# CENTER FOR DRUG EVALUATION AND RESEARCH

# Approval Package for:

# APPLICATION NUMBER:

# 20-907/S-002

| | |
|---|---|
| Trade Name: | Activelle 1mg/0.5mg Tablets |
| Generic Name: | estradiol / norethindrone acetate |
| Sponsor: | Novo Nordisk |
| Approval Date: | February 10, 2000 |

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 20-907/S-002

**CONTENTS**

Reviews / Information Included in this NDA Review.

| | |
|---|---|
| Approval Letter(s) | X |
| Tentative Approval Letter(s) | |
| Final Printed Labeling | X |
| CSO Labeling Review(s) | |
| Medical Officer Review(s) | |
| Chemistry Review(s) | X |
| Microbiology Review(s) | |
| Bioequivalence Review(s) | |
| Administrative Document(s) | X |
| Correspondence | X |

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 20-907/S-002

# APPROVAL LETTER

NDA 20-907/S-002

FEB 1 0 2000

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

Dear: Dr. Reit:

Please refer to your supplemental new drug application dated November 16, 1999, received November 17, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Activelle™, (estradiol/northindrone acetate) tablet, 1mg/0.5mg per day.

This "Changes Being Effected" supplemental new drug application provides for the change of the proprietary name from Activelle to Activella (change from "e" to an "a").

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted November16, 1999, patient package insert submitted November 16, 1999, immediate container and carton labels submitted November 16, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-907/S-002." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Dornette Spell-LeSane, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Susan Allen, MD 2/10/00

Susan Allen, M.D.
Acting Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-907
HFD-580/Div. Files
HFD-580/D.Spell-LeSane
HFD-580/Slaughter/Price/Lin/Rheem/Jordan/Parekh/Rumble
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: dsl/January 31, 2000
Initialed by: Rumble, 2.3.00/Price, 2.3.00/Lin, 2.3.00/Rhee, 2.3.00/Slaughter, 2.3.00/
Mann, 2.4.00/Allen, 2.7.00
final:Spell-LeSane, 2.10.00
filename: ap002.doc

**APPROVAL (AP)**

APPEARS THIS WAY
ON ORIGINAL

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 20-907/S-002

# FINAL PRINTED LABELING

**ACTIVELLE™**

(estradiol/norethindrone acetate tablets)

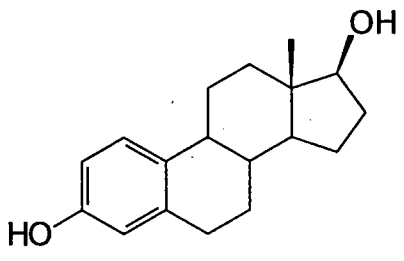
1mg/0.5mg

Rx only

## DESCRIPTION

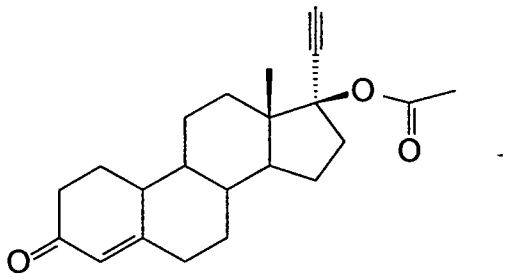
Activelle™ is a single tablet containing an estrogen, estradiol ($E_2$), and a progestin, norethindrone acetate (NETA), for oral administration. Each tablet contains 1 mg estradiol and 0.5 mg norethindrone acetate and the following excipients: lactose monohydrate, starch (corn), copovidone, talc, magnesium stearate, hydroxypropyl methylcellulose and triacetin.

Estradiol ($E_2$) is a white or almost white crystalline powder. Its chemical name is estra-1, 3 ,5 (10)-triene-3, 17β-diol hemihydrate with the empirical formula of $C_{18}H_{24}O_2$, ½ $H_2O$ and a molecular weight of 281.4. The structural formula of $E_2$ is as follows:




**Estradiol**

Norethindrone acetate (NETA) is a white or yellowish-white crystalline powder. Its chemical name is 17β -acetoxy-19-nor-17α -pregn-4-en-20-yn-3-one with the empirical formula of $C_{22}H_{28}O_3$ and molecular weight of 340.5. The structural formula of NETA is as follows:



**Norethindrone Acetate**

## CLINICAL PHARMACOLOGY

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes and bind to and activate the nuclear estrogen receptor, a DNA-binding protein that is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, that 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 in women.

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its

metabolites, estrone and estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 $\mu$g of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion in peripheral tissues of androstenedione which is secreted by the adrenal cortex, to estrone. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) through a negative feedback mechanism, and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

Progestin compounds enhance cellular differentiation and generally oppose the actions of estrogens by decreasing estrogen receptor levels, increasing local metabolism of estrogens to less active metabolites, or inducing gene products that blunt cellular responses to estrogen. Progestins exert their effects in target cells by binding to specific progesterone receptors that interact with progesterone response elements in target genes. Progesterone receptors have been identified in the female reproductive tract, breast, pituitary, hypothalamus, and central nervous system. Progestins produce similar endometrial changes to those of the naturally occurring hormone progesterone.

The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. The addition of a progestin, in adequate doses and appropriate duration, to an estrogen replacement regimen reduces the incidence of endometrial hyperplasia, and the attendant risk of carcinoma in women with intact uterus.

## PHARMACOKINETICS

### ABSORPTION

Estradiol is well absorbed through the gastrointestinal tract. Following oral administration of Activelle™, peak plasma estradiol concentrations are reached slowly within 5-8 hours. When given orally, estradiol is extensively metabolized (first-pass effect) to estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogens. After oral administration, norethindrone acetate is rapidly absorbed and transformed to norethindrone. It undergoes first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration within 0.5-1.5 hours. The oral bioavailability of estradiol and norethindrone following administration of Activelle™ when compared to a combination oral solution is 53% and 100%, respectively. The pharmacokinetic parameters of estradiol ($E_2$), estrone ($E_1$), and norethindrone (NET) following single oral administration of Activelle™ in 25 volunteers are summarized in TABLE 1.

**TABLE 1**
**PHARMACOKINETIC PARAMETERS**
**AFTER A SINGLE DOSE OF ACTIVELLE™**
**IN HEALTHY POSTMENOPAUSAL WOMEN**

| | Activelle™ (n=25) Mean[C] ± SD |
|---|---|
| Estradiol [a] ($E_2$) | |
| AUC (0-72h) (pg/mL*h) | 1053 ± 310 |
| $C_{max}$ (pg/mL) | 34.6 ± 10.8 |
| $t_{max}$ (h) | 6.8 ± 2.9 |
| $t_{1/2}$ (h) [d] | 13.2 ± 4.7 |
| Estrone [a] ($E_1$) | |
| AUC (0-72h) (pg/mL*h) | 5223 ± 1618 |
| $C_{max}$ (pg/mL) | 251.1 ± 91.0 |
| $t_{max}$ (h) | 5.7 ± 1.4 |
| $t_{1/2}$ (h) [d] | 12.2 ± 4.6 |
| Norethindrone (NET) | |
| AUC (0-72h) (pg/mL*h) | 23681 ± 9023 [b] |
| $C_{max}$ (pg/mL) | 5308 ± 1510 |
| $t_{max}$ (h) | 1.0 ± 0.0 |
| $t_{1/2}$ (h) | 11.4 ± 2.7 |

AUC = area under the curve, $C_{max}$ = maximum plasma concentration, $t_{max}$ = time at maximum plasma concentration, $t_{1/2}$ = half-life, SD = standard deviation

[a] baseline unadjusted data; [b] (n=23); [c] arithmetic mean; [d] baseline adjusted data

Following continuous dosing with once-daily administration of Activelle™ , serum levels of estradiol, estrone, and norethindrone reached steady-state within two weeks with an accumulation of 33-47% above levels following single dose administration. Unadjusted circulating levels of $E_2$, $E_1$, and NET during Activelle™ treatment at steady state (dosing at time 0) are provided in Figures 1a and 1b.

**Figure 1a**
**Levels of Estradiol and Estrone at Steady State during Continuous Dosing with Activelle™ (n=24)**

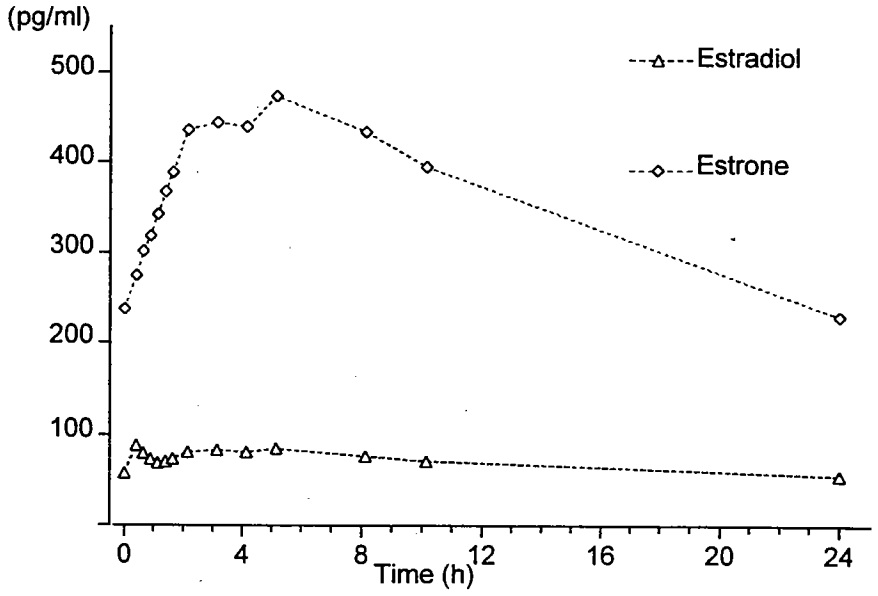
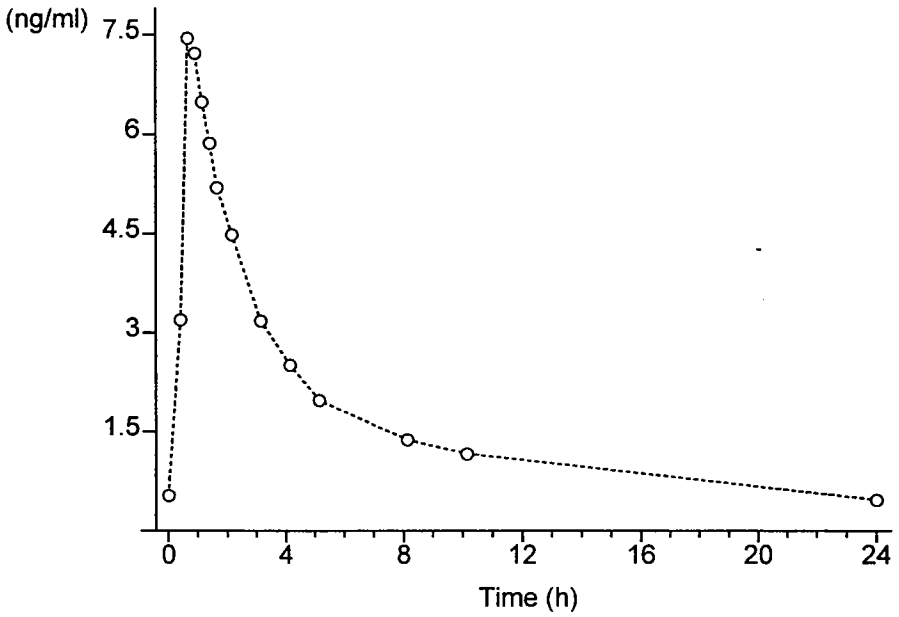


**Figure 1b**
**Levels of Norethindrone at Steady State during Continuous Dosing with Activelle™ (n=24)**




## DISTRIBUTION

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol circulates in the blood bound to sex-hormone-binding globulin (SHBG) (37%) and to albumin (61%), while only approximately 1-2% is unbound. Norethindrone also binds to a similar extent to SHBG (36%) and to albumin (61%).

## METABOLISM AND EXCRETION

*Estradiol:* Exogenous estrogens are metabolized in the same manner as endogenous

estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. The half-life of estradiol following single dose administration of Activelle™ is 12-14 hours.

*Norethindrone Acetate*: The most important metabolites of norethindrone are isomers of 5α-dihydro-norethindrone and tetrahydro-norethindrone, which are excreted mainly in the urine as sulfate or glucuronide conjugates. The terminal half-life of norethindrone is about 8-11 hours.

## DRUG-DRUG INTERACTIONS

Coadministration of estradiol with norethindrone acetate did not elicit any apparent influence on the pharmacokinetics of norethindrone. Similarly, no relevant interaction of norethindrone on the pharmacokinetics of estradiol was found within the NETA dose range investigated in a single dose study.

## FOOD-DRUG INTERACTIONS

A single-dose study in 24 healthy postmenopausal women was conducted to investigate any potential impact of administration of Activelle™ with and without food. Administration of Activelle™ with food did not modify the bioavailability of estradiol, although increases in $AUC_{0-72}$ of 19% and decreases in $C_{max}$ of 36% for norethindrone

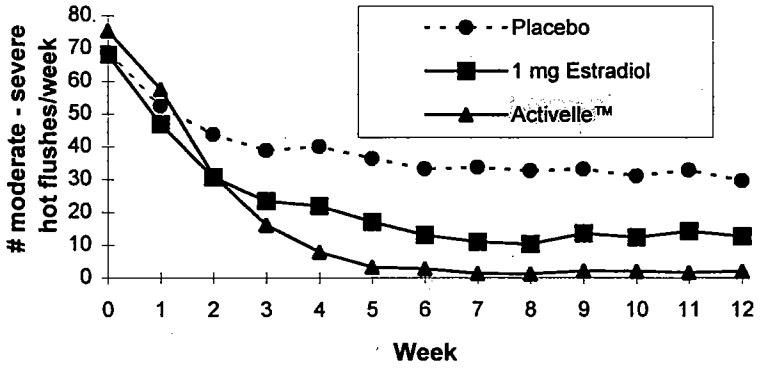
were seen.

## CLINICAL STUDIES

### VASOMOTOR SYMPTOMS

Activelle™ is effective in reducing the number of moderate-to-severe vasomotor symptoms in postmenopausal women. In a 12-week randomized clinical trial involving 92 subjects, Activelle™ was compared to 1 mg of estradiol and to placebo. The mean number and intensity of hot flushes were significantly reduced from baseline to week 12 in both the Activelle™ and the 1 mg estradiol group compared to placebo (see Figure 2).

**Figure 2**
**Mean Weekly Number of Moderate and Severe Hot Flushes in a 12-Week Study**




### ENDOMETRIAL HYPERPLASIA

Activelle™ reduced the incidence of estrogen-induced endometrial hyperplasia at 1 year

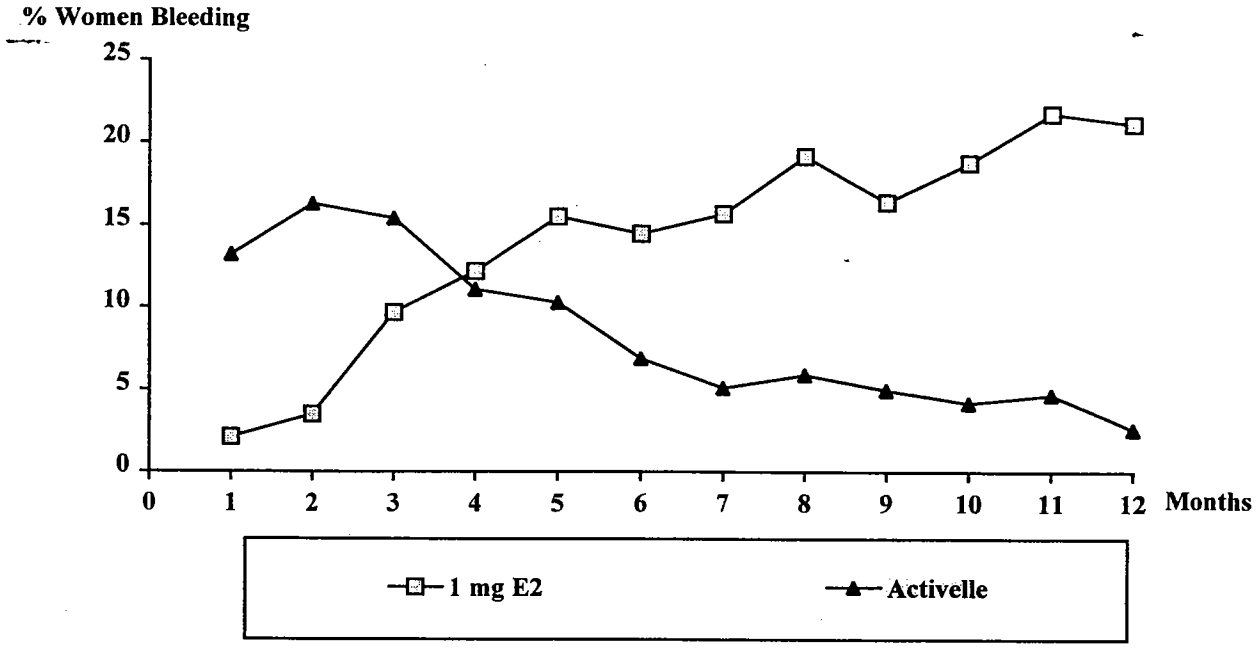
in a randomized, controlled clinical trial. This trial enrolled 1,176 subjects who were randomized to one of 4 arms: 1 mg estradiol unopposed (n=296), 1 mg $E_2$ + 0.1 mg NETA (n=294), 1 mg $E_2$ + 0.25 mg NETA (n=291), and Activelle™ [1 mg $E_2$ + 0.5 mg NETA] (n=295). At the end of the study, endometrial biopsy results were available for 988 subjects. The results of the 1 mg estradiol unopposed arm compared to Activelle™ are shown in TABLE 2.

**TABLE 2**
**INCIDENCE OF ENDOMETRIAL HYPERPLASIA WITH UNOPPOSED ESTRADIOL AND ACTIVELLE™ IN A 12-MONTH STUDY**

| | 1 mg $E_2$ (n=296) | Activelle™ (n=295) |
|---|---|---|
| No. of subjects with histological evaluation at the end of the study | 247 | 241 |
| No. (%) of subjects with endometrial hyperplasia at the end of the study | 36 (14.6%) | 1 (0.4%) |

During the initial months of therapy, irregular bleeding or spotting occurred with Activelle™ treatment. However, bleeding tended to decrease over time, and after 12 months of treatment with Activelle™, fewer than 3% of women reported bleeding (see Figure 3).

**Figure 3**
**Percentage of Women Bleeding at Each Month**
**in a 12-Month Study**




n=number of women
1 mg $E_2$ (3, 6, 9 and 12 months): n=278, 255, 226, 212
Activelle™ (3, 6, 9 and 12 months): n=273, 246, 238, 232

INFORMATION REGARDING LIPID EFFECTS

A 12-month, placebo-controlled clinical trial in 80 postmenopausal Caucasian women at low risk for cardiovascular disease compared the effects of Activelle™ to placebo on lipid parameters. These results are shown in TABLE 3.

**TABLE 3**
**PERCENTAGE CHANGE FROM BASELINE**
**IN SELECTED LIPID PARAMETERS WITH ACTIVELLE™**
**IN A 12-MONTH PLACEBO-CONTROLLED STUDY**

| Lipid Parameter % | Activelle (n=35) | Placebo (n=34) |
|---|---|---|
| Total Cholesterol | -10.5% | -0.8% |
| HDL-C[1] | -12.4% | -6.1% |
| LDL-C[2] | -10.8% | 0.8% |
| LDL: HDL Ratio | 0.1% | 9.2% |
| Triglycerides | 2.2% | 4.4% |

[1] High density lipoprotein-cholesterol
[2] Low density lipoprotein-cholesterol

## INDICATIONS AND USAGE

Activelle™ therapy is indicated in women with an intact uterus for 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 that might occur during menopause and they should not be used to treat these conditions.

2. Treatment of vulvar and vaginal atrophy.

## CONTRAINDICATIONS

Estrogens/progestins combined should not be used in women under any of the following conditions or circumstances:

1. Known or suspected pregnancy, including use for missed abortions or as a diagnostic test for pregnancy. Estrogen or progestin may cause fetal harm when administered to a pregnant woman.

2. Known or suspected breast cancer, or past history of breast cancer associated with the use of estrogens.

3. Known or suspected estrogen-dependent neoplasia, e.g., endometrial cancer.

4. Abnormal genital bleeding of unknown etiology.

5. Known or suspected active deep venous thrombosis, thromboembolic disorders or stroke or past history of these conditions associated with estrogen use.

6. Liver dysfunction or disease.

7. Hypersensitivity to any of the components of Activelle™.

**WARNINGS**

ALL WARNINGS BELOW PERTAIN TO THE USE OF THIS COMBINATION PRODUCT.

Based on experience with estrogens and/or progestins:

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. There is no significant increased risk

associated with the use of estrogens for less than one year. The greatest risk appears to be associated with prolonged use with increased risks of 15- to 24-fold with five or more years of use. 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 withdrawal.
Progestins taken with estrogens have been shown to significantly reduce, but not eliminate, the risk of endometrial cancer associated with estrogen use. In a large clinical trial, the incidence of endometrial hyperplasia with Activelle™ was 0.4% (one simple hyperplasia without atypia) compared to 14.6% with 1 mg estradiol unopposed (see CLINICAL STUDIES).

Clinical surveillance of all women taking estrogen/progestin combinations 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 equivalent estrogen doses.

*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 doses, or in those taking lower doses for prolonged periods of time, especially in excess of 10 years.

While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggest that progestins do not reduce, and may enhance, the moderately increased breast cancer risk that has been reported with prolonged estrogen replacement therapy.

In a one-year trial among 1,176 women who received either unopposed 1 mg estradiol

or a combination of 1 mg estradiol plus one of three different doses of NETA (0.1, 0.25 and 0.5 mg), seven new cases of breast cancer were diagnosed, two of which occurred among the group of 295 Activelle™ - treated women.

Women on hormone replacement therapy should have regular breast examinations and should be instructed in breast self-examination, and women over the age of 40 should have regular mammograms.

2. *Congenital Lesions with Malignant Potential:* Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possible 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. Although some of these changes are benign, others are precursors of malignancy.

3. *Cardiovascular disease.* Large doses of estrogens (5 mg conjugated estrogen 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 risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women or from unopposed estrogen to combination estrogen/progestin therapy. 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. *Hypercalcemia.* Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drugs should be stopped and appropriate measures taken to reduce the serum calcium level.

5. *Effects during pregnancy.* Use in pregnancy is not recommended.

6. *Gallbladder disease.* Two studies have reported a 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens. Among the 1,516 women treated in clinical trials with 1 mg estradiol alone or in combination with several doses of NETA, 3 women had surgically confirmed cholelithiasis, none of them on Activelle™ treatment.

7. *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 non-users. Two other studies showed slightly lower blood pressure among estrogen users compared to non-users. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.

8. *Thromboembolic disorders.* The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drugs should be discontinued immediately. In a one-year study where 295 women were exposed to Activelle™, there were two cases of deep vein thromboses reported.

9. *Visual abnormalities.* Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examinations reveal papilledema or retinal vascular lesions, medication should be withdrawn.

## PRECAUTIONS

### GENERAL

Based on experience with estrogens and/or progestins:

1. *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 that 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.
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.

Current medical practice often includes the use of concomitant progestin therapy in women with intact uterus. While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins attenuate at least some of the favorable effects of estrogens on HDL levels, although they maintain the favorable effect of estrogens on LDL levels.

The safety data regarding Activelle™ were obtained primarily from clinical trials and epidemiologic studies of postmenopausal Caucasian women, who were at generally low risk of cardiovascular disease and higher than average risk for osteoporosis. The safety profile of Activelle™ derived from these study populations cannot necessarily be extrapolated to other populations of diverse racial and/or demographic composition. When considering prescribing Activelle™, physicians are advised to weigh the potential benefits and risks of therapy as applicable to each individual patient.

2. *Use in hysterectomized women.* Existing data do not support the use of the combination of estrogen and progestin in postmenopausal women without a uterus. Risks that may be associated with the inclusion of progestin in estrogen replacement regimens include deterioration in glucose tolerance, and less favorable effects on lipid metabolism compared to the effects of estrogen alone. The effects of Activelle™ on glucose tolerance and lipid metabolism have been studied (see CLINICAL PHARMACOLOGY, Clinical Studies, and PRECAUTIONS, Drug/Laboratory Test Interactions).

3. *Physical examination.* A complete medical and family history should be taken prior to the initiation of any estrogen/progestin 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 another physical examination being performed.

4. *Fluid retention.* Because estrogens/progestins may cause some degree of fluid retention, conditions that might be influenced by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

5. *Uterine bleeding.* Certain patients may develop abnormal uterine bleeding. In cases of undiagnosed abnormal uterine bleeding, adequate diagnostic measures are indicated. (see WARNINGS).

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

Based on experience with estrogens:

1. *Familial hyperlipoproteinemia.* Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects in lipoprotein metabolism.

2. *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 changes in levels of coagulation parameters at baseline compared to premenopausal women. Epidemiological studies have suggested that estrogen use is associated with a higher relative risk of developing venous thromboembolism, i.e., deep vein thrombosis or pulmonary embolism. The studies found a 2-3 fold higher risk for estrogen users

compared to non-users. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease. The effects of Activelle™ (n=40) compared to placebo (n=40) on selected clotting factors were evaluated in a 12-month study with postmenopausal women. Activelle™ decreased factor VII, plasminogen activator inhibitor-1, and, to a lesser extent, antithrombin III activity, compared to placebo. Fibrinogen remained unchanged during Activelle™ treatment in comparison with an increase over time in the placebo group.

*Mastodynia.* Certain patients may develop undesirable manifestations of estrogenic stimulation such as mastodynia. In clinical trials, less than one-fifth of the women treated with Activelle™ reported breast tenderness or breast pain. The majority of the cases were reported as breast tenderness, primarily during the initial months of the treatment.

Based on experience with progestins:

1. *Lipoprotein metabolism.* (see CLINICAL STUDIES)

2. *Impaired glucose tolerance.* Diabetic patients should be carefully observed while receiving estrogen/progestin therapy. The effects of Activelle™ on glucose tolerance have been studied (see PRECAUTIONS, Drug/Laboratory Test Interactions).

3. *Depression.* Patients who have a history of depression should be observed and the drugs discontinued if the depression recurs to a serious degree.

INFORMATION FOR THE PATIENT

See text of Patient Package Insert which appears after the **How Supplied** section.

DRUG/LABORATORY TEST INTERACTIONS

The following interactions have been observed with estrogen therapy, and/or Activelle™:

1. Activelle™ decreases factor VII, plasminogen activator inhibitor-1, and, to a lesser extent, antithrombin III activity.

2. Estrogen therapy increases thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), $T_4$ levels (by column or by radioimmunoassay) or $T_3$ levels by radioimmunoassay. $T_3$ resin uptake is decreased, reflecting the elevated TBG. Free $T_4$ and free $T_3$ concentrations are unaltered.

3. Estrogen therapy may elevate other binding proteins 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). In a 12-month clinical trial, SHBG (sex-hormone-binding globulin) was found to increase with Activelle™.

4. Estrogen therapy increases plasma HDL and HDL-2 subfraction concentrations, reduces LDL cholesterol concentration, and increases triglyceride levels. (For effects during Activelle™ treatment, see CLINICAL PHARMACOLOGY, Clinical Studies).

5. Activelle™ treatment of healthy postmenopausal women does not decrease glucose tolerance when assessed by an oral glucose tolerance test; the insulin response decreases without any increase in the glucose serum levels. Activelle™ treatment does not deteriorate insulin sensitivity in healthy postmenopausal women when assessed by

an hyperinsulinemic euglycemic clamp.

6. Estrogen therapy reduces response to metyrapone test.

7. Estrogen therapy reduces serum folate concentration.

CARCINOGENESIS, MUTAGENESIS, and IMPAIRMENT OF INFERTILITY

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.)

PREGNANCY CATEGORY X: Estrogens/progestins should not be used during pregnancy. (See CONTRAINDICATIONS and WARNINGS.)

NURSING MOTHERS: Detectable amounts of estradiol and norethindrone acetate have been identified in the milk of mothers receiving these products and has been reported to decrease the quantity and the quality of the milk. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

**ADVERSE REACTIONS**

(See WARNINGS regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, elevated blood pressure, thromboembolic disorders, cardiovascular disease, visual abnormalities, and hypercalcemia and PRECAUTIONS regarding cardiovascular disease.)

Adverse events reported by investigators in the Phase 3 studies regardless of causality assessment are shown in TABLE 4.

**TABLE 4**
**ALL TREATMENT-EMERGENT ADVERSE EVENTS REGARDLESS OF RELATIONSHIP REPORTED AT A FREQUENCY OF ≥ 5% WITH ACTIVELLE™**

| | Endometrial Hyperplasia Study (12-Months) | | Vasomotor Symptoms Study (3-Months) | |
|---|---|---|---|---|
| | Activelle (n=295) | 1 mg E2 (n=296) | Activelle (n=29) | Placebo (n=34) |
| ***Body as a Whole*** | | | | |
| Back Pain | 6% | 5% | 3% | 3% |
| Headache | 16% | 16% | 17% | 18% |
| ***Digestive System*** | | | | |
| Nausea | 3% | 5% | 10% | 0% |
| ***Nervous System*** | | | | |
| Insomnia | 6% | 4% | 3% | 3% |
| ***Respiratory System*** | | | | |
| Upper Respiratory Tract Infection | 18% | 15% | 10% | 6% |
| Sinusitis | 7% | 11% | 7% | 0% |
| ***Urogenital System*** | | | | |
| Breast Pain | 24% | 10% | 21% | 0% |
| Post-Menopausal Bleeding | 5% | 15% | 10% | 3% |
| Uterine Fibroid | 5% | 4% | 0% | 0% |
| Ovarian Cyst | 3% | 2% | 7% | 0% |

The following adverse reactions have been reported with estrogen and/or progestin therapy:

*Genitourinary system:* changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, increase in size of uterine leiomyomata, vaginal candidiasis, changes in amount of cervical secretion, pre-menstrual-like syndrome, cystitis-like syndrome.

*Breasts:* tenderness, enlargement.

*Gastrointestinal:* nausea, vomiting, changes in appetite, cholestatic jaundice, abdominal pain, flatulence, bloating, increased incidence of gallbladder disease.

*Skin:* chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, itching, skin rash and pruritus.

*Cardiovascular:* changes in blood pressure, cerebrovascular accidents, deep venous thrombosis and pulmonary embolism.

*CNS:* headache, migraine, dizziness, depression, chorea, insomnia, nervousness.

*Eyes:* steepening of corneal curvature, intolerance to contact lenses.

*Miscellaneous:* increase or decrease in weight, aggravation of porphyria, edema, changes in libido, fatigue, allergic reactions, back pain, arthralgia, myalgia.

## OVERDOSAGE

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

## DOSAGE AND ADMINISTRATION

Activelle™ therapy consists of a single tablet to be taken once daily.

For the treatment of moderate to severe vasomotor symptoms associated with the menopause, and treatment of vulvar and vaginal atrophy - **Activelle™** 1 mg $E_2$ / 0.5 mg NETA daily.

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

## HOW SUPPLIED

Activelle™, 1mg estradiol and 0.5 mg norethindrone acetate, is a white, film-coated tablet, engraved with NOVO 288 on one side and the APIS bull on the other. It is round, 6mm in diameter and bi-convex. Activelle™ is supplied as:

| | | |
|---|---|---|
| 28 tablets in a calendar dial pack dispenser | NDC # xxxx-xxxx-xx | Bar code |
| Three 28-Day calendar packs | NDC # xxxx-xxxx-xx | Bar code |

Store in a dry place protected from light. Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [See USP]

**ACTIVELLE™**
**(estradiol/norethindrone acetate tablets)**

**INFORMATION FOR THE PATIENT**

Your doctor has prescribed ACTIVELLE™, a combination of two hormones, estradiol an estrogen, and norethindrone acetate, a progestin. This leaflet describes the major benefits and risks of your treatment, as well as directions for use. Before you start taking ACTIVELLE™, please read this package leaflet carefully. If you have any questions, please contact your physician, nurse or pharmacist.

**ESTROGENS ARE KNOWN TO INCREASE THE RISK OF CANCER OF THE UTERUS IN MENOPAUSAL WOMEN. THIS FINDING REFERS TO ESTROGENS GIVEN WITHOUT PROGESTIN.**

Progestin-containing drugs taken with estrogen-containing drugs significantly reduce but do not eliminate this risk completely. 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.

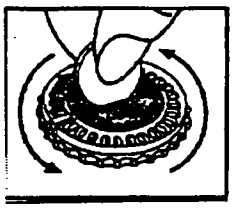
If you take ACTIVELLE™, and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible.

**How to use the ACTIVELLE™ Dispenser**

**1. Set the Day Reminder**

Turn the inner disc so the current day of the week is lined up with the little plastic tab.

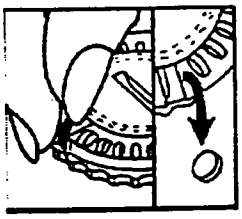
1.



**2. How to Take the First Tablet**

Pull plastic tab up and break off. Tip out the first tablet.

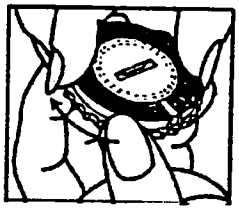
2.



**3. Every Day**

Turn the outer transparent dial one space clockwise as indicated by the arrow. Tip out the next tablet.

3.



**Note: The transparent dial can only be turned after the tablet in the opening has been removed.**

ACTIVELLE™ contains two hormones that are similar to naturally occurring hormones in the body that decrease at menopause. The hormone combination you will be taking, estradiol and norethindrone acetate, has been shown to provide the benefits of estrogen therapy while lowering the frequency of a precancerous condition of the uterine lining known as endometrial hyperplasia (excessive reproduction of normal cells). The use of an estrogen without also using a progestin increases a woman's chance of getting endometrial hyperplasia. ACTIVELLE™ should be used only by women who have a uterus.

**Estrogen Drugs**

Estrogens have several important benefits but also some risks. Discuss with your doctor whether the risks of estrogens are acceptable compared to their benefits for you. Check with your doctor to make sure you are using the lowest effective dose of estrogens, and that you don't use them longer than necessary. The length of treatment with estrogen will depend upon the reason for use and will vary from woman to woman.

ACTIVELLE™ is a continuous combined hormone replacement therapy (HRT). During the initial months of therapy, bleeding or spotting episodes may occur; however, these episodes tend to decrease with time. The advantage of using a continuous-combined HRT regimen is that it is not associated with the regular monthly bleeding that occurs with sequential HRT regimens. If you experience vaginal bleeding while taking ACTIVELLE™, you should discuss it with your doctor. Your doctor will decide if follow-up care is needed.

**Uses of Estrogen**

*To reduce moderate to severe vasomotor symptoms.* Estrogens are hormones produced by the ovaries of premenopausal women. Between ages 45 and 55, the ovaries stop making estrogen and the monthly menstrual periods eventually come to an end. This is referred to as the "change of life" or menopause. When both ovaries are removed by an operation before natural menopause, a sudden drop in estrogen levels causes "surgical menopause." When 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 flushes" or "hot flashes"). Some women may have only mild menopausal symptoms, while for others they may be severe. These symptoms may last only a few months or longer. Therapy with ACTIVELLE™ can provide relief from these symptoms. You should decide along with your doctor how long your therapy will last. The majority of women do not need to take estrogen replacement for longer than six months for these symptoms.

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

**When Estrogen Should Not be Used**

*During pregnancy.* If you think you may be pregnant, do not use any estrogen-containing drug product. Use of estrogen during pregnancy may cause birth defects in your unborn child. Estrogen does not prevent miscarriage.

*If you have unusual vaginal bleeding that has not been evaluated by your doctor.* Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it occurs after menopause. If you have vaginal bleeding caused by uterine cancer, taking estrogens can cause you serious harm. Your doctor is the only one who can determine the cause of bleeding and recommend proper treatment.

*If you have had cancer.* Since estrogens are known to increase the risk of certain types of cancer, you should not take estrogen if you have ever had cancer of the breast or uterus.

*If you have had deep vein thrombosis or other blood clotting disorders.* You should use estrogen only after consultation with your physician and only in recommended doses. (see **Risks of Estrogens and/or Progestins** below).

*When they are ineffective.* ACTIVELLE™ is not recommended for use other than what is approved by the FDA. For example, sometimes women experience nervous symptoms or depression during menopause. Estrogens do not relieve these symptoms. You may have heard that taking estrogen for long periods (years) after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence that this is so and such long-term treatment may have serious risks.

*After childbirth or when breast-feeding a baby.* Estrogens should not be used to try to stop the breast from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see **Risks of Estrogens and/or Progestins** below).

Many drugs can pass through to the baby in the milk when you are breast feeding. While breast feeding, you should only take medicine on the advice of your health care provider.

**Risks of Estrogens and/or Progestins**

*Cancer of the uterus.* Your risk of getting cancer of the uterus gets higher when estrogens are used alone, when estrogens are used for longer times, and when larger doses are taken. There is a higher risk of cancer of the uterus if you are overweight, diabetic, or have high blood pressure. ACTIVELLE™ contains both an estrogen and a

progestin. The combination reduces the increased risk of a precancerous condition of the uterine lining compared to estrogen alone (see **Other Information** below).

Additional risks may be associated with the inclusion of a progestin with estrogen treatment. These possible risks include unfavorable effects on blood fats and sugars, and a possible increase in the risk of breast cancer (see *Cancer of the breast*, below). Generally, the lower the dose and the shorter the duration of treatment, the more these effects are minimized. You should talk with your doctor to be sure you are using the lowest effective dose and only for as long as necessary.

If you have had your uterus removed (total hysterectomy), there is no risk of developing cancer of the uterus. ACTIVELLE™ is not intended for use in women who have had a hysterectomy because these women do not need to take the progestin part of the drug.

*Cancer of the breast.* Most studies have shown no association with estrogen and breast cancer. Some studies have suggested a possible increased incidence up to twice the usual rate of breast cancer in those women who took estrogens for long periods of time (especially more than 10 years) or took higher doses for short periods. The effects of added progestin on the risks of breast cancer are unknown. Some studies have reported a somewhat increased risk, even higher than the possible risk associated with estrogens alone, while others have not. Monthly self-examinations and regular breast examinations by a Healthcare professional are recommended for all women. The American Cancer Society recommends mammogram every year for women over 50 years of age.

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

*Abnormal blood clotting.* Taking estrogens may cause changes in your blood clotting

system, thereby increasing the risk of clots to form in your blood. By cutting off blood supply to vital organs, these clots can cause a stroke, heart attack, or lung clot, any of which 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.

*Excess calcium in the blood.* Taking estrogens may lead to severe elevations in blood calcium levels in women with breast and/or bone cancer. Therefore, ACTIVELLE™ should be used with caution if you have these conditions.

*During pregnancy.* You should not take estrogen when you are pregnant as there is a greater than usual chance that your child will be born with a birth defect. If you take ACTIVELLE™ and later find that you were pregnant when you took it, discuss this with your doctor as soon as possible.

**Side Effects with Estrogens and/or Progestins**

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

- Nausea, vomiting, pain, cramps, swelling, or tenderness in the abdomen.
- Breast tenderness or enlargement.
- Enlargement of benign tumors (fibroids) of the uterus.
- Yellowing of the skin and/or whites of the eyes.
- Irregular bleeding or spotting.
- Change in amount of cervical secretion.
- Vaginal yeast infections.
- 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; reddening of the skin; skin rashes.
- Worsening of porphyria.

- Headache, migraines, dizziness, faintness, or changes in vision (including intolerance to contact lenses).
- Mental depression.
- Involuntary muscle spasms.
- Hair loss or abnormal hairiness.
- Increase or decrease in weight.
- Changes in sex drive.
- Possible changes in blood sugar.

**Reducing Risk of Estrogen/Progestin Use**

If you decide to take an estrogen/progestin combination product, you can reduce your risks by carefully monitoring your treatment.

*Contact your doctor regularly.* While you are taking ACTIVELLE™, it is important that you consult at least every six months with your doctor and have a check up least once a year. If members of your family have had breast cancer or if you have ever had a breast lump or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations. If you develop vaginal bleeding while taking ACTIVELLE™, talk to your doctor.

*Reevaluate your need for estrogen.* You and your doctor should reevaluate your need for estrogen at least every six months.

*Be alert for signs of trouble.* Report these or any other unusual side effects to your doctor immediately:

- Abnormal bleeding from the vagina (possible uterine abnormality).
- Pains in the calves or chest, a sudden shortness of breath, or coughing blood (indicates possible clot in the legs, heart, or lungs).

- Severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg (indicates possible clot in the brain or eye).
- Breast lumps (possible breast cancer; ask your health care professional to show you how to examine your breasts monthly).
- Yellowing of the skin or whites of the eyes (possible liver problem).
- Pain, swelling, or tenderness in the abdomen (possible gallbladder problem).

**Other Information**

- Since you still have your uterus, your doctor has prescribed ACTIVELLE™ which has both an estrogen and a progestin. Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking a progestin, another hormone drug, along with estrogen reduces the increased risk of developing this condition. There are however, possible additional risks that may be associated with the inclusion of a progestin with estrogen treatment. The possible risks include: unfavorable effects on blood fats and sugars, which may make a diabetic condition worse; possible further increase in breast cancer risk which may be associated with long-term estrogen use.

*You are encouraged 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.*

- Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.
- 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 the most important information about ACTIVELLE™. If you have any questions about you and ACTIVELLE™, please speak to your doctor or pharmacist.

**How Supplied**

Your doctor has prescribed ACTIVELLE™, a single white tablet containing 1 mg estradiol and 0.5 mg norethindrone acetate (NETA) for oral administration.

ACTIVELLE™ is supplied in a dispenser containing 28 tablets. Take one tablet daily.

The appearance of these tablets is a trademark of Novo Nordisk A/S.

Store in a dry place protected from light. Store at room temperature 77°F (25°C).

Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Printed in USA Issued: 18 November 1997 (Parts No.)

November 18, 1998 (Revision 4)

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ON ORIGINAL

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Pharmacia &Upjohn

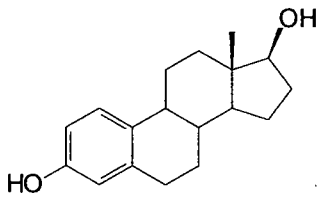
**Activella™**
(estradiol/norethindrone acetate tablets)

1 mg estradiol
0.5 mg norethindrone acetate

## DESCRIPTION

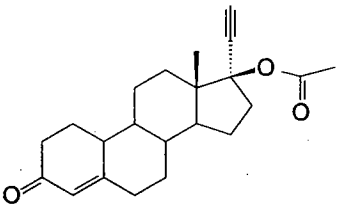
Activella™ is a single tablet containing an estrogen, estradiol ($E_2$), and a progestin, norethindrone acetate (NETA), for oral administration. Each tablet contains 1 mg estradiol and 0.5 mg norethindrone acetate and the following excipients: lactose monohydrate, starch (corn), copovidone, talc, magnesium stearate, hydroxypropyl methylcellulose and triacetin.

Estradiol ($E_2$) is a white or almost white crystalline powder. Its chemical name is estra-1, 3, 5 (10)-triene-3, 17ß-diol hemihydrate with the empirical formula of $C_{18}H_{24}O_2$, 1/2 $H_2O$ and a molecular weight of 281.4. The structural formula of $E_2$ is as follows:




**Estradiol**

Norethindrone acetate (NETA) is a white or yellowish-white crystalline powder. Its chemical name is 17ß-acetoxy-19-nor-17α-pregn-4-en-20-yn-3-one with the empirical formula of $C_{22}H_{28}O_3$ and molecular weight of 340.5. The structural formula of NETA is as follows:




**Norethindrone Acetate**

## CLINICAL PHARMACOLOGY

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes and bind to and activate the nuclear estrogen receptor, a DNA-binding protein that is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, that 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 in women.

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 µg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion in peripheral tissues of androstenedione which is secreted by the adrenal cortex, to estrone. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) through a negative feedback mechanism, and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

Progestin compounds enhance cellular differentiation and generally oppose the actions of estrogens by decreasing estrogen receptor levels, increasing local metabolism of estrogens to less active metabolites, or inducing gene products that blunt cellular responses to estrogen.

Progestins exert their effects in target cells by binding to specific progesterone receptors that interact with progesterone response elements in target genes. Progesterone receptors have been identified in the female reproductive tract, breast, pituitary, hypothalamus, and central nervous system. Progestins produce similar endometrial changes to those of the naturally occurring hormone progesterone.

The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. The addition of a progestin, in adequate doses and appropriate duration, to an estrogen replacement regimen reduces the incidence of endometrial hyperplasia, and the attendant risk of carcinoma in women with intact uterus.

## PHARMACOKINETICS

### ABSORPTION

Estradiol is well absorbed through the gastrointestinal tract. Following oral administration of Activella™ (estradiol/norethindrone acetate tablets), peak plasma estradiol concentrations are reached slowly within 5-8 hours. When given orally, estradiol is extensively metabolized (first-pass effect) to estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogens. After oral administration, norethindrone acetate is rapidly absorbed and transformed to norethindrone. It undergoes first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration within 0.5-1.5 hours. The oral bioavailability of estradiol and norethindrone following administration of Activella™ when compared to a combination oral solution is 53% and 100%, respectively. The pharmacokinetic parameters of estradiol ($E_2$), estrone ($E_1$), and norethindrone (NET) following single oral administration of Activella™ in 25 volunteers are summarized in TABLE 1.

**TABLE 1**
PHARMACOKINETIC PARAMETERS AFTER A SINGLE DOSE OF ACTIVELLA™ IN HEALTHY POSTMENOPAUSAL WOMEN

| | Activella™ (n=25) Mean[c] ± SD |
|---|---|
| Estradiol [a] ($E_2$) | |
| AUC (0-72h)(pg/ml*h) | 1053 ± 310 |
| $C_{max}$ (pg/ml) | 34.6 ± 10.8 |
| $t_{max}$ (h) | 6.8 ± 2.9 |
| $t_{½}$ (h) [d] | 13.2 ± 4.7 |
| Estrone [a] ($E_1$) | |
| AUC (0-72h)(pg/ml*h) | 5223 ± 1618 |
| $C_{max}$ (pg/ml) | 251.1 ± 91.0 |
| $t_{max}$ (h) | 5.7 ± 1.4 |
| $t_{½}$ (h) [d] | 12.2 ± 4.6 |
| Norethindrone (NET) | |
| AUC (0-72h)(pg/ml*h) | 23681 ± 9023 [b] |
| $C_{max}$ (pg/ml) | 5308 ± 1510 |
| $t_{max}$ (h) | 1.0 ± 0.0 |
| $t_{½}$ (h) | 11.4 ± 2.7 |

AUC= area under the curve,
$C_{max}$= maximum plasma concentration,
$t_{max}$= time at maximum plasma concentration,
$t_{½}$= half-life,
SD= standard deviation
[a] baseline unadjusted data; [b] (n=23); [c] arithmetic mean; [d] baseline adjusted data.

Following continuous dosing with once-daily administration of Activella™ (estradiol/norethindrone acetate tablets), serum levels of estradiol, estrone, and norethindrone reached steady-state within two weeks with an accumulation of 33-47% above levels following single dose administration. Unadjusted circulating levels of $E_2$, $E_1$, and NET during Activella™ treatment at steady state (dosing at time 0) are provided in Figures 1a and 1b.

**Figure 1a**
**Levels of Estradiol and Estrone at Steady State during Continuous Dosing with Activella™ (n=24)**

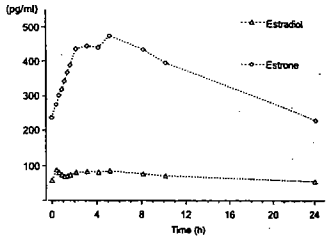
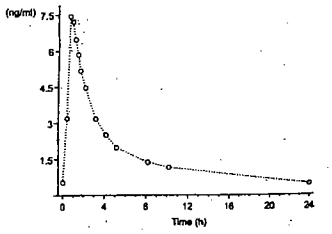



**Figure 1b**
**Levels of Norethindrone at Steady State during Continuous Dosing with Activella™ (n=24)**




### DISTRIBUTION

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol circulates in the blood bound to sex-hormone-binding globulin (SHBG) (37%) and to albumin (61%), while only approximately 1-2% is unbound. Norethindrone also binds to a similar extent to SHBG (36%) and to albumin (61%).

Pharmacia &Upjohn
Activella™
(estradiol/norethindrone acetate tablets)

8-2900-31-001-1

8-2900-31-001-1

Pharmacia &Upjohn
Activella™
(estradiol/norethindrone acetate tablets)

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Pharmacia &Upjohn

# 'ella™

)l/norethindrone
tablets)

tradiol
norethindrone acetate

## PTION

™ is a single tablet contain-
strogen, estradiol ($E_2$), and
itin, norethindrone acetate
for oral administration. Each
ontains 1 mg estradiol and
norethindrone acetate and
wing excipients: lactose
drate, starch (corn), copovi-
ılc, magnesium stearate,
propyl methylcellulose and

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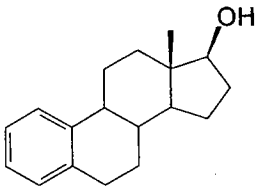
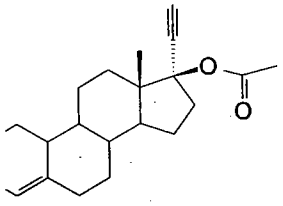
olecular weight of 281.4. The
al formula of $E_2$ is as follows:




**Estradiol**

ndrone acetate (NETA) is a
r yellowish-white crystalline
. Its chemical name is 17β-
-19-nor-17α-pregn-4-en-20-
ıe with the empirical formula
$_{28}O_3$ and molecular weight of
The structural formula of
as follows:




**lorethindrone Acetate**

## AL PHARMACOLOGY

ın drug products act by regu-
he transcription of a limited
r of genes. Estrogens diffuse
h cell membranes and bind to
tivate the nuclear estrogen re-
a DNA-binding protein that is
in estrogen-responsive tissues.
tivated estrogen receptor
o specific DNA sequences, or
ne-response elements, that
ce the transcription of adjacent
and in turn lead to the ob-
effects. Estrogen receptors
een identified in tissues of the
uctive tract, breast, pituitary,
ıalamus, liver, and bone in
ı.

ens are largely responsible for
velopment and maintenance
female reproductive system
condary sexual characteristics.
ıgh circulating estrogens exist
namic equilibrium of metabol-
conversions, estradiol is the
ıal intracellular human estro-
ıd is substantially more potent than its metabolites, estrone and estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 µg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion in peripheral tissues of androstenedione which is secreted by the adrenal cortex, to estrone. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) through a negative feedback mechanism, and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

Progestin compounds enhance cellular differentiation and generally oppose the actions of estrogens by decreasing estrogen receptor levels, increasing local metabolism of estrogens to less active metabolites, or inducing gene products that blunt cellular responses to estrogen.

Progestins exert their effects in target cells by binding to specific progesterone receptors that interact with progesterone response elements in target genes. Progesterone receptors have been identified in the female reproductive tract, breast, pituitary, hypothalamus, and central nervous system. Progestins produce similar endometrial changes to those of the naturally occurring hormone progesterone.

The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. The addition of a progestin, in adequate doses and appropriate duration, to an estrogen replacement regimen reduces the incidence of endometrial hyperplasia, and the attendant risk of carcinoma in women with intact uterus.

## PHARMACOKINETICS

ABSORPTION

Estradiol is well absorbed through the gastrointestinal tract. Following oral administration of Activella™ (estradiol/norethindrone acetate tablets), peak plasma estradiol concentrations are reached slowly within 5-8 hours. When given orally, estradiol is extensively metabolized (first-pass effect) to estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogens. After oral administration, norethindrone acetate is rapidly absorbed and transformed to norethindrone. It undergoes first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration within 0.5-1.5 hours. The oral bioavailability of estradiol and norethindrone following administration of Activella™ when compared to a combination oral solution is 53% and 100%, respectively. The pharmacokinetic parameters of estradiol ($E_2$), estrone ($E_1$), and norethindrone (NET) following single oral administration of Activella™ in 25 volunteers are summarized in TABLE 1.

**TABLE 1**
PHARMACOKINETIC PARAMETERS AFTER A SINGLE DOSE OF ACTIVELLA™ IN HEALTHY POSTMENOPAUSAL WOMEN

| | Activella™ (n=25) Mean[c] ± SD |
|---|---|
| Estradiol [a] ($E_2$) | |
| AUC (0-72h)(pg/ml*h) | 1053 ± 310 |
| $C_{max}$ (pg/ml) | 34.6 ± 10.8 |
| $t_{max}$ (h) | 6.8 ± 2.9 |
| $t_{½}$ (h) [d] | 13.2 ± 4.7 |
| Estrone [a] ($E_1$) | |
| AUC (0-72h)(pg/ml*h) | 5223 ± 1618 |
| $C_{max}$ (pg/ml) | 251.1 ± 91.0 |
| $t_{max}$ (h) | 5.7 ± 1.4 |
| $t_{½}$ (h) [a] | 12.2 ± 4.6 |
| Norethindrone (NET) | |
| AUC (0-72h)(pg/ml*h) | 23681 ± 9023 [b] |
| $C_{max}$ (pg/ml) | 5308 ± 1510 |
| $t_{max}$ (h) | 1.0 ± 0.0 |
| $t_{½}$ (h) | 11.4 ± 2.7 |

AUC= area under the curve,
$C_{max}$= maximum plasma concentration,
$t_{max}$= time at maximum plasma concentration,
$t_{½}$= half-life,
SD= standard deviation
[a] baseline unadjusted data; [b] (n=23); [c] arithmetic mean; [d] baseline adjusted data

Following continuous dosing with once-daily administration of Activella™ (estradiol/norethindrone acetate tablets), serum levels of estradiol, estrone, and norethindrone reached steady-state within two weeks with an accumulation of 33-47% above levels following single dose administration. Unadjusted circulating levels of $E_2$, $E_1$, and NET during Activella™ treatment at steady state (dosing at time 0) are provided in Figures 1a and 1b.

**Figure 1a**
**Levels of Estradiol and Estrone at Steady State during Continuous Dosing with Activella™ (n=24)**

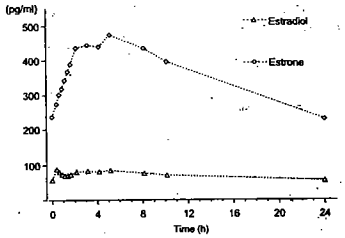
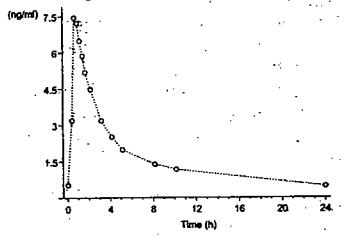



**Figure 1b**
**Levels of Norethindrone at Steady State during Continuous Dosing with Activella™ (n=24)**




DISTRIBUTION

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol circulates in the blood bound to sex-hormone-binding globulin (SHBG) (37%) and to albumin (61%), while only approximately 1-2% is unbound. Norethindrone also binds to a similar extent to SHBG (36%) and to albumin (61%).

METABOLISM AND EXCRETION

*Estradiol:* Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. The half-life of estradiol following single dose administration of Activella™ (estradiol/norethindrone acetate tablets) is 12-14 hours.

*Norethindrone Acetate:* The most important metabolites of norethindrone are isomers of 5α-dihydro-norethindrone and tetrahydro-norethindrone, which are excreted mainly in the urine as sulfate or glucuronide conjugates. The terminal half-life of norethindrone is about 8-11 hours.

DRUG-DRUG INTERACTIONS

Coadministration of estradiol with norethindrone acetate did not elicit any apparent influence on the pharmacokinetics of norethindrone. Similarly, no relevant interaction of norethindrone on the pharmacokinetics of estradiol was found within the NETA dose range investigated in a single dose study.

FOOD-DRUG INTERACTIONS

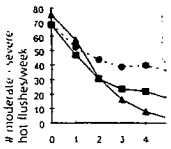
A single-dose study in 24 healthy postmenopausal women was conducted to investigate any potential impact of administration of Activella™ with and without food. Administration of Activella™ with food did not modify the bioavailability of estradiol, although increases in $AUC_{0-72}$ of 19% and decreases in $C_{max}$ of 36% for norethindrone were seen.

## CLINICAL STUDIES

VASOMOTOR SYMPTOMS

Activella™ is effective in reducing the number of moderate-to-severe vasomotor symptoms in postmenopausal women. In a 12-week randomized clinical trial involving 92 subjects, Activella™ was compared to 1 mg of estradiol and to placebo. The mean number and intensity of hot flushes were significantly reduced from baseline to week 12 in both the Activella™ and the 1 mg estradiol group compared to placebo (see Figure 2).

**Figu**
**Mean Week**
**Moderate and Se**
**in a 12-W**




ENDOMETRIAL H
Activella™ (estradi
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randomized to or
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$E_2$ + 0.1 mg NETA
+ 0.25 mg NETA
Activella™ [1 mg
(n=295). At the e
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compared to Acti
TABLE 2.

**TA**
INCIDENCE O
HYPERPLASIA
ESTRADIOL AN
A 12-MC

| | |
|---|---|
| No. of subjects with histological evaluation at the end of the study | |
| No. (%) of subjects wi endometrial hyperplas at the end of the stud | |

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**Fi**
**Percentage of**
**at Each Mon**
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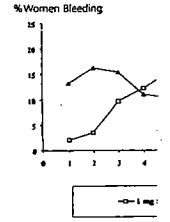


n=number of women
1 mg $E_2$ (3, 6, 9 and 12 m
Activella™ (3, 6, 9 and 12

INFORMATION F
EFFECTS
A 12-month, pl
ical trial in 80 p
Caucasian wom
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fects of Activell
parameters. The
in TABLE 3.

AND EXCRETION

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## CLINICAL STUDIES

VASOMOTOR SYMPTOMS

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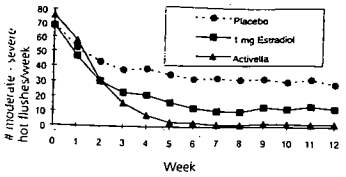
**Figure 2**
**Mean Weekly Number of Moderate and Severe Hot Flushes in a 12-Week Study**




ENDOMETRIAL HYPERPLASIA

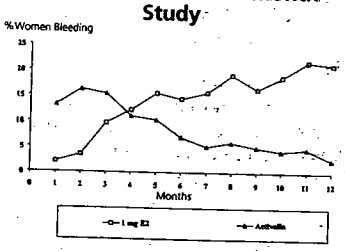
Activella™ (estradiol/norethindrone acetate tablets) reduced the incidence of estrogen-induced endometrial hyperplasia at 1 year in a randomized, controlled clinical trial. This trial enrolled 1,176 subjects who were randomized to one of 4 arms: 1 mg estradiol unopposed (n=296), 1 mg $E_2$ + 0.1 mg NETA (n=294), 1 mg $E_2$ + 0.25 mg NETA (n=291), and Activella™ [1 mg $E_2$ + 0.5 mg NETA] (n=295). At the end of the study, endometrial biopsy results were available for 988 subjects. The results of the 1 mg estradiol unopposed arm compared to Activella™ are shown in TABLE 2.

**TABLE 2**
INCIDENCE OF ENDOMETRIAL HYPERPLASIA WITH UNOPPOSED ESTRADIOL AND ACTIVELLA™ IN A 12-MONTH STUDY

| | 1 mg $E_2$ (n=296) | Activella™ (n=295) |
|---|---|---|
| No. of subjects with histological evaluation at the end of the study | 247 | 241 |
| No. (%) of subjects with endometrial hyperplasia at the end of the study | 36 (14.6%) | 1 (0.4%) |

During the initial months of therapy, irregular bleeding or spotting occurred with Activella™ treatment. However, bleeding tended to decrease over time, and after 12 months of treatment with Activella™, fewer than 3% of women reported bleeding (see Figure 3).

**Figure 3**
**Percentage of Women Bleeding at Each Month in a 12-Month Study**




n=number of women
1 mg $E_2$ (3, 6, 9 and 12 months): n=278, 255, 226, 212
Activella™ (3, 6, 9 and 12 months): n=273, 246, 238, 232

INFORMATION REGARDING LIPID EFFECTS

A 12-month, placebo-controlled clinical trial in 80 postmenopausal Caucasian women at low risk for cardiovascular disease compared the effects of Activella™ to placebo on lipid parameters. These results are shown in TABLE 3.

**TABLE 3**
PERCENTAGE CHANGE FROM BASELINE IN SELECTED LIPID PARAMETERS WITH ACTIVELLA™ IN A 12-MONTH PLACEBO-CONTROLLED STUDY

| Lipid Parameter % | Activella™ (n=35) | Placebo (n=34) |
|---|---|---|
| Total Cholesterol | -10.5% | -0.8% |
| HDL-C[1] | -12.4% | -6.1% |
| LDL-C[2] | -10.8% | 0.8% |
| LDL: HDL Ratio | 0.1% | 9.2% |
| Triglycerides | 2.2% | 4.4% |

[1] High density lipoprotein-cholesterol
[2] Low density lipoprotein-chlolesterol

## INDICATIONS AND USAGE

Activella™ (estradiol/norethindrone acetate tablets) therapy is indicated in women with an intact uterus for 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 that might occur during menopause and they should not be used to treat these conditions.
2. Treatment of vulvar and vaginal atrophy.

## CONTRAINDICATIONS

Estrogens/progestins combined should not be used in women under any of the following conditions or circumstances:

1. Known or suspected pregnancy, including use for missed abortions or as a diagnostic test for pregnancy. Estrogen or progestin may cause fetal harm when administered to a pregnant woman.
2. Known or suspected breast cancer, or past history of breast cancer associated with the use of estrogens.
3. Known or suspected estrogen-dependent neoplasia, e.g., endometrial cancer.
4. Abnormal genital bleeding of unknown etiology.
5. Known or suspected active deep venous thrombosis, thromboembolic disorders or stroke or past history of these conditions associated with estrogen use.
6. Liver dysfunction or disease.
7. Hypersensitivity to any of the components of Activella™.

## WARNINGS

ALL WARNINGS BELOW PERTAIN TO THE USE OF THIS COMBINATION PRODUCT.

Based on experience with estrogens and/or progestins:

**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. There is no significant increased risk associated with the use of estrogens for less than one year. The greatest risk appears to be associated with prolonged use with increased risks of 15- to 24-fold with five or more years of use. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treament. In one study, a significant decrease in the incidence of endometrial cancer occurred six months after withdrawal. Progestins taken with estrogens have been shown to significantly reduce, but not eliminate, the risk of endometrial cancer associated with estrogen use. In a large clinical trial, the incidence of endometrial hyperplasia with Activella™ (estradiol/norethindrone acetate tablets) was 0.4% (one simple hyperplasia without atypia) compared to 14.6% with 1 mg estradiol unopposed (see CLINICAL STUDIES). Clinical surveillance of all women taking estrogen/progestin combinations 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 equivalent estrogen doses.

*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 doses, or in those taking lower doses for prolonged periods of time, especially in excess of 10 years.

While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggest that progestins do not reduce, and may enhance, the moderately increased breast cancer risk that has been reported with prolonged estrogen replacement therapy.

In a one-year trial among 1,176 women who received either unopposed 1 mg estradiol or a combination of 1 mg estradiol plus one of three different doses of NETA (0.1, 0.25 and 0.5 mg), seven new cases of breast cancer were diagnosed, two of which occurred among the group of 295 Activella™ treated women.

Women on hormone replacement therapy should have regular breast examinations and should be instructed in breast self-examination, and women over the age of 40 should have regular mammograms.

**2. Congenital lesions with malignant potential.** Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possible 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. Although some of these changes are benign, others are precursors of malignancy.

**3. Cardiovascular disease.** Large doses of estrogens (5 mg conjugated estrogen 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 risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

These risks cannot necessarily be extrapolated from men to women or from unopposed estrogen to combination estrogen/progestin therapy. 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. Hypercalcemia.** Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drugs should be stopped and appropriate measures taken to reduce the serum calcium level.

**5. Effects during pregnancy.** Use in pregnancy is not recommended.

**6. Gallbladder disease.** Two studies have reported a 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.
Among the 1,516 women treated in clinical trials with 1 mg estradiol alone or in combination with several doses of NETA, 3 women had surgically confirmed cholelithiasis, none of them on Activella™ (estradiol/rethindrone acetate tablets) treatment.

**7. 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 non-users. Two other studies showed slightly lower blood pressure among estrogen users compared to non-users. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.

**8. Thromboembolic disorders.** The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drugs should be discontinued immediately. In a one-year study where 295 women were exposed to Activella™, there were two cases of deep vein thromboses reported.

**9. Visual abnormalities.** Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examinations reveal papilledema or retinal vascular lesions, medication should be withdrawn.

## PRECAUTIONS

GENERAL

Based on experience with estrogens and/or progestins:

**1. 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 that 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. 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.
Current medical practice often includes the use of concomitant progestin therapy in women with intact uterus. While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins attenuate at least some of the favorable effects of estrogens on HDL levels, although they maintain the favorable effect of estrogens on LDL levels.
The safety data regarding Activella™ (estradiol/norethindrone acetate tablets) were obtained primarily from clinical trials and epidemiologic studies of postmenopausal Caucasian women, who were at generally low risk of cardiovascular disease and higher than average risk for osteoporosis. The safety profile of Activella™ derived from these study populations cannot necessarily be extrapolated to other populations of diverse racial and/or demographic composition. When considering prescribing Activella™, physicians are advised to weigh the potential benefits and risks of therapy as applicable to each individual patient.

**2. Use in hysterectomized women.** Existing data do not support the use of the combination of estrogen and progestin in postmenopausal women without a uterus. Risks that may be associated with the inclusion of progestin in estrogen replacement regimens include deterioration in glucose tolerance, and less favorable effects on lipid metabolism compared to the effects of estrogen alone.
The effects of Activella™ on glucose tolerance and lipid metabolism have been studied (see CLINICAL PHARMACOLOGY, Clinical Studies, and PRECAUTIONS, Drug/Laboratory Test Interactions).

**3. Physical examination.** A complete medical and family history should be taken prior to the initiation of any estrogen/progestin 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 another physical examination being performed.

**4. Fluid retention.** Because estrogens/progestins may cause some degree of fluid retention, conditions that might be influenced by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

**5. Uterine bleeding.** Certain patients may develop abnormal uterine bleeding. In cases of undiagnosed abnormal uterine bleeding, adequate diagnostic measures are indicated (see WARNINGS).

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

Based on experience with estrogens:

**1. Familial hyperlipoproteinemia.** Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects in lipoprotein metabolism.

**2. 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 changes in levels of coagulation parameters at baseline compared to premenopausal women. Epidemiological studies have suggested that estrogen use is associated with a higher relative risk of developing venous thromboembolism, i.e., deep vein thrombosis or pulmonary embolism. The studies found a 2- 3- fold higher risk for estrogen users compared to non-users. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease. The effects of Activella™ (estradiol/norethindrone acetate tablets) (n=40) compared to placebo (n=40) on selected clotting factors were evaluated in a 12-month study with postmenopausal women. Activella™ decreased factor VII, plasminogen activator inhibitor-1, and, to a lesser extent, antithrombin III activity, compared to placebo. Fibrinogen remained unchanged during Activella™ treatment in comparison with an increase over time in the placebo group.

**3. Mastodynia.** Certain patients may develop undesirable manifestations of estrogenic stimulation such as mastodynia. In clinical trials, less than one-fifth of the women treated with Activella™ reported breast tenderness or breast pain. The majority of the cases were reported as breast tenderness, primarily during the initial months of the treatment.

Based on experience with progestins:

**1. Lipoprotein metabolism.** (see CLINICAL STUDIES)

**2. Impaired glucose tolerance.** Diabetic patients should be carefully observed while receiving estrogen/progestin therapy.
The effects of Activella™ (estradiol/norethindrone acetate tablets) on glucose tolerance have been studied (see PRECAUTIONS, Drug/Laboratory Test Interactions).

**3. Depression.** Patients who have a history of depression should be observed and the drugs discontinued if the depression recurs to a serious degree.

INFORMATION FOR THE PATIENT

See text of Patient Package Insert which appears after the **How Supplied** section.

DRUG/LABORATORY TEST INTERACTIONS

The following interactions have been observed with estrogen therapy, and/or Activella™:
1. Activella™ decreases factor VII, plasminogen activator inhibitor-1, and, to a lesser extent, antithrombin III activity.
2. Estrogen therapy increases thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), $T_4$ levels (by column or by radioimmunoassay) or $T_3$ levels by radioimmunoassay. $T_3$ resin uptake is decreased, reflecting the elevated TBG. Free $T_4$ and free $T_3$ concentrations are unaltered.
3. Estrogen therapy may elevate other binding proteins 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). In a 12-month clinical trial, SHBG was found to increase with Activella™.
4. Estrogen therapy increases plasma HDL and HDL-2 subfraction concentrations, reduces LDL cholesterol concentration, and increases triglyceride levels. (For effects during Activella™ treatment, see CLINICAL PHARMACOLOGY, Clinical Studies).
5. Activella™ treatment of healthy postmenopausal women does not decrease glucose tolerance when assessed by an oral glucose tolerance test; the insulin response decreases without any increase in the glucose serum levels. Activella™ treatment does not deteriorate insulin sensitivity in healthy postmenopausal women when assessed by an hyperinsulinemic euglycemic clamp.
6. Estrogen therapy reduces response to metyrapone test.
7. Estrogen therapy reduces serum folate concentration.

CARCINOGENESIS, MUTAGENESIS, and IMPAIRMENT OF INFERTILITY

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.)

PREGNANCY CATEGORY X:
Estrogens/progestins should not be used during pregnancy. (See CONTRAINDICATIONS and WARNINGS.)

NURSING MOTHERS:
Detectable amounts of estradiol and norethindrone acetate have been identified in the milk of mothers receiving these products and has been reported to decrease the quantity and the quality of the milk.
As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

## ADVERSE REACTIONS

(See WARNINGS regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, elevated blood pressure, thromboembolic disorders, cardiovascular disease, visual abnormalities, and hypercalcemia and PRECAUTIONS regarding cardiovascular disease.)
Adverse events reported by investigators in the Phase 3 studies regardless of causality assessment are shown in TABLE 4.

**TABLE 4**
ALL TREATMENT-EMERGENT ADVERSE EVENTS REGARDLESS OF RELATIONSHIP REPORTED AT A FREQUENCY OF ≥5% WITH ACTIVELLA™

| | Endometrial Hyperplasia Study (12-Months) | | Vasomotor Symptoms Study (3-Months) | |
|---|---|---|---|---|
| | Activella[a] (n=295) | 1 mg E2 (n=296) | Activella[a] (n=29) | Placebo (n=34) |
| ***Body as a Whole*** | | | | |
| Back Pain | 6% | 5% | 3% | 3% |
| Headache | 16% | 16% | 17% | 18% |
| ***Digestive System*** | | | | |
| Nausea | 3% | 5% | 10% | 0% |
| ***Nervous System*** | | | | |
| Insomnia | 6% | 4% | 3% | 3% |
| ***Respiratory System*** | | | | |
| Upper Respiratory Tract Infection | 18% | 15% | 10% | 6% |
| Sinusitis | 7% | 11% | 7% | 0% |
| ***Urogenital System*** | | | | |
| Breast Pain | 24% | 10% | 21% | 0% |
| Post-Menopausal Bleeding | 5% | 15% | 10% | 3% |
| Uterine Fibroid | 5% | 4% | 0% | 0% |
| Ovarian Cyst | 3% | 2% | 7% | 0% |

The following adverse reactions have been reported with estrogen and/or progestin therapy:
*Genitourinary system:* changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, increase in size of uterine leiomyomata, vaginal candidiasis, changes in amount of cervical secretion, premenstrual-like syndrome, cystitis-like syndrome.
*Breasts:* tenderness, enlargement.
*Gastrointestinal:* nausea, vomiting, changes in appetite, cholestatic jaundice, abdominal pain, flatulence, bloating, increased incidence of gallbladder disease.
*Skin:* chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, itching, skin rash and pruritus.
*Cardiovascular:* changes in blood pressure, cerebrovascular accidents, deep venous thrombosis and pulmonary embolism.
*CNS:* headache, migraine, dizziness, depression, chorea, insomnia, nervousness.
*Eyes:* steepening of corneal curvature, intolerance to contact lenses.
*Miscellaneous:* increase or decrease in weight, aggravation of porphyria, edema, changes in libido, fatigue, allergic reactions, back pain, arthralgia, myalgia.

## OVERDOSAGE

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

## DOSAGE AND ADMINISTRATION

Activella™ (estradiol/norethindrone acetate tablets) therapy consists of a single tablet to be taken once daily.
For the treatment of moderate to severe vasomotor symptoms associated with the menopause, and treatment of vulvar and vaginal atrophy - Activella™ 1 mg $E_2$/0.5 mg NETA daily.
Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

## HOW SUPPLIED

Activella™, 1 mg estradiol and 0.5 mg norethindrone acetate, is a white, film-coated tablet, engraved with NOVO 288 on one side and the APIS bull on the other. It is round, 6 mm in diameter and bi-convex.

Activella™ is supplied as:
28 tablets in a calendar dial pack dispenser

NDC# 0009-5174-02

Store in a dry place protected from light. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]

**Rx only**



Manufactured for
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA
By

deep venous thrombosis and pulmonary embolism.
*CNS:* headache, migraine, dizziness, depression, chorea, insomnia, nervousness.
*Eyes:* steepening of corneal curvature, intolerance to contact lenses.
*Miscellaneous:* increase or decrease in weight, aggravation of porphyria, edema, changes in libido, fatigue, allergic reactions, back pain, arthralgia, myalgia.

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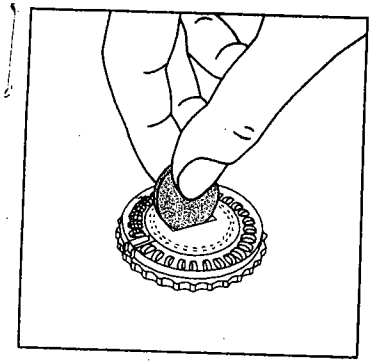
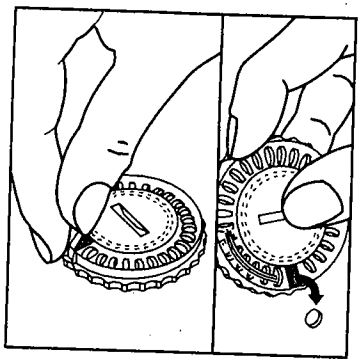
Manufactured for
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA
By
Novo Nordisk A/S
2880 Bagsværd, Denmark

Original
NDA No. 20907 4-18-00
Reviewed by PBL 6/2/00

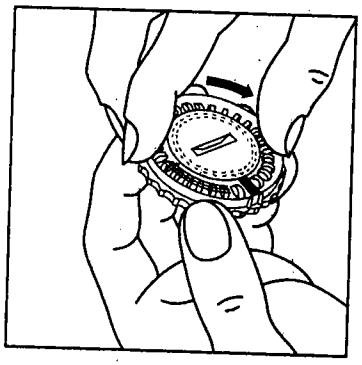


**How to use the ACTIVELLA™ Dispenser**

**1. Set the Day Reminder**
Turn the inner disc so the current day of the week is lined up with the little plastic tab.



**2. How to Take the First Tablet**
Pull plastic tab up and break off. Tip out the first tablet.



**3. Every Day**
Turn the outer transparent dial one space clockwise as indicated by the arrow. Tip out the next tablet.

**Note: The transparent dial can only be turned after the tablet in the opening has been removed.**

Pharmacia &Upjohn

# Activella™

**(estradiol/norethindrone acetate tablets)**

INFORMATION FOR THE PATIENT
Your doctor has prescribed ACTIVELLA™, a combination of two hormones, estradiol an estrogen, and norethindrone acetate, a progestin. This leaflet describes the major benefits and risks of your treatment, as well as directions for use. Before you start taking ACTIVELLA™, please read this package leaflet carefully. If you have any questions, please contact your physician, nurse or pharmacist.

**ESTROGENS ARE KNOWN TO INCREASE THE RISK OF CANCER OF THE UTERUS IN MENOPAUSAL WOMEN. THIS FINDING REFERS TO ESTROGENS GIVEN WITHOUT PROGESTIN.**

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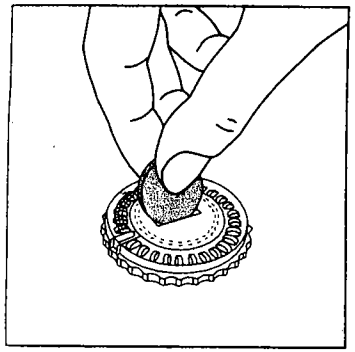

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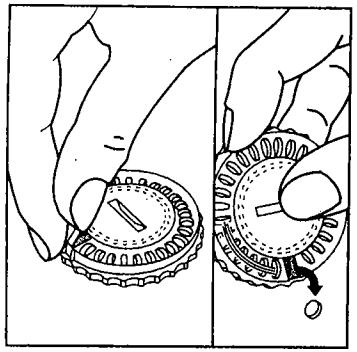
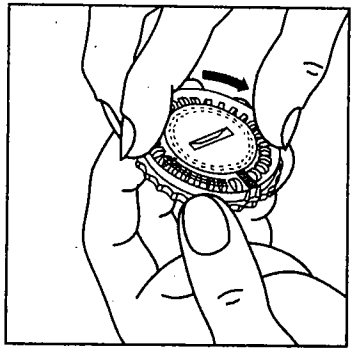


**2. How to Take the First Tablet**
Pull plastic tab up and break off. Tip out the first tablet.



**3. Every Day**
Turn the outer transparent dial one space clockwise as indicated by the arrow. Tip out the next tablet.

**Note: The transparent dial can only be turned after the tablet in the opening has been removed.**

Pharmacia & Upjohn

# Activella™

**(estradiol/norethindrone acetate tablets)**

INFORMATION FOR THE PATIENT
Your doctor has prescribed ACTIVELLA™, a combination of two hormones, estradiol an estrogen, and norethindrone acetate, a progestin. This leaflet describes the major benefits and risks of your treatment, as well as directions for use. Before you start taking ACTIVELLA™, please read this package leaflet carefully. If you have any questions, please contact your physician, nurse or pharmacist.

**ESTROGENS ARE KNOWN TO INCREASE THE RISK OF CANCER OF THE UTERUS IN MENOPAUSAL WOMEN. THIS FINDING REFERS TO ESTROGENS GIVEN WITHOUT PROGESTIN.**

8-2900-31-041-1

Progestin-containing drugs taken with estrogen-containing drugs significantly reduce but do not eliminate this risk completely. 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.
If you take ACTIVELLA™ (estradiol/norethindrone acetate tablets), and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible.
ACTIVELLA™ contains two hormones that are similar to naturally occurring hormones in the body that decrease at menopause. The hormone combination you will be taking, estradiol and norethindrone acetate, has been shown to provide the benefits of estrogen therapy while lowering the frequency of a precancerous condition of the uterine lining known as endometrial hyperplasia (excessive reproduction of normal cells). The use of an estrogen without also

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**Estrogen Drugs**
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using a progestin increases a woman's chance of getting endometrial hyperplasia. ACTIVELLA™ (estradiol/norethindrone acetate tablets), should be used only by women who have a uterus.

**Estrogen Drugs**
Estrogens have several important benefits but also some risks. Discuss with your doctor whether the risks of estrogens are acceptable compared to their benefits for you. Check with your doctor to make sure you are using the lowest effective dose of estrogens, and that you don't use them longer than necessary. The length of treatment with estrogen will depend upon the reason for use and will vary from woman to woman.
ACTIVELLA™ is a continuous combined hormone replacement therapy (HRT). During the initial months of therapy, bleeding or spotting episodes may occur; however, these episodes tend to decrease with time. The advantage of using a continuous-combined HRT regimen is that it is not associated with the regular monthly bleeding that occurs with sequential HRT regimens. If you experience vaginal bleeding while taking ACTIVELLA™ (estradiol/norethindrone acetate tablets), you should discuss it with your doctor. Your doctor will decide if follow-up care is needed.

**Uses of Estrogen**
*To reduce moderate to severe vasomotor symptoms.* Estrogens are hormones produced by the ovaries of premenopausal women. Between ages 45 and 55, the ovaries stop making estrogen and the monthly menstrual periods eventually come to an end. This is referred to as the "change of life" or menopause. When both ovaries are removed by an operation before natural menopause, a sudden drop in estrogen levels causes "surgical menopause." When 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 flushes" or "hot flashes"). Some women may have only mild menopausal symptoms, while for others they may be severe. These symptoms may last only a few months or longer.
Therapy with ACTIVELLA™ (estradiol/norethindrone acetate tablets), can provide relief from these symptoms. You should decide along with your doctor how long your therapy will last. The majority of women do not need to take estrogen replacement for longer than six months for these symptoms.

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

**When Estrogen Should Not be Used**
*During pregnancy.* If you think you may be pregnant, do not use any estrogen-containing drug product. Use of estrogen during pregnancy may cause birth defects in your unborn child. Estrogen does not prevent miscarriage.

*If you have unusual vaginal bleeding that has not been evaluated by your doctor.* Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it occurs after menopause. If you have vaginal bleeding caused by uterine cancer, taking estrogens can cause you serious harm. Your doctor is the only one who can determine the cause of bleeding and recommend proper treatment.

*If you have had cancer.* Since estrogens are known to increase the risk of certain types of cancer, you should not take estrogen if you have ever had cancer of the breast or uterus.

*If you have had deep vein thrombosis or other blood clotting disorders.* You should use estrogen only after consultation with your physician and only in recommended doses. (see **Risks of Estrogens and/or Progestins** below).

*When they are ineffective.* ACTIVELLA™ (estradiol/norethindrone acetate tablets) is not recommended for use other than what is approved by the FDA. For example, sometimes women experience nervous symptoms or depression during menopause. Estrogens do not relieve these symptoms. You may have heard that taking estrogen for long periods (years) after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence that this is so and such long-term treatment may have serious risks.

*After childbirth or when breast-feeding a baby.* Estrogens should not be used to try to stop the breast from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see **Risks of Estrogens and/or Progestins** below).

Many drugs can pass through to the baby in the milk when you are breast-feeding. While breast-feeding, you should only take medicine on the advice of your health care provider.

**Risks of Estrogens and/or Progestins**
*Cancer of the uterus.* Your risk of getting cancer of the uterus gets

higher when estrogens are used alone, when estrogens are used for longer times, and when larger doses are taken.
There is a higher risk of cancer of the uterus if you are overweight, diabetic, or have high blood pressure.
ACTIVELLA™ (estradiol/norethindrone acetate tablets) contains both an estrogen and a progestin. The combination reduces the increased risk of a precancerous condition of the uterine lining compared to estrogen alone (see **Other Information** below).
Additional risks may be associated with the inclusion of a progestin with estrogen treatment. These possible risks include unfavorable effects on blood fats and sugars, and a possible increase in the risk of breast cancer (see *Cancer of the breast* below).
Generally, the lower the dose and the shorter the duration of treatment, the more these effects are minimized. You should talk with your doctor to be sure you are using the lowest effective dose and only for as long as necessary.
If you have had your uterus removed (total hysterectomy), there is no risk of developing cancer of the uterus.

ACTIVELLA™ (estradiol/norethindrone acetate tablets) is not intended for use in women who have had a hysterectomy because these women do not need to take the progestin part of the drug.

*Cancer of the breast.* Most studies have shown no association with estrogen and breast cancer. Some studies have suggested a possible increased incidence up to twice the usual rate of breast cancer in those women who took estrogens for long periods of time (especially more than 10 years) or took higher doses for short periods. The effects of added progestin on the risks of breast cancer are unknown. Some studies have reported a somewhat increased risk, even higher than the possible risk associated with estrogens alone, while others have not. Monthly self-examinations and regular breast examinations by a Healthcare professional are recommended for all women. The American Cancer Society recommends mammogram every year for women over 50 years of age.

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

*Abnormal blood clotting.* Taking estrogens may cause changes in your blood clotting system, thereby increasing the risk of clots to form in your blood. By cutting off blood supply to vital organs, these clots can cause a stroke, heart attack, or lung clot, any of which 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.

*Excess calcium in the blood.* Taking estrogens may lead to severe elevations in blood calcium levels in women with breast and/or bone cancer. Therefore, ACTIVELLA™ (estradiol/norethindrone acetate tablets) should be used with caution if you have these conditions.

*During pregnancy.* You should not take estrogen when you are pregnant as there is a greater than usual chance that your child will be born with a birth defect. If you take ACTIVELLA™ and later find that you were pregnant when you took it, discuss this with your doctor as soon as possible.

**Side Effects with Estrogens and/or Progestins**
In addition to the risks listed above, the following side effects have been reported with estrogen and/or progestin use:
- Nausea, vomiting, pain, cramps, swelling, or tenderness in the abdomen.
- Breast tenderness or enlargement.
- Enlargement of benign tumors (fibroids) of the uterus.
- Yellowing of the skin and/or whites of the eyes.
- Irregular bleeding or spotting.
- Change in amount of cervical secretion.
- Vaginal yeast infections.
- 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; reddening of the skin; skin rashes.
- Worsening of porphyria.
- Headache, migraines, dizziness, faintness, or changes vision (including intolerance to contact lenses).
- Mental depression.
- Involuntary muscle spasms.
- Hair loss or abnormal hairiness
- Increase or decrease in weight.
- Changes in sex drive.
- Possible changes in blood sugar

**Reducing Risk of Estrogen/Progestin Use**
If you decide to take an estrogen progestin combination product, y can reduce your risks by carefully monitoring your treatment.

*Contact your doctor regularly.* W you are taking ACTIVELLA™ (estr diol/norethindrone acetate tablet is important that you consult at l every six months with your docto and have a check up least once a year. If members of your family h had breast cancer or if you have had a breast lump or an abnorm mammogram (breast x-ray), you may need to have more frequent breast examinations. If you devel vaginal bleeding while taking ACTIVELLA™, talk to your doctor

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**Reducing Risk of Estrogen/Progestin Use**

If you decide to take an estrogen/progestin combination product, you can reduce your risks by carefully monitoring your treatment.

*Contact your doctor regularly.* While you are taking ACTIVELLA™ (estradiol/norethindrone acetate tablets), it is important that you consult at least every six months with your doctor and have a check up least once a year. If members of your family have had breast cancer or if you have ever had a breast lump or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations. If you develop vaginal bleeding while taking ACTIVELLA™, talk to your doctor.

*Reevaluate your need for estrogen.* You and your doctor should reevaluate your need for estrogen at least every six months.

*Be alert for signs of trouble.* Report these or any other unusual side effects to your doctor immediately:

- Abnormal bleeding from the vagina (possible uterine abnormality).
- Pains in the calves or chest, a sudden shortness of breath, or coughing blood (indicates possible clot in the legs, heart, or lungs).
- Severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg (indicates possible clot in the brain or eye).
- Breast lumps (possible breast cancer; ask your health care professional to show you how to examine your breasts monthly).
- Yellowing of the skin or whites of the eyes (possible liver problem).
- Pain, swelling, or tenderness in the abdomen (possible gallbladder problem).

**Other Information**

- Since you still have your uterus, your doctor has prescribed ACTIVELLA™ (estradiol/norethindrone acetate tablets) which has both an estrogen and a progestin. Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking a progestin, another hormone drug, along with estrogen reduces the increased risk of developing this condition. There are however, possible additional risks that may be associated with the inclusion of a progestin with estrogen treatment. The possible risks include: unfavorable effects on blood fats and sugars, which may make a diabetic condition worse; possible further increase in breast cancer risk which may be associated with long-term estrogen use. *You are encouraged 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.*
- Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.
- 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 the most important information about ACTIVELLA™ (estradiol/norethindrone acetate tablets). If you have any questions about you and ACTIVELLA™ please speak to your doctor or pharmacist.

**How Supplied**

Your doctor has prescribed ACTIVELLA™, a single white tablet containing 1 mg estradiol and 0.5 mg norethindrone acetate (NETA) for oral administration.

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The appearance of these tablets is a trademark of Novo Nordisk A/S.

Store in a dry place protected from light. Store at room temperature 77°F (25°C).

**Rx only**

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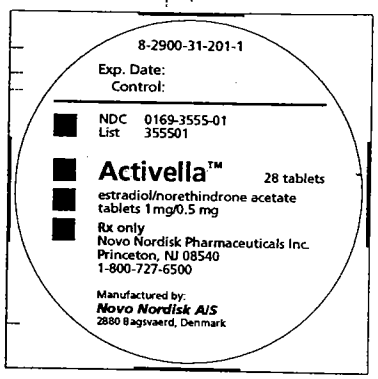
Novo Nordisk A/S
2880 Bagsværd, Denmark

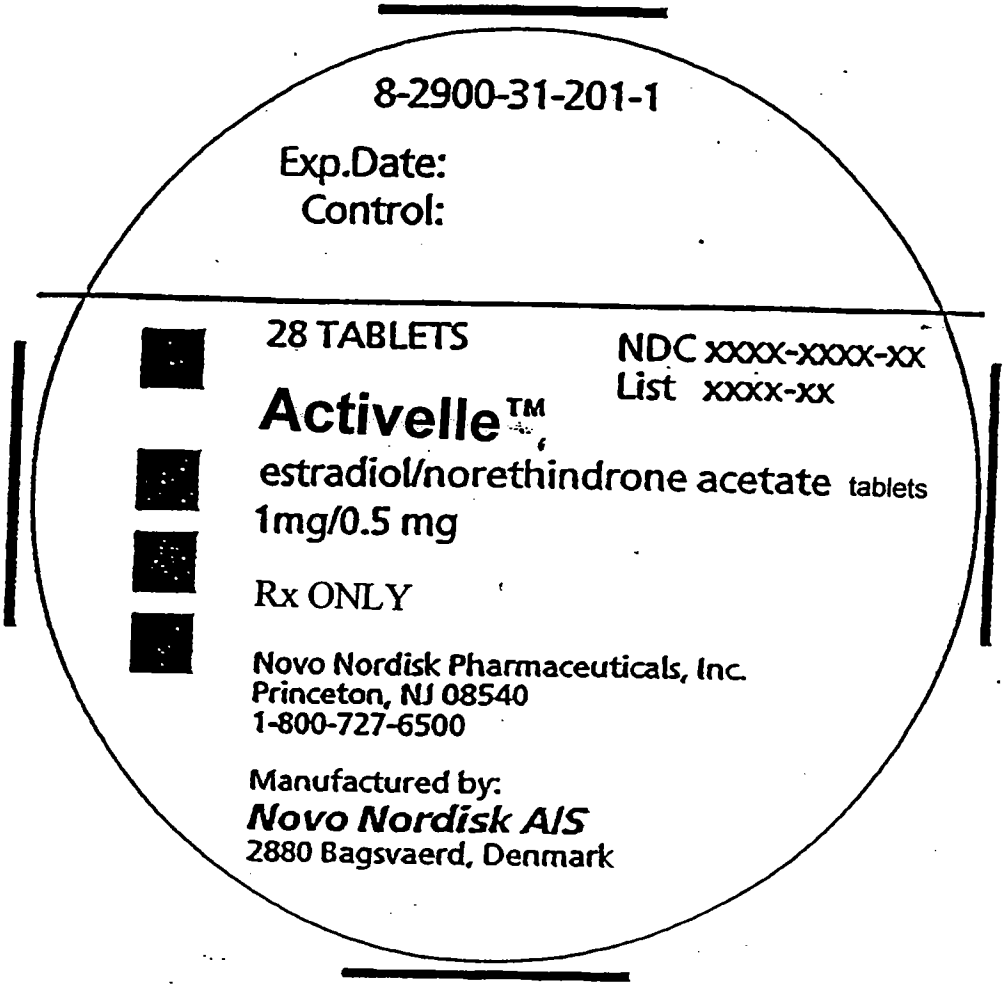



RBS Labelling & Graphics

Label size: Ø 46 mm
Edition: 09.98-201-1
Colour band: 8-151

**Colour PMS: 289C + 285C**

**Dispenser Label**



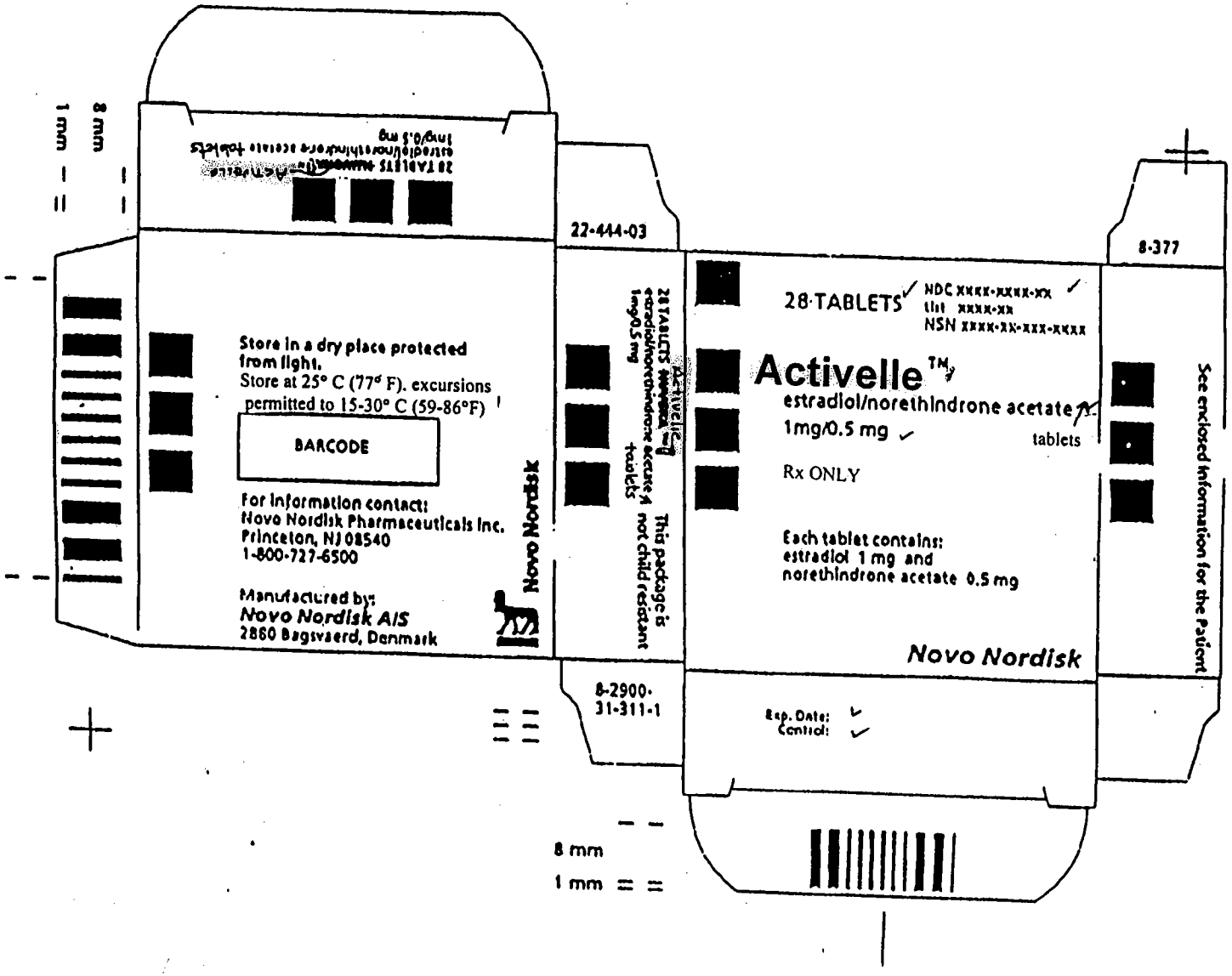

PMS 285C + Varnish

Label size: Ø 46 mm - Original size: 3:1
Edition: 10.91-202-1
Colour band: 8-150

Property of:
Novo Nordisk A/S
PrePress Service Centre

"Revised" Label

# Carton Label




"Revised Label"

Original
20-907 4-18-00
DRL 6/2/00

6

22-430-16

NDC 0009-5174-02

Manufactured for
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA
By
Novo Nordisk A/S
2880 Bagsværd, Denmark

# Activella™

estradiol/norethindrone acetate tablets

1 mg/0.5 mg

28 tablets

Pharmacia &Upjohn

8-2900-
31-311-1

EXP.:
LOT:

# Activella™

estradiol/norethindrone acetate tablets

1 mg/0.5 mg

℞ only

See enclosed information for the patient.
This package is not child resistant.

Each tablet contains:
estradiol 1 mg and
norethindrone acetate 0.5 mg

Store in a dry place protected from light.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

3 00095 17402 1

List 517402

Pharmacia&Upjohn

original
20-907 4-18-00
DSL 6/2/00

7
22-430-16

NDC 0009-5174-99

Complimentary
Package
- NOT FOR SALE -

# Activella™

estradiol/norethindrone
acetate tablets

1 mg/0.5 mg

28 tablets

Pharmacia
&Upjohn

Manufactured for
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA
By
Novo Nordisk A/S
2880 Bagsværd, Denmark

8-2900-
31-312-1

EXP.:
LOT:

**Activella™**
estradiol/norethindrone
acetate tablets

1 mg/0.5 mg

℞ only

See enclosed information for the patient.
This package is not child resistant.

Each tablet contains:
estradiol 1 mg and
norethindrone acetate 0.5 mg

Store in a dry place protected from light.
Store at 25°C (77°F); excursions permitted
to 15-30°C (59-86°F).

Pharmacia&Upjohn

List 517499

Labeling: Original
NDA No. 20-907 Rec'd. 4.18.00
Reviewed by: DSL 6/2/00

8-2900-31-204-1

EXP.:
LOT:

NDC 0009-5174-99 Sample

**Activella™**
estradiol/norethindrone acetate tablets

1 mg estradiol
0.5 mg norethindrone acetate

℞ only
28 tablets

Manufactured for
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA
By
Novo Nordisk A/S
2880 Bagsværd, Denmark

JUN 8 2000

Labeling: Original

NDA No. 20-907 Rcvd. 4.18.00

Reviewed by: DBL 6/2/00

8-2900-31-201-1

EXP.:
LOT:

NDC 0009-5174-02

**Activella™**
estradiol/norethindrone acetate tablets

1 mg estradiol
0.5 mg norethindrone acetate

℞ only
28 tablets

Manufactured for
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA
By
Novo Nordisk A/S
2880 Bagsværd, Denmark

Original
20-907 4.18.00

NDC 0009-5174-01

(Contains:
5 of NDC 0009-5174-02)

**Activella™**
estradiol/norethindrone acetate tablets

Each tablet contains:
estradiol 1 mg and
norethindrone acetate 0.5 mg.

JUN

Pharmacia &Upjohn

5-28 packs

℞ only
See enclosed information for the patient.
This package is not child resistant.
Store in a dry place protected from light.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
[See USP Controlled Room Temperature.]

Manufactured for
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA
By
Novo Nordisk A/S
2880 Bagsværd, Denmark

3 00095 17401 4

List 517401

8-2900-31-203-1

Labeling: Original

NDA No. 20-907 Date: 4.18.00

Reviewer: 08C 6/2/00

NDC 0009-5174-99

Complimentary Package
- NOT FOR SALE -

**Activella™**
estradiol/norethindrone acetate tablets

Each tablet contains:
estradiol 1 mg and
norethindrone acetate
0.5 mg

JUN 2 8 2000

5-28 packs

Pharmacia &Upjohn

℞ only

See enclosed information for the patient.

This package is not child resistant.

Store in a dry place protected from light.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
[See USP Controlled Room Temperature.]

Manufactured for
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA
By
Novo Nordisk A/S
2880 Bagsværd, Denmark

3 00095 17499 1

List 517499

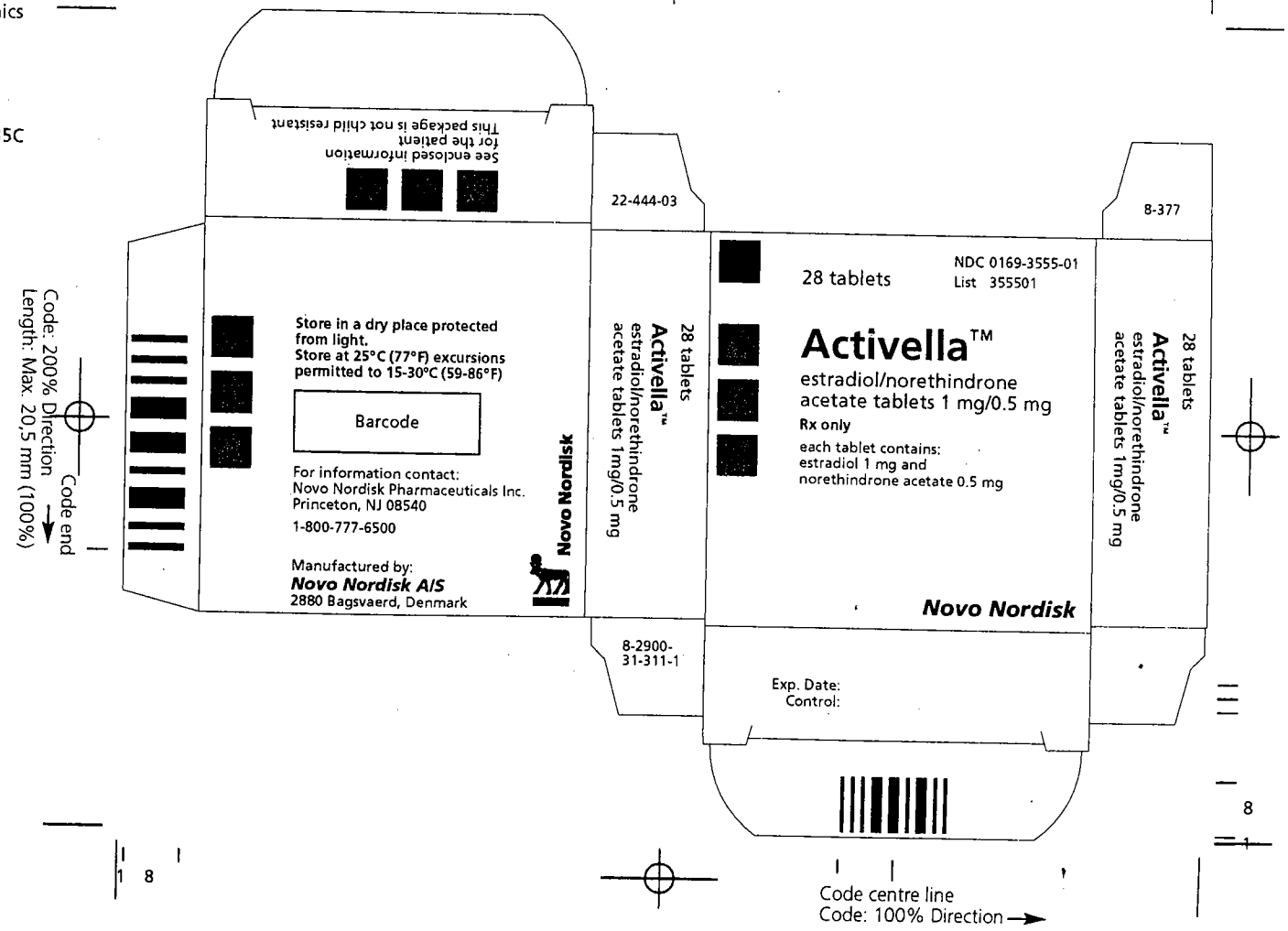
8-2900-31-205-1

8-2900-31-311-1.qxd 10-11-99 12:13 Side 1

RBS Labelling & Graphics

Carton: 22-444-03
Edtion: 08.98-301-1
Colour band: 8-377

**Colour PMS: 289C + 285C**



# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 20-907/S-002

# CHEMISTRY REVIEW(S)

FEB - 1 2000

CHEMIST REVIEW
OF **SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 20-907/SLR-002
3. **SUPPLEMENT NUMBERS/DATES:**
   **Letterdate:** 16-NOV-1999
   **Stampdate:** 17-NOV-1999
4. **AMENDMENTS/REPORTS/DATES:**
   **Letterdate:**
   **Stampdate:**
5. **RECEIVED BY CHEMIST:** 17-NOV-1999

6. **APPLICANT NAME AND ADDRESS:**
   Novo Nordisk Pharmaceuticals, Inc.
   Suite 200, 100 Overlook Center
   Princeton, NJ 08540-7810

7. **NAME OF DRUG:**
   Activella (previously was Activelle)

8. **NONPROPRIETARY NAME:**
   Estradiol/Norethindrone acetate Tablets

9. **CHEMICAL NAME/STRUCTURE:**
   a. Estradiol: estra-1,3,5(10)-triene-3,17β-diol hemihydrate
   b. Norethindrone acetate: 17β-acetoxy-19-nor-17α-pregn-4-en-20-yn-3-one

   See USP Dictionary of Drug Names for structures.

10. **DOSAGE FORM(S):**
    Tablet

11. **POTENCY:**
    1 mg estradiol/0.5 mg norethindrone acetate

12. **PHARMACOLOGICAL CATEGORY:**
    Estrogen and progestin/Treatment of Post Menopausal Vasomotor Symptoms

13. **HOW DISPENSED:**
    RX

14. **RECORDS & REPORTS CURRENT:**
    Yes

15. **RELATED IND/NDA/DMF:**
    None

16. **SUPPLEMENT PROVIDES FOR:**
    Change of proprietary name from Activelle to Activella (change "e" to "a").

**17. COMMENTS**

The sponsor proposes to change the approved proprietary name from Activelle to Activella. The supplement contains the revised physician insert, patient information insert, carton label, and dispenser label. The revised inserts and labels have been changed in the appropriate areas and are satisfactory.

A consult for a review of the proposed proprietary name was submitted to OPDRA (Office of Post-Marketing Drug Risk Assessment) on November 17, 1999. The Office determined the name to be acceptable on December 23, 1999 (see attached response).

**18. CONCLUSIONS AND RECOMMENDATIONS:**

This CBE Supplement may be approved. **Issue an approval letter.**

| **19. REVIEWER NAME** | **SIGNATURE** | **DATE COMPLETED** |
|---|---|---|
| David T. Lin, Ph.D.<br>Review Chemist | 1/31/00 | 31-JAN-2000 |

**cc: Original: NDA 20-907/SLR-002**
**HFD-580/Division File**
**HFD-580/DSpell-LeSane**
**HFD-580/MRhee/DLin**

**INIT by MJ Rhee** 2/1/00

Filename: S20907.002 (doc)

APPEARS THIS WAY
ON ORIGINAL

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 20-907/S-002

# ADMINISTRATIVE DOCUMENTS

FEB 14 2000

NDA 20-907/SLR-002
ACTIVELLE™ Physician labeling label Review
Date received: November 16, 1999
Date revised: December 29, 1999

The purpose of this "Changes Being effected" (CBE) supplement is to revise the physician package insert, the patient information insert and the carton and dispenser with the name change from "e" to "a" in the name of the product (Activelle to Activella). The name change was accepted by the Labeling and Normenclature Committee September 21, 1999, and reviewed and accepted by the Office of Post Marketing Drug Approval (OPDRA) December 23, 1999.

The supplement provides for change of proprietary name from **Activelle to Activella** in :
physician package insert,
patient information insert
carton and dispenser

This is acceptable

Proposed Regulatory Action (MO to complete)

☒ Approval

☐ Approvable

☐ Not Approvable

PM signature 2/3/00 Date

Medical Officer Signature 2/3/00 Date

Team Leader Signature 2/3/00 Date

Deputy Director Signature 2/14/00 Date

Archival NDA 20-472
HFD-580/Div. Files
HFD-580/D.Spell-LeSane
HFD-580/Mann/Slaughter/Price/Rhee/Lin/Raheja/Jordan/Parekh/Jarugula/Rumble

Drafted By: dsl
Initialed by:
final:
filename:

DEC 27 1999

## CONSULTATION RESPONSE
### Office of Post-Marketing Drug Risk Assessment
### (OPDRA; HFD-400)

| **DATE SENT:** December 23, 1999 | **DUE DATE:** 12/16/1999 | **OPDRA CONSULT #:** 99-087 |
|---|---|---|

**TO (Division):**
Susan Allen, M.D.
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

| **PRODUCT NAME:**<br>**Activella™**<br>( 1mg estradiol/0.5mg norethindrone acetate tablets)<br><br>**NDA #:** 20-907 | **MANUFACTURER:** Novo Nordisk Pharmaceuticals, Inc. |
|---|---|

**CASE REPORT NUMBER(S):** N/A

**SUMMARY:**
In response to a November 17, 1999 consult from the Division of Reproductive and Urologic Drug Prducts (HFD 580), OPDRA conducted a review of the proposed proprietary name Activella™ to determine the potential for confusion with approved/unapproved proprietary and generic names.

**OPDRA RECOMMENDATION:**
OPDRA has no objections to the use of proprietary name "Activella™".

Jerry Phillips 12/23/99

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 827-8173

12/27/99

Peter Honig, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

**Office of Post-Marketing Drug Risk Assessment**
**HFD-400; Rm 15B03**
**Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** December 9, 1999

**NDA#:** 20-907

**NAME OF DRUG:** Activella™

**NDA Holder:** Novo Nordisk

## I. INTRODUCTION

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) on November 17, 1999 to review the proposed proprietary drug name, Activella™ regarding potential name confusion with existing proprietary/generic drug name. This NDA was approved on 11/18/98 under the proprietary name, Activelle™. The firm has not yet marketed the product with this name.

The sponsor submitted a special supplement changes being effected on November 16, 1999 requesting the use of a new proprietary name Activella. The sponsor requested the name change because they feel that Activelle is too similar to Aconel™ (approved 3/27/98 for the treatment of Paget's disease).

The Labeling and Nomenclature Committee (LNC) reviewed the newly proposed proprietary name Activella™ on 8/11/99 and found the name acceptable.

PRODUCT INFORMATION

Activella™ is a single tablet containing an estrogen, estradil ($E_2$), and a progestin, norethindrone acetate (NETA), for oral administration.

Estradiol is well absorbed through the gastrointestinal tract. Following oral administration of Activella™, peak plasma estradiol concentrations are reached slowly within 5-8 hours. When given orally, estradiol is extensively metabolized (first-pass effect) to estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogens. After oral administration, norethindrone acetate is rapidly absorbed and transformed to norethindrone. It undergoes first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration within 0.5-1.5 hours.

Activella™ is supplied in a dispenser containing 28 tablets. Each tablet contains 1 mg estradiol and 0.5mg norethindrone acetate.

## II. RISK ASSESSMENT

In order to determine the potential for medication errors and to find out the degree of confusion of the proposed proprietary name, Activella™, with other drug names, the medication error staff of OPDRA searched American Drug Index (43rd Edition), Drug Facts and Comparison (update monthly), PDR (53rd Edition 1999), Drug Product Reference File (DPR), Electronic Orange Book, Microdex online, Medline online, and the Patent and Trademark Office online for possible sound alike or look alike names to approved and unapproved drug products. A focus group was conducted to review all the findings from the searches. In addition, OPDRA conducted studies of written and verbal analysis of the proposed proprietary name involving health practitioners within CDER to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

### A. STUDY CONDUCTED WITHIN OPDRA

Methodology:

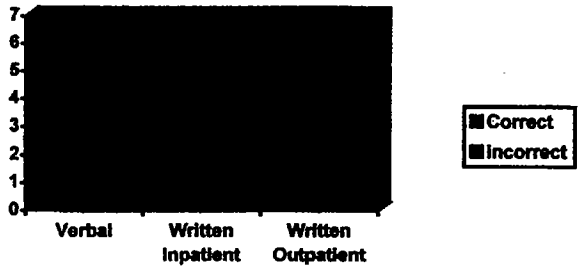
This study involved 22 health professionals consisting of physicians, nurses pharmacists within CDER to determine the degree of confusion of Activella™ with other drug names due to the similarity in handwriting and verbal pronunciation of the name. OPDRA staff members wrote two outpatient and inpatient orders, each consisting of a known drug product and a prescription for Activella. These prescriptions were scanned into the computer and a random sample of the written orders were then delivered to the participating health professionals via e-mail. In addition, one pharmacist with an accent recorded the outpatient orders on voice mail. The voice mail messages were then sent to the participating health professionals for their review and interpretation. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Results:

We received responses from 15 participants, thirteen of which interpreted the name correctly. Seven participants interpreted inpatient prescription orders, three interpreted outpatient prescription orders and five interpreted verbal orders. Results are summarized in Table 1.

Table 1

| Study | # of Sample | # of Responses (%) | Correctly Interpreted | Incorrectly Interpreted |
|---|---|---|---|---|
| Written Inpatient | 7 | 7 (100%) | 7 | 0 |
| Written Outpatient | 8 | 3 (27%) | 3 | 0 |
| Verbal | 7 | 5 (71%) | 3 | 2 |




Fifty nine percent of the participants responded with correct name Activella™. All written prescriptions were interpreted correctly. The incorrect verbal responses are as follows:

Activelle
Actifed

B. FOCUS GROUP FINDING:

The group did not uncover any existing drug names that could cause confusion with Activella™, and thus pose a significant safety risk.

C. DISCUSSION:

The results of the verbal and written analysis studies show thirteen out of fifteen participants interpreted the proprietary name Activella™ correctly. We recognize that our study sampling size is small. There are also high scores of correct interpretations for a new proposed proprietary name which is uncommon for an unapproved drug product name since health professionals are not familiar with the

name. There were two incorrect responses that needed to be addressed. One participant interpreted Activella as Activelle. This will not cause any concern since Activelle will no longer be marketed. Another participant interpreted Activella as Actifed which has been on the market for many years and is a combination of an antihistamine and decongestant. Activella is a combination of female hormones containing estradiol and norethindrone . It will be supplied in a dispenser containing 28 tablets. OPDRA does not believe the potential for confusion is significant. Finally, the studies and searches conducted within OPDRA did not reveal any existing drug names that would render the proprietary name, Activella, objectionable.

## III. RECOMMENDATIONS

OPDRA has no objections to the use of the proprietary name Activella™.

Should you have any questions concerning this review, please contact Peter Tam at 301-827-3241.

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips 12/23/99
Jerry Phillips, RPh.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

C.C. NDA 20-907
HFD-580; Dornette Spell-LeSane, Project Manager, DRUDP
HFD-580; Susan Allen, Acting Division Director, DRUDP
Office Files
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

DEC 27 1999

# CONSULTATION RESPONSE
## Office of Post-Marketing Drug Risk Assessment
## (OPDRA; HFD-400)

| DATE SENT: December 23, 1999 | DUE DATE: 12/16/1999 | OPDRA CONSULT #: 99-087 |
|---|---|---|

**TO (Division):**
Susan Allen, M.D.
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

| PRODUCT NAME: **Activella™** ( 1mg estradiol/0.5mg norethindrone acetate tablets)<br><br>NDA #: 20-907 | MANUFACTURER: Novo Nordisk Pharmaceuticals, Inc. |
|---|---|

**CASE REPORT NUMBER(S):** N/A

**SUMMARY:**
In response to a November 17, 1999 consult from the Division of Reproductive and Urologic Drug Prducts (HFD 580), OPDRA conducted a review of the proposed proprietary name Activella™ to determine the potential for confusion with approved/unapproved proprietary and generic names.

**OPDRA RECOMMENDATION:**
OPDRA has no objections to the use of proprietary name "Activella™".

Jerry Phillips 12/23/99
Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 827-8173

12/27/99
Peter Honig, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

**Office of Post-Marketing Drug Risk Assessment**
**HFD-400; Rm 15B03**
**Center for Drug Evaluation and Research**

## PROPRIETARY NAME REVIEW

**DATE OF REVIEW:** December 9, 1999

**NDA#:** 20-907

**NAME OF DRUG:** Activella™

**NDA Holder:** Novo Nordisk

## I. INTRODUCTION

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In order to determine the potential for medication errors and to find out the degree of confusion of the proposed proprietary name, Activella™, with other drug names, the medication error staff of OPDRA searched American Drug Index (43rd Edition), Drug Facts and Comparison (update monthly), PDR (53rd Edition 1999), Drug Product Reference File (DPR), Electronic Orange Book, Microdex online, Medline online, and the Patent and Trademark Office online for possible sound alike or look alike names to approved and unapproved drug products. A focus group was conducted to review all the findings from the searches. In addition, OPDRA conducted studies of written and verbal analysis of the proposed proprietary name involving health practitioners within CDER to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

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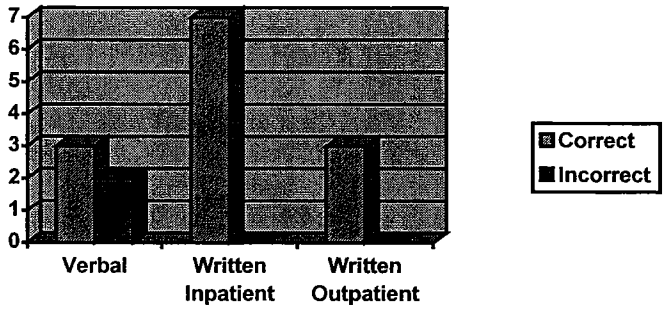


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Actifed

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Should you have any questions concerning this review, please contact Peter Tam at 301-827-3241.

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips 12/23/99
Jerry Phillips, RPh.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

C.C. NDA 20-907
HFD-580; Dornette Spell-LeSane, Project Manager, DRUDP
HFD-580; Susan Allen, Acting Division Director, DRUDP
Office Files
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

JUN 2 0 2000

# NDA 20-907/SLR002
## ACTIVELLA™
## FINAL PRINTED LABEL REVIEW

Submitted: April 18, 2000
Date Received: April 19, 2000
Date reviewed: June 2, 2000

The following minor changes were made to the label after approval of the draft label dated November 16, 1999.

1. Novo Nordisk logo and tradedress replaced by Pharmacia & Upjohn logo and tradedress due to marketing/partnering agreement.

2. Formatting changes such as eliminating spaces between paragraphs, section headers, etc., for consistency.

3. Changing Activella™ to Activella™ (estradiol/norethindrone acetate tablets) wherever Activella™ appears for the first time in running text of each column.

4. 5-pack package label which has replaced the 3-pack package.

5. Labels for corresponding free samples, which were not submitted to the original NDA.

APPEARS THIS WAY
ON ORIGINAL

The final printed label is in compliance with the request of the Division.

Dornette Spell-LeSane, NP-C
Regulatory Project Manager

6/9/00
Terri Rumble, R.N., B.S.N
Chief, Project Management Staff

6/12/00
Phil Price, M.D.
Medical Officer

6/12/00
Shelley Slaughter, M.D.
Medical Team Leader

6/9/00
David Lin, Ph.D.
Chemist

6/12/00
MooJhong Rhee, Ph.D.
Chemistry Team Leader

6/20/00
Susan Allen, M.D., M.P.H.
Division Director

CC:
ARCHIVAL NDA 20907/
HFD-580/DIV. FILES
HFD-580/D.SPELL-LESANE
HFD-580/Allen/Slaughter/Price/Rhee/Lin/

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 20-907/S-002

# CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-907/S-002

Novo Nordisk Pharmaceuticals Inc.
100 Overlook Center, Suite 200
Princeton, NJ 08540-7810

NOV 18 1999

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

Dear Dr. Reit:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Activelle™

NDA Number: 20-907

Supplement Number: S-002

Date of Supplement: November 16, 1999

Date of Receipt: November 17, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on January 16, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Terri F. Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-907/S-002
HFD-580/Div. Files
HFD-580/CSO/Spelllesane

SUPPLEMENT ACKNOWLEDGEMENT

**Changes Being Effected Supplement**

See Clin. Rev. dated 1/31/00.

DTC 2/1/00 NDA NO. 20-907 SEQ NO. 002

NDA SUPPLEMENT SLR

November 16, 1999

Dr. Lisa Rarick
Director, Division of Reproductive and
Urologic Drug Products, HFD 580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV 17 1999
HFD-580

Novo Nordisk

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

**Re: S-002**
**Changes Being Effected Supplement for Label Change (Activelle™ to Activella™)**
**Activelle™, NDA 20-907**

Dear Dr. Rarick:

Reference is made to Activelle™ (1 mg estradiol/0.5 mg norethindrone acetate tablets), NDA 20-907 and to the accepted name change to Activella as the new brand name for the product by the CDER Labeling and Nomenclature Committee (fax of 9/21/99).

Reference is also made to the October 20, 1999 telephone conversation with the Activelle project manager, Ms. Darnet Spell-LeSane, regarding the filing of the name change. On October 20, 1999 Ms. Spell-LeSane informed Novo Nordisk that we could submit the name change as a Changes Being Effected supplement. The only changes in the label involve changing an "e" to an "a" in the name of the product (Activelle to Activella). The content has not changed from the November 18, 1998 approved label.

Enclosed in duplicate are revised labels (Tab 1) for the physician insert, the patient information insert, and the carton and dispenser with the changes ("e" to an "a" in the name of the product) highlighted for convenience of review. We have also enclosed highlighted copies of the original approved label (Tab 2) for your convenience.

Final printed copies will be forwarded when produced for the marketed product as per the letter of November 18, 1998. We expect to market the drug product in the spring of 2000.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Asst. Dir. Regulatory Affairs at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

M A Mc Elligott for Barry Reit

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

REVIEWS COMPLETED
CSO ACTION:
☒ LETTER ☐ E.A.L. ☐ MEMO
AP 2/29/00 RSL
CSO INITIALS DATE

AP Letter 2/10/00

NDA 20-907/SLR-002

JUN 28 2000

**ACKNOWLEDGE AND RETAIN**

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President Regulatory Affairs
100 Overlook Center Suite 200
Princeton, NJ 08540

Dear Dr. Reit:

We acknowledge the receipt of your April 18, 2000 submission containing final printed labeling in response to our November 18, 2000 letter approving your supplemental new drug application for Activella™, (estradiol 1mg/northindrone acetate 0.5mg).

We have reviewed the labeling that you submitted in accordance with our November 18, 2000 letter, and we find it acceptable.

If you have any questions, call Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4210.

Sincerely,

Susan Allen, MD 6/20/00

Susan Allen, M.D., M.P.H.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 20-907/SLR-002

**ACKNOWLEDGE AND RETAIN**

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President Regulatory Affairs
100 Overlook Center Suite 200
Princeton, NJ 08540

Dear Dr. Reit:

We acknowledge the receipt of your April 18, 2000 submission containing final printed labeling in response to our November 18, 2000 letter approving your supplemental new drug application for Activella™, (estradiol 1mg/northindrone acetate 0.5mg).

We have reviewed the labeling that you submitted in accordance with our November 18, 2000 letter, and we find it acceptable.

If you have any questions, call Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Susan Allen, M.D., M.P.H.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20907/
HFD-580/Div. Files
HFD-580/D.Spell-LeSane
HFD-580/Allen/Slaughter/Price/Rhee/Lin/Parekh/Jordan
HF-2/Medwatch (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/OPDRA (with labeling)
DISTRICT OFFICE

Drafted by: dsl/June 5, 2000
Initialed by:Rumble, 6.9.00/Price, 6.12.00/Slaughter, 6.12.00/Lin, 6.9.00/Rhee, 6.12.00/
final: Spell-LeSane, 6.14.00
filename: NDA/20907/letter/apslr002.doc

**ACKNOWLEDGE AND RETAIN (AR)**

**FPL for Approved Supplement NDA 20-907/S-002**

April 18, 2000

Susan Allen, M.D.
Acting Director, Division of Reproductive and
Urologic Drug Products, HFD 580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857



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

**Re: Activella™ NDA 20-907; Supplement S-002**
**Final Printed Labeling**

NDA SUPP AMEND
SLR-002-FA

Dear Dr. Allen:

Reference is made to Activella™ (1 mg estradiol/ 0.5 mg norethindrone acetate tablets), NDA 20-907 and to the NDA approval letter of November 18, 1998 and the label supplement, S-002, approval letter of February 10, 2000.

As requested, Novo Nordisk Pharmaceuticals, Inc. is submitting 20 copies of the Final Printed Labeling (physician and patient inserts, dispenser, carton, 5-pack shrink wrap). This labeling is identical to the draft physician and patient labeling dated November 16, 1999 and the draft carton and container labels dated November 16, 1999 with minor exceptions described in the attached tables. These changes are considered to be annual reportable and will be reported in the next NDA annual report. Also included is a 5 pack package label which is replacing the 3 pack package listed in the original physician insert. In addition, there are labels for corresponding free samples which were not submitted in the original NDA. These labels are identical to the approved labels, with the exception of the addition of required regulatory language identifying them as free samples [21 CFR 210.10(g)(1)].

Please note that the "Manufactured by" information and tradedress/logo have been changed because of a marketing agreement with Pharmacia & Upjohn Company, Kalamazoo, MI.

Samples of the marketed drug product will be submitted separately at a future date.

If you have any questions concerning this submission, please contact Lieselotte Bloss, DVM, Assistant Director, Regulatory Affairs at 609-987-5852.

Sincerely,

NOVO NORDISK PHARMACUETICALS, INC.

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

REVIEWS COMPLETED
CSO ACTION
LETTER ☐ N/A ☐ MEMO
6/3/00
CSO INITIALS DATE

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

FOOD AND DRUG ADMINISTRATION

# APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

*(Title 21, Code of Federal Regulations, 314 & 601)*

*Form Approved : OMB No. 0910-0338*
*Expiration Date: April 30, 2000*
*See OMB Statement on page 2.*

**FOR FDA USE ONLY**

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Novo Nordisk Pharmaceuticals Inc. | 04/18/00 |
| TELEPHONE NO. *(Include Area Code)* (609) 987-5800 | FACSIMILE (FAX) Number *(Include Area Code)* (609) 987-3916 |

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
100 Overlook Center, Suite 200
Princeton, NJ 08540-7810

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number )* IF APPLICABLE

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-907

| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY |
|---|---|
| estradiol/norethindrone acetate | Activella |

| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* | CODE NAME *(If any)* |
|---|---|
| estra-1,3,5(10)-triene,5, 17ß-diolhemihydrate 17ß-acetoxy-19-nor-17a-pregn-4-en-20-yn-3-one | Kliogest Low Dose |

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Tablets | 1mg NETA/.5mg E2 | Oral |

(PROPOSED) INDICATION(S) FOR USE:
Indicated for use in the treatment of moderate to severe vasomotor symptoms associated with the menopause and in the treatment of vulvar and vaginal atrophy, in women with an intact uterus.

## APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☒ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION Final printed labeling for approved supplement S-002

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

## ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

**Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)**

IND 38,483

| This application contains the following items: *(Check all that apply)* | |
|---|---|
| | 1. Index |
| X | 2. Labeling (check one) ☐ Draft Labeling ☒ Final Printed Labeling |
| | 3. Summary (21 CFR 314.50 (c)) |
| | 4. Chemistry section |
| | A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2) |
| | B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| | C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2) |
| | 5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2) |
| | 6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2) |
| | 7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4)) |
| | 8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2) |
| | 9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2) |
| | 10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2) |
| | 11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2) |
| | 12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2) |
| | 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)) |
| | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A)) |
| | 15. Establishment description (21 CFR Part 600, if applicable) |
| | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| | 17. Field copy certification (21 CFR 314.50 (k) (3)) |
| | 18. User Fee Cover Sheet (Form FDA 3397) |
| X | 19. OTHER (Specify) Final printed labeling for approved supplement S-002 |

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
|  | Barry Reit, Ph. D., Vice President | April 18, 2000 |

| ADDRESS *(Street, City, State, and ZIP Code)* | Telephone Number |
|---|---|
| 100 Overlook Center, Suite 200<br>Princeton, NJ 08540-7810 | (609)987-5800 |

**Public reporting burden for this collection of information** is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.