc. is hereby submitting an Abbreviated New Drug Application pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, and to Section 21 CFR 314.92 -341.94 of the Code of Federal Regulations for Innofem™ (estradiol tablets USP) 0.5 mg. 1 mg, and 2 mg.

A comprehensive table of contents is provided which shows the volume and page number of our submission's contents, as required by the regulations part 314.94(a)(2).

A copy of page 3-130 of the list of Approved Prescription Drug Products with Therapeutic Equivalence Evaluations, 17th Edition (1997), is enclosed showing the inclusion of the referenced listed drug, Estrace® (estradiol tablets USP), manufactured by Bristol-Myers Squibb Co.

The proposed labeling of the generic drug is the same as that for the reference listed drug; differences are editorial in nature except for those having to do with inactive formulation ingredients, manufacturer, dosage form descriptions and market package presentations.

The bioequivalence of Innofem™ (estradiol tablets USP) 2 mg (Novo Nordisk) has been compared with that of the reference listed drug, Estrace® (estradiol tablets USP) 2 mg (Bristol-Myers Squibb Co.) in a fasting *in-vivo* bioequivalence study. The statistical analysis of the results obtained from the study has shown that the two drug products are bioequivalent. This information is provided in Volumes 2 and 3 (Section VI) of the application.

This product is currently marketed in Europe under the European-registered tradename of Estrofem® Tablets. This application does contain certain developmental documentation that employs the use of Estrofem® Tablets rather than Innofem™ Tablets or Estradiol Tablets USP. Please note that Estrofem® Tablets and Innofem™ Tablets are the same product.

This submission is being provided in duplicate: one Archival copy (blue jackets) and one Review copy containing two parts (Chemistry, Manufacturing and Controls data in red jackets; Bioavailability/bioequivalence data in orange jackets). In addition, we certify that a third copy containing only CMC information (burgundy jacket) has been forwarded to the FDA Field Office in Parsippany, New Jersey.

Any questions concerning this application can be addressed to Michael Barbush, Regulatory Affairs, at 609-987-5973 (phone) or 609-987-3916 (fax).

We look forward to your prompt review and approval of the application.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Maryellen McElligott for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosures