DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-907/S-005

Novo Nordisk Inc.
Attention: Mary Ann McElligott
Associate Vice President
Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Ms. McElligtott:

Please refer to your supplemental new drug application dated May 24, 2001, received May 25, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Activella®.

We acknowledge receipt of your submissions dated February 15 and June 17, 2005.

This supplemental new drug application provides for revisions to the Warnings and Precautions sections for breast cancer and cardiovascular effects as requested in our letters dated August 11, 2000, January 8, 2001. It also provides for updates to the labeling regarding the Women's Health Initiative (WHI) trials and Women's Health Initiative Memory Study (WHIMS) and the Million Women Study as requested in our letters dated January 7, 2003 and February 11, 2004.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to enclosed labeling (text for the package insert, text for the patient package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-907/S-005**." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kassandra Sherrod, R.Ph., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

ACTIVELLA®

(estradiol/norethindrone acetate tablets)

1mg/0.5mg

Rx only

WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease or dementia. (See **WARNINGS, Cardiovascular disorders** and **Dementia.)**

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **WARNINGS, Cardiovascular disorders** and **Malignant neoplasms, *Breast Cancer*.)**

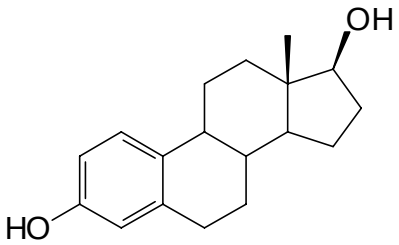
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **WARNINGS, Dementia** and **PRECAUTIONS, Geriatric Use.)**

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these trials, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

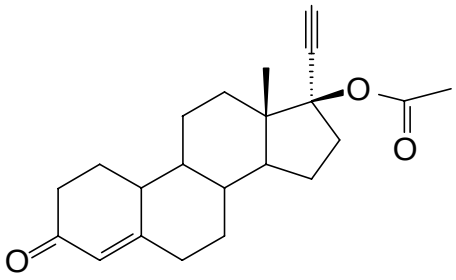
Activella® is a single tablet containing an estrogen, estradiol (E_2), and a progestin, norethindrone acetate (NETA), for oral administration. Each tablet contains 1 mg estradiol and 0.5 mg norethindrone acetate and the following excipients: lactose monohydrate, starch (corn), copovidone, talc, magnesium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

Endogenous 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 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act 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.

PHARMACOKINETICS

ABSORPTION

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. 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
$t_{1/2}$ (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 Activella, 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)

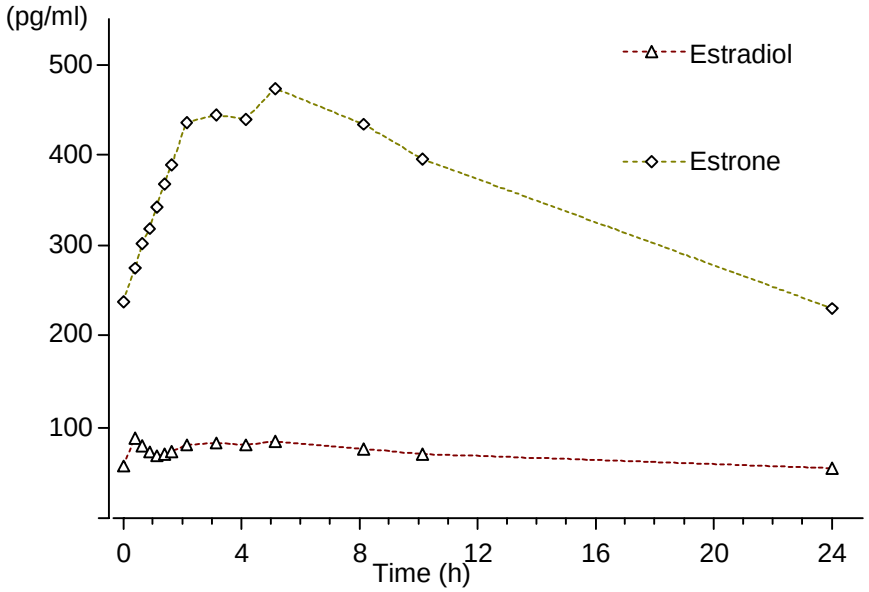
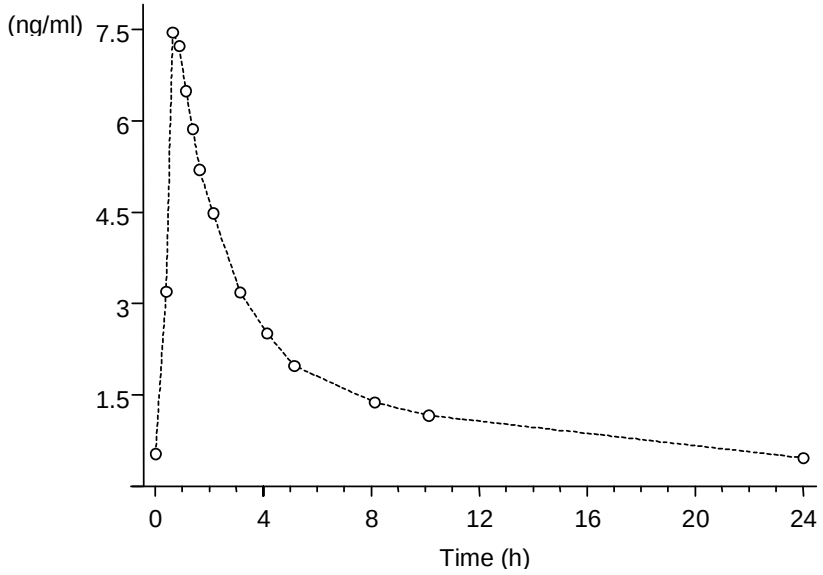


Figure 1b
Levels of Norethindrone at Steady State during Continuous Dosing with Activella (n=24)



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 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.

In-vitro and in-vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), Phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

FOOD-DRUG INTERACTIONS

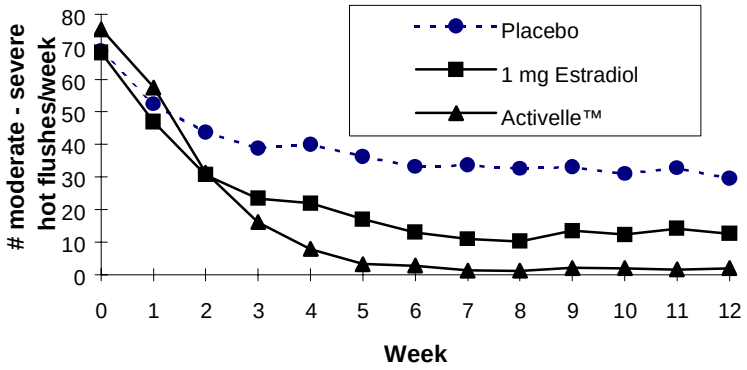
A single-dose study in 24 healthy postmenopausal women was conducted to investigate any potential impact of administration of Activella with and without food. Administration of Activella with food did not modify the bioavailability of estradiol, although increases in AUC_{0-72} of 19% and decreases in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

CLINICAL STUDIES

Effects on 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).

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



Effects on the endometrium

Activella 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

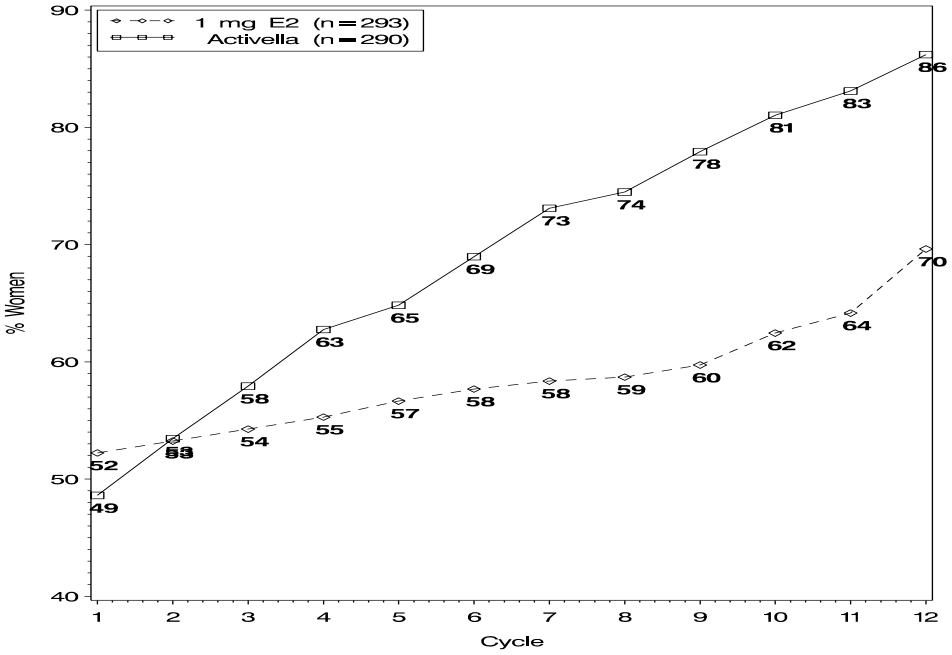
	1 mg E_2 (n=296)	Activella (n=295)
No. of subjects with histological evaluation at the end of the study	247	241
No. (%) of subjects with endometrial hyperplasia at the end of the study	36 (14.6%)	1 (0.4%)

Effects on uterine bleeding or spotting

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, about 86% of women were amenorrheic (see Figure 3).

Figure 3

Patients with Cumulative Amenorrhea over Time
Percentage of Women with no Bleeding or Spotting
at any Cycle Through Cycle 13
Intent to Treat Population, LOCF



Note: the percentage of patients who were amenorrheic in a given cycle and through cycle 13 is shown. If data were missing, the bleeding value from the last reported day was carried forward (LOCF).

Effects on bone mineral density

The results of two randomized, multicenter, calcium-supplemented (500-1000 mg/day), placebo-controlled, 2 year clinical trials have shown that Activella (1 mg estradiol and 0.5 mg norethindrone acetate) is effective in preventing bone loss in postmenopausal women. A total of 462 postmenopausal women with intact uteri and baseline BMD values for lumbar spine within 2 standard deviations of the mean in healthy young women were enrolled. In a US trial, 327 postmenopausal women (mean time from menopause 2.5 to 3.1 years) with a mean age of 53 years were randomized to 7 groups (0.25 mg, 0.5mg, and 1 mg of estradiol alone, 1 mg estradiol with 0.25 mg norethindrone acetate, 1 mg estradiol with 0.5 mg norethindrone acetate, and 2 mg estradiol with 1 mg norethindrone acetate, and placebo. In a European trial, 135 postmenopausal women (mean time from menopause 8.4 to 9.3 years) with a mean age of 58 years were randomized to 1 mg estradiol with 0.25 mg norethindrone acetate, 1 mg estradiol with 0.5 mg norethindrone acetate, and placebo. Approximately 58% and 67% of the randomized subjects in the two clinical trials, respectively, completed the two clinical trials. BMD was measured using dual-energy x-ray absorptiometry (DEXA).

A summary of the results comparing Activella (1 mg estradiol and 0.5 mg norethindrone acetate) and placebo from the two prevention trials is shown in Table 3.

TABLE 3

PERCENTAGE CHANGE (MEAN ± SEM) IN BONE MINERAL DENSITY (BMD)

(Intent to Treat Analysis, Last Observation Carried Forward)

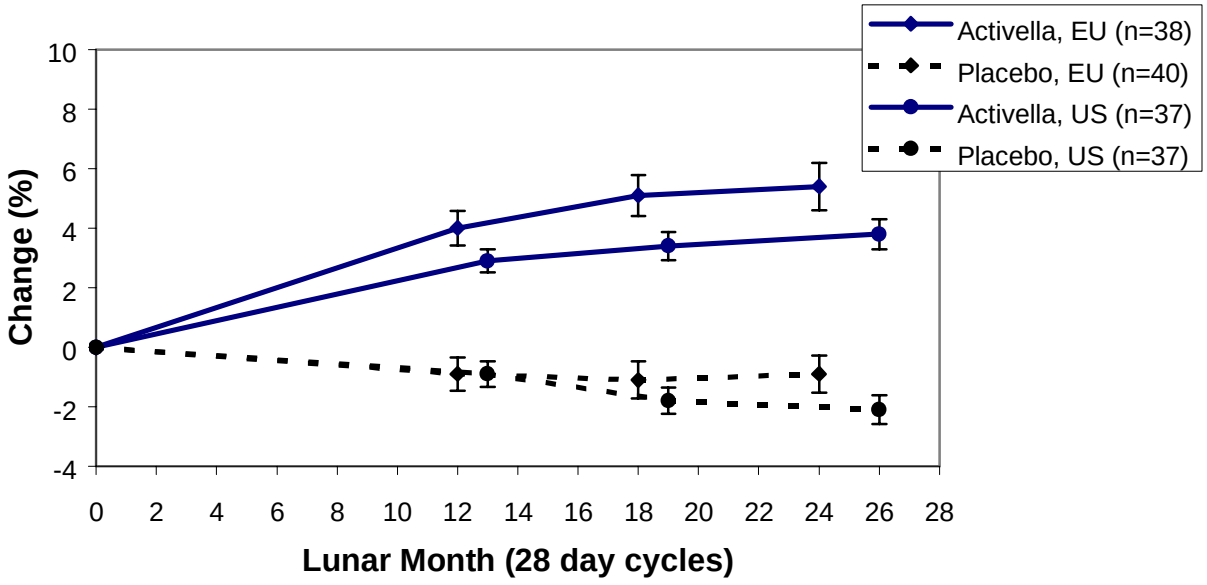
	US Trial		EU trial	
	Placebo (n=37)	Activella (n=37)	Placebo (n=40)	Activella (n=38)
Lumbar spine	-2.1 ± 0.5	3.8 ± 0.5 *	-0.9 ± 0.6	5.4 ± 0.8 *
Femoral neck	-2.3 ± 0.6	1.8 ± 0.7 *	-1.0 ± 0.7	0.7 ± 0.9
Femoral trochanter	-2.0 ± 0.7	3.7 ± 0.7 *	0.8 ± 1.1	6.3 ± 1.2 *
Ward's triangle	-	-	-1.6 ± 1.3	2.7 ± 1.7
Distal radius	-	-	-0.7 ± 0.5	2.1 ± 0.5 *
Total body	-	-	0.4 ± 0.4	3.0 ± 0.5 *

US= United States, EU = European
* Significantly ($p<0.001$) different from placebo

The overall difference in mean percentage change in BMD at the lumbar spine between Activella (1 mg estradiol and 0.5 mg norethindrone acetate) and placebo was 5.9% in the US trial (1000 mg/day calcium) and 6.3% in the European trial (500 mg/day calcium). Activella also increased BMD at the femoral neck and femoral trochanter compared to placebo. The increase in lumbar spine BMD in the US and European clinical trials is displayed in Figure 4.

FIGURE 4

Percentage Change in Bone Mineral Density (BMD) of the Lumbar Spine (L1-L4)
(Intent to Treat Analysis with Last Observation Carried Forward)



Effect on bone turnover

Activella significantly reduced serum and urine markers of bone turnover with a marked decrease in bone resorption markers (e.g., urinary pyridinoline crosslinks Type 1 collagen C-telopeptide, pyridinoline, deoxypyridinoline) and to a lesser extent in bone formation markers (e.g., serum osteocalcin, bone-specific alkaline phosphatase, C-terminal propetide of type 1 collagen). The suppression of bone turnover markers was evident by 3 months and persisted throughout the 24-month treatment period.

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral 0.625 mg conjugated estrogens (CE) per day alone or the use of oral 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms. Activella (estradiol/norethindrone acetate tablets) was not evaluated in the trial.

The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 4 below:

Table 4: RELATIVE AND ABSOLUTE RISK SEEN IN THE CE/MPA SUBSTUDY OF WHI*			
Event[c]	Relative Risk CE/MPA vs placebo at 5.2 Years (95% CI*)	Placebo n=8102	CE/MPA n=8506
		Absolute Risk per 10,000 Person-years	
CHD events Non-fatal MI CHD death	1.29 (1.02-1.63) 1.32 (1.02-1.72) 1.18 (0.70-1.97)	30 23 6	37 30 7
Invasive breast cancer [b]	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index [c]	1.15 (1.03-1.28)	151	170
Deep vein thrombosis [d]	2.07 (1.49-2.87)	13	26
Vertebral fractures [d]	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures [d]	0.77 (0.69-0.86)	170	131

[a]adapted from JAMA, 2002; 288:321-333
[b]includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer
[c]a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.
[d] not included in Global Index
*nominal confidence intervals unadjusted for multiple looks and multiple comparisons

For those outcomes included in the "global index," the absolute excess risks per 10,000 women-years in the group treated with CE/MPA was 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer his fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause morality. (See **BOXED WARNINGS, WARNINGS,** and **PRECAUTIONS.**)

Women's Health Initiative Memory Study

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of

CE/MPA (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these finding apply to younger postmenopausal women. (See **BOXED WARNINGS** and **WARNINGS, Dementia** and **PRECAUTIONS, Geriatric Use.**)

INDICATIONS AND USAGE

Activella is indicated in women who have a uterus for the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe vulvar and vaginal atrophy associated with the menopause. When used solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

CONTRAINDICATIONS

Activella should not be used in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.

2. Known, suspected, or history of cancer of the breast.

3. Known or suspected estrogen-dependent neoplasia.

4. Active deep vein thrombosis, pulmonary embolism or history of these conditions.

5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).

6. Liver dysfunction or disease.

7. Activella should not be used in patients with know hypersensitivity to its ingredients.

8. Known or suspected pregnancy. There is no indication for Activella in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy (See **PRECAUTIONS**.)

WARNINGS

See **BOXED WARNINGS**

1. Cardiovascular disorders.

Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Coronary heart disease and stroke

In the Women's Health Initiative (WHI) study, an increased risk of stroke was observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infraction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000 women-years). The increase in risk was observed in year one and persisted.

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n=2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA-0.625mg/2.5mg per day demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

b. Venous thromboembolism (VTE)

In the Women's Health Initiative (WHI) study, an increased risk of deep vein thrombosis was observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies.)**

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant neoplasms

a. *Endometrial cancer*

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

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 the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the women's Health Initiative (WHI) substudy of CE/MPA (see **CLINICAL PHARMACOLOGY, Clinical Studies**). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer

was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24% (95% confidence interval 1.01 – 1.54), and the overall absolute risk was 41 vs 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs 25 cases per 10,000 women years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a health care provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

3. Dementia

In the Women's Health Initiative Memory Study (WHIMS), 4532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n=2,229) and 21 women in the placebo group (0.9%, n=2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21 – 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **PRECAUTIONS, Geriatric Use**).

4. Gallbladder disease

A 2-to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5. Hypercalcemia

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

6. Visual abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. 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 examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

PRECAUTIONS

A. GENERAL

1. *Addition of a progestin when a woman has not had a hysterectomy*

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone treatment. These include a possible increased risk of breast cancer.

2. *Elevated blood pressure*

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. *Hypertriglyceridemia*

In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. *Impaired liver function and past history of cholestatic jaundice*

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

5. *Hypothyroidism*

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogen may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. *Fluid retention*

Because estrogens and progestins may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. *Hypocalcemia*

Estrogens should be used with caution in individuals with severe hypocalcemia.

8. *Ovarian cancer*

The CE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77 – 3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen alone, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

9. **Exacerbation of endometriosis**

Endometriosis may be exacerbated with administration of estrogens. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-

hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

10. *Exacerbation of other conditions*

Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

B. PATIENT INFORMATION

Physicians are advised to discuss the contents of the PATIENT INFORMATION leaflet with patients for whom they prescribe Activella.

C. LABORATORY TESTS

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response, rather than by serum hormone levels (e.g., estradiol, FSH).

D. 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. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels 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. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum i.e., corticosteriod binding globulin (CBG), sex hormone-binding globulin (SHBG) leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/rennin substrate, alpha-1 antitrypsin, ceruloplasmin).

4. Activella reduces LDL and total cholesterol concentration, and decreases HDL without changes to HDL/LDL ratio. Activella does not increase triglycerides.

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 reduce insulin sensitivity in healthy postmenopausal women when assessed by an hyperinsulinemic euglycemic clamp.

6. Reduced response to metyrapone test.

E. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen alone in women with a uterus has shown an increased risk of endometrial cancer. Long-term administration of estrogens and estrogen-progestin combinations in women has shown an increased risk of breast cancer (which may be more pronounced in women treated with estrogen-progestin combinations than in women treated with estrogen alone) and ovarian cancer. (See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS.**)

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.

F. PREGNANCY

Activella should not be used during pregnancy. (See **CONTRAINDICATIONS.**)

G. NURSING MOTHERS

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of breast milk. Detectable amounts of estrogens and progestins have been identified in the milk of mothers receiving this drug. Caution should be exercised when Activella is administered to a nursing mother.

H. PEDIATRIC USE

Activella is not indicated in children.

I. GERIATRIC USE

Clinical studies of Activella did not include sufficient number of subjects aged 65 and over to determine if they responded differently from younger subjects.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n=3,729) were 65 to 74 while 18% (n=803) were 75 and

over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women that were older than 70. (See **BOXED WARNINGS** and **WARNINGS, Dementia**.)

In the CE-alone substudy of WHIMS, 2,947 women 65 years of age and older, followed for mean observation period of 5.4 years, 81% ((n=2,383) were 65 to 74 while 19% (n=564) were 75 and over. Women treated with conjugated estrogens were reported to have a 1.5-fold increase in the risk of developing probable dementia, with Alzheimer's disease being the most common classification of probable dementia in both the conjugated estrogens and the placebo groups.

ADVERSE REACTIONS

See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Adverse events reported by investigators in the Phase 3 studies regardless of causality assessment are shown in Table 5.

TABLE 5
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)		Osteoporosis Study (2 years)	
	Activella (n=295)	1 mg E2 (n=296)	Activella (n=29)	Placebo (n=34)	Activella (n=47)	Placebo (n=48)
Body as a Whole						
Back Pain	6%	5%	3%	3%	6%	4%
Headache	16%	16%	17%	18%	11%	6%
Digestive System						
Nausea	3%	5%	10%	0%	11%	0%
Gastroenteritis	2%	2%	0%	0%	6%	4%
Nervous System						
Insomnia	6%	4%	3%	3%	0%	8%
Emotional Liability	1%	1%	0%	0%	6%	0%
Respiratory System						
Upper Respiratory Tract Infection	18%	15%	10%	6%	15%	19%
Sinusitis	7%	11%	7%	0%	15%	10%
Metabolic and Nutritional						
Weight Increase	0%	0%	0%	0%	9%	6%
Urogenital System						
Breast Pain	24%	10%	21%	0%	17%	8%
Post-Menopausal Bleeding	5%	15%	10%	3%	11%	0%
Uterine Fibroid	5%	4%	0%	0%	4%	8%
Ovarian Cyst	3%	2%	7%	0%	0%	8%
Resistance mechanism						
Infection Viral	4%	6%	0%	3%	6%	6%
Moniliasis Genital	4%	7%	0%	0%	6%	0%
Secondary Terms						
Injury Accidental	4%	3%	3%	0%	17%*	4%*
Other Events	2%	3%	3%	0%	6%	4%

* including one upper extremity fracture in each group

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

1. **Genitourinary system**

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, dysmenorrhea, increase in size of uterine leiomyomata, vaginitis including vaginal candidiasis, changes in amount of cervical secretion; changes in cervical ectropion; pre-menstrual-like syndrome, cystitis-like syndrome, ovarian cancer, endometrial hyperplasia, endometrial cancer.

2. Breasts:
Tenderness, enlargement, pain; galactorrhea; nipple discharge; fibrocystic breast changes; breast cancer.

3. Cardiovascular:
Cerebrovascular accidents, deep and superficial venous thrombosis, pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.

4. Gastrointestinal:
Nausea, vomiting, changes in appetite, cholestatic jaundice, abdominal pain/cramps, flatulence, bloating, increased incidence of gallbladder disease, pancreatitis; enlargement of hepatic hemangiomas.

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

6. Eyes*:*

Retinal vascular thrombosis, intolerance to contact lenses.

7. Central nervous system:
Headache, migraine, dizziness, mental depression, chorea, insomnia, nervousness, mood disturbances, irritability, exacerbation of epilepsy, probable dementia.

8. Miscellaneous:

Increase or decrease in weight, aggravation of porphyria, edema, leg cramps, changes in libido, fatigue, reduced carbohydrate tolerance, anaphylactoid/anaphylactic reactions, hypocalcemia, exacerbation of asthma, increased triglycerides, back pain, arthralgia, myalgia.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., 3 to 6 month intervals) to determine if treatment is still necessary (See **BOXED WARNINGS** and **WARNINGS).** For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

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

For the treatment of moderate to severe vasomotor symptoms associated with the menopause, treatment of vulvar and vaginal atrophy, and the prevention of postmenopausal osteoporosis –Activella 1 mg E_2/0.5 mg NETA daily. The doses of 17 beta-estradiol and norethindrone acetate in Activella may not be the lowest effective dose-combination for the treatment of vasomotor symptoms and prevention of postmenopausal osteoporosis.

HOW SUPPLIED

Activella, 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.

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

Activella is a trademark owned by Novo Nordisk FemCare AG

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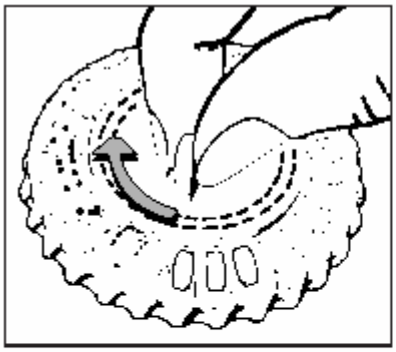
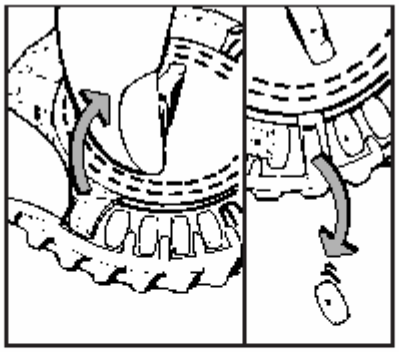
Novo Nordisk Inc.
Princeton, NJ 08540
1-866-668-6336
www.novonordisk-us.com

Manufactured by
Novo Nordisk A/S
2880 Bagsvaerd, Denmark

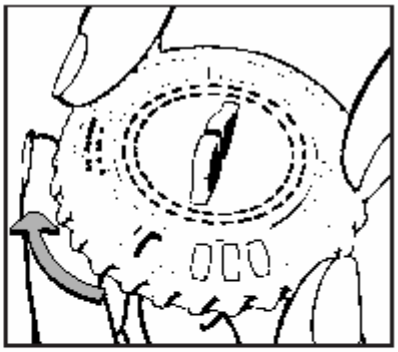


How to use the ACTIVELLA® Dispenser

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.

PATIENT INFORMATION
(2005)

Activella®
(estradiol/norethindrone acetate tablets 1mg/0.5mg)

Read this PATIENT INFORMATION before you start taking Activella and read what you get each time you refill Activella. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT Activella (a combination of estrogen and progestin hormones)?

- Do not use estrogens and progestins to prevent heart disease, heart attacks, strokes or dementia.

Using estrogens and progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens with progestins may increase your risk of dementia. You and your healthcare provider should talk regularly about whether you still need treatment with Activella.

What is Activella?

Activella is a medicine that contains two kinds of hormones, estrogen and progestin.

What is Activella used for?

Activella is used after menopause to:

- **reduce moderate to severe hot flashes.** Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 to 55 yrs old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with Activella.

- **treat moderate to severe dryness, itching, and burning in or around the vagina.** You and your healthcare provider should talk regularly about whether you still need treatment with Activella to control these problems. If you use Activella only to treat your dryness, itching, and burning in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

- **help reduce your chances of getting osteoporosis (thin weak bones).** Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use Activella only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you should continue with Activella.

Weight-bearing exercises, like walking or running, and taking calcium and vitamin D supplements may also lower your chances of getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

Who should not take Activella?

Do not take Activella if you have had your uterus removed (hysterectomy). Activella contains a progestin to decrease the chances of getting cancer of the uterus. If you do not have a uterus, you do not need a progestin and you should not take Activella.

Do not start taking Activella if you:

- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.** Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take Activella.
- **had a stroke or heart attack in the past year.**
- **currently have or have had blood clots.**

- **currently have or have had liver problems**
- **are allergic to Activella or any of its ingredients**. See the end of this leaflet for a list of ingredients in Activella.
- **think you may be pregnant.**

Tell your healthcare provider:

- **if you are breast feeding.** The hormones in Activella can pass into your milk.
- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Activella works. Activella may also affect how your other medicines work.
- **If you are going to have surgery or will be on bed rest.** You may need to stop taking estrogens and progestins.

How should I take Activella?

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

Estrogens and progestins should be used at the lowest dose possible for your treatment only as long as needed. The doses of the estrogen and progestin in Activella may not be the lowest effective dose-combination to reduce your moderate to severe hot flashes and your chances of getting osteoporosis (thin weak bones). You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about whether you still need treatment with Activella.

What are the possible side effects of estrogens?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps/bloating
- Nausea and vomiting
- Mental depression
- Back pain
- Weight increase
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus (“fibroids”)
- Vaginal yeast infection
- Hirsutism
- Acne

- Weight decrease
- Sleep disturbances
- Allergic reactions
- Nervousness

These are not all the possible side effects of Activella. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of a serious side effect with Activella?

Talk with your healthcare provider regularly about whether you should continue taking Activella. If you have a uterus, talk to your healthcare provider about whether the addition of a progestin in right for you. See your healthcare provider right away if you get vaginal bleeding while taking Activella. Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often. If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your health care healthcare provider for ways to lower your chances for getting heart disease.

General information about the safe and effective use of Activella.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take Activella for conditions for which it was not prescribed. Do not give Activella to other people, even if they have the same symptoms you have. It may harm them. **Keep Activella out of the reach of children.**

This leaflet provides a summary of the most important information about Activella. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Activella that is written for health professionals. You can get more information by calling the toll free number 1-XXX-XXX-XXXX.

What are the ingredients in Activella?

Each tablet contains 1 mg estradiol and 0.5 mg norethindrone acetate and the following excipients: lactose monohydrate, starch (corn), copovidone, talc, magnesium stearate, hypromellose, and triacetin for oral administration.

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

Activella is supplied in a calendar dial pack dispenser containing 28 tablets.

The embossed (Apis) bull symbol on the tablets is a trademark of Novo Nordisk® A/S.

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

Rx only

Activella is a trademark owned by Novo Nordisk® FemCare AG

Novo Nordisk Inc.
Princeton, NJ 08540
1-866-668-6336
www.novonordisk-us.com

Manufactured by
Novo Nordisk A/S
2880 Bagsvaerd, Denmark

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daniel A. Shames

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