

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-001

LABELING



Activella®
(estradiol/norethindrone acetate) tablets
1.0 mg/0.5 mg
0.5 mg/0.1 mg

Rx Only

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders and Dementia.**)

The estrogen plus progestin substudy of the Women's Health Initiative (WHI) 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 5.6 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) per day, relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders and Malignant neoplasms, Breast cancer.**)

The estrogen-alone substudy of the WHI reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 6.8 years and 7.1 years, respectively, of treatment with oral conjugated estrogens (CE 0.625 mg) per day, relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders.**)

The Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI study, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with CE 0.625 mg combined with MPA 2.5 mg and during 5.2 years of treatment with CE 0.625 mg alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES, 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.

Women's Health Initiative Memory Study

The estrogen plus progestin Women's Health Initiative Memory Study (WHIMS) substudy of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 %, age 65 to 69 years, 35 %, age 70 to 74 years, 18 %, 75 years of age and older) to evaluate the effects of CE 0.625 mg plus MPA 2.5 mg daily on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of four years, 40 women in the estrogen-plus-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, 1.21-3.48) compared to placebo. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS, WARNINGS, Dementia, and PRECAUTIONS, Geriatric Use.**)

The estrogen-alone WHIMS, a substudy of the WHI study, enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45 %, age 65 to 69 years, 36 %, age 70 to 74 years, 19 %, 75 years of age and older) to evaluate the effects of conjugated estrogens (CE 0.625 mg) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the estrogen-alone group was 1.49 (95% CI 0.83-2.66) compared to placebo.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS, WARNINGS, Dementia, and PRECAUTIONS, Geriatric Use.**)

INDICATIONS AND USAGE

Activella 1.0 mg/0.5 mg and 0.5 mg/0.1 mg are indicated in women who have a uterus for the:

1. Treatment of moderate to severe vasomotor symptoms associated with menopause.
2. 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.

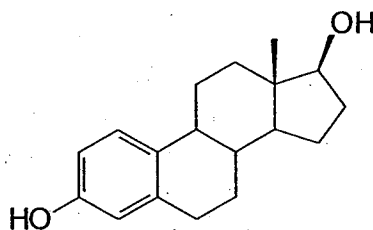
The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Therefore,

DESCRIPTION

Activella® 1.0 mg/0.5 mg is a single tablet for oral administration containing 1 mg of estradiol and 0.5 mg of norethindrone acetate and the following excipients: lactose monohydrate, starch (corn), copovidone, talc, magnesium stearate, hypromellose and triacetin.

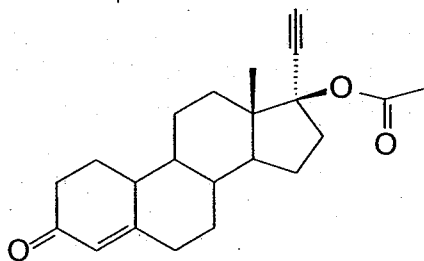
Activella® 0.5 mg/0.1 mg is a single tablet for oral administration containing 0.5 mg of estradiol and 0.1 mg of norethindrone acetate and the following excipients: lactose monohydrate, starch (corn), hydroxypropylcellulose, talc, magnesium stearate, hypromellose and triacetin.

Estradiol (E₂) 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 C₁₈H₂₄O₂ · ½ H₂O and a molecular weight of 281.4. The structural formula of E₂ 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 C₂₂H₂₈O₃ 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

A. Absorption

Estradiol is well absorbed through the gastrointestinal tract. Following oral administration of Activella 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 after the administration of Activella tablets. The oral bioavailability of estradiol and norethindrone following administration of Activella 1.0 mg/0.5 mg when compared to a combination oral solution is 53% and 100%, respectively. Administration of Activella 1.0 mg/0.5 mg with food did not modify the bioavailability of estradiol, although increases in AUC₀₋₇₂ of 19% and decreases in C_{max} of 36% for norethindrone were seen.

The pharmacokinetic parameters of estradiol (E₂), estrone (E₁), and norethindrone (NET) following oral administration of 1 Activella 1.0 mg/0.5 mg or 2 Activella 0.5 mg/0.1 mg tablet(s) to healthy postmenopausal women are summarized in Table 1.

TABLE 1
PHARMACOKINETIC PARAMETERS
AFTER ADMINISTRATION OF
1 TABLET OF ACTIVELLA 1.0 MG/0.5 MG OR 2 TABLETS OF ACTIVELLA 0.5 MG/0.1 MG
TO HEALTHY POSTMENOPAUSAL WOMEN

	1 x Activella 1.0 mg/0.5 mg (n=24) Mean ^a (%CV) ^b	2 x Activella 0.5 mg/0.1 mg (n=24) Mean ^a (%CV) ^b
Estradiol^c (E₂)		
AUC _{0-t} (pg/mL*h)	766.5 (48)	697.3 (53)
C _{max} (pg/mL)	26.8 (36)	26.5 (37)
t _{max} (h): median (range)	6.0 (0.5-16.0)	6.5 (0.5-16.0)
t _{1/2} (h) ^d	14.0 ^e (29)	14.5 ^f (27)
Estrone^c (E₁)		
AUC _{0-t} (pg/mL*h)	4469.1 (48)	4506.4 (44)
C _{max} (pg/mL)	195.5 (37)	199.5 (30)
t _{max} (h): median (range)	6.0 (1.0-9.0)	6.0 (2.0-9.0)
t _{1/2} (h) ^d	10.7 (44) ^g	11.8 (25) ^g
Norethindrone (NET)		
AUC _{0-t} (pg/mL*h)	21043 (41)	8407.2 (43)
C _{max} (pg/mL)	5249.5 (47)	2375.4 (41)
t _{max} (h) : median (range)	0.7 (0.7-1.25)	0.8 (0.7-1.3)
t _{1/2} (h)	9.8 (32) ^h	11.4 (36) ⁱ

AUC = area under the curve, 0 – last quantifiable sample

C_{max} = maximum plasma concentration,

t_{max} = time at maximum plasma concentration,

t_{1/2} = half-life,

^a geometric mean; ^b geometric % coefficient of variation; ^c baseline unadjusted data;

^d baseline unadjusted data; ^e n=18; ^f n=16; ^g n=13; ^h n=22; ⁱ n=21

Following continuous dosing with once-daily administration of Activella 1.0 mg/0.5 mg, 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 E₂, E₁, and NET during Activella 1.0 mg/0.5 mg 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 1.0 mg/0.5 mg
(n=24)

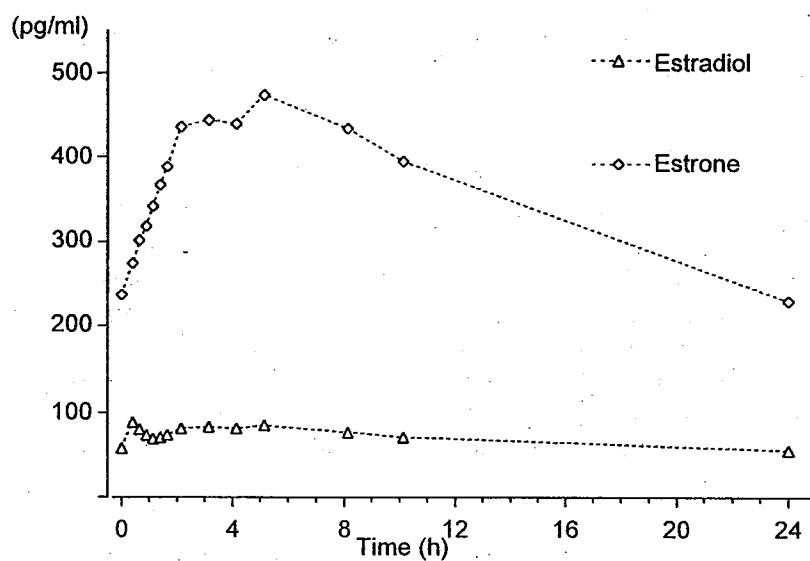
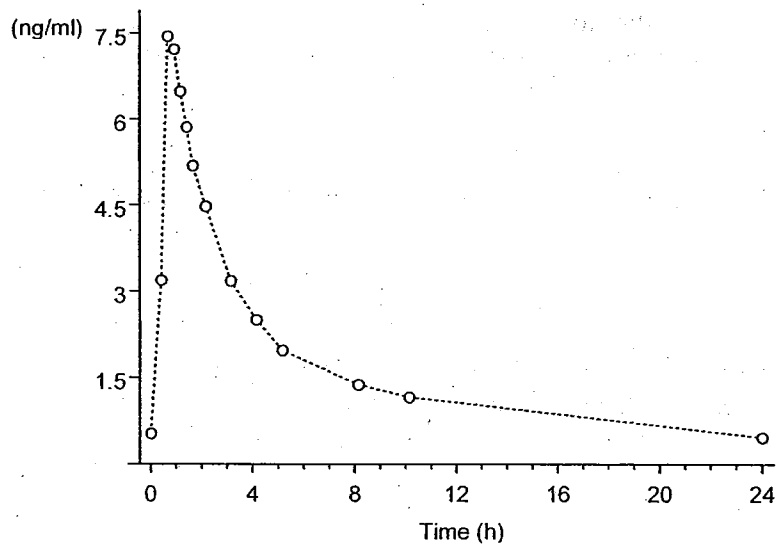


Figure 1b
Levels of Norethindrone at Steady State
During Continuous Dosing with Activella 1.0 mg/0.5 mg
(n=24)



B. 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%).

C. Metabolism

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 intestine followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Norethindrone Acetate: The most important metabolites of norethindrone are isomers of 5 α -dihydro-norethindrone and tetrahydro-norethindrone, which are excreted mainly in the urine as sulfate or glucuronide conjugates.

D. Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The half-life of estradiol following single dose administration of Activella 1.0 mg/0.5 mg is 12-14 hours. The terminal half-life of norethindrone is about 8-11 hours.

E. Special Populations

No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

F. 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.

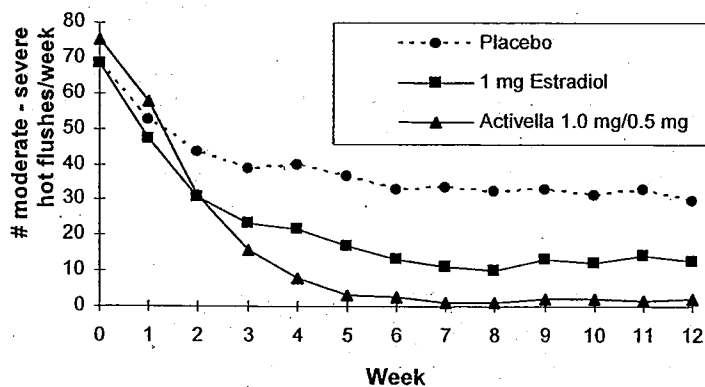
In-vitro and in-vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (*Hypericum perforatum*), phenobarbital, carbamazepine, 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 result in side effects.

CLINICAL STUDIES

Effects on Vasomotor Symptoms

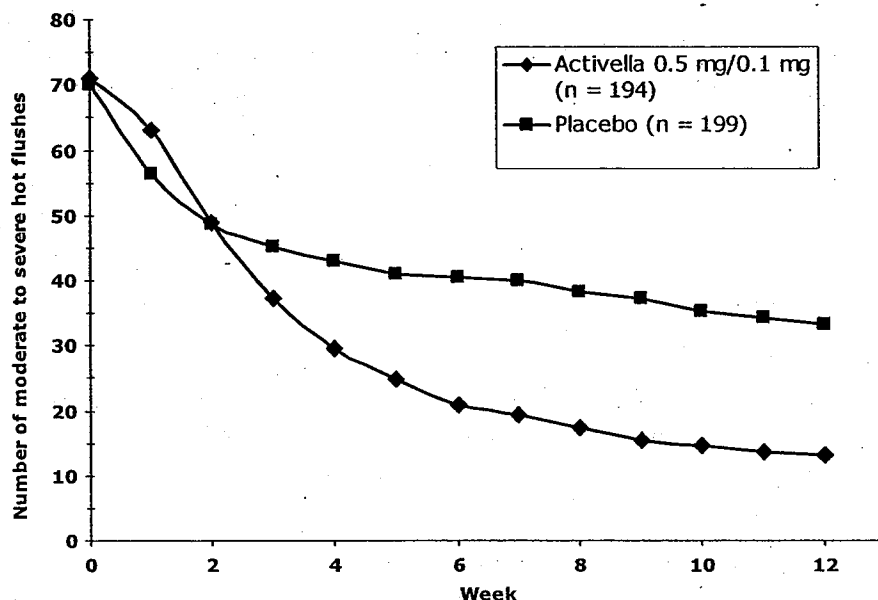
In a 12-week randomized clinical trial involving 92 subjects, Activella 1.0 mg/0.5 mg was compared to 1 mg of estradiol and to placebo. The mean number and intensity of hot flushes were significantly reduced from baseline to week 4 and 12 in both the Activella 1.0 mg/0.5 mg and the 1 mg estradiol group compared to placebo (see Figure 2).

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



In a study conducted in Europe a total of 577 postmenopausal women were randomly assigned to either Activella 0.5 mg/0.1 mg, 0.5 mg E₂/0.25 mg NETA, or placebo for 24 weeks of treatment. The mean number and severity of hot flushes were significantly reduced at week 4 and week 12 in the Activella 0.5 mg/0.1 mg (see Figure 3) and 0.5 mg E₂/0.25 mg NETA groups compared to placebo.

Figure 3
Mean Number of Moderate to Severe Hot
Flashes for Weeks 0 Through 12



Effects on the Endometrium

Activella 1.0 mg/0.5 mg 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 E₂ + 0.1 mg NETA (n=294), 1 mg E₂ + 0.25 mg NETA (n=291), and Activella 1.0 mg/0.5 mg (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 1.0 mg/0.5 mg are shown in Table 2.

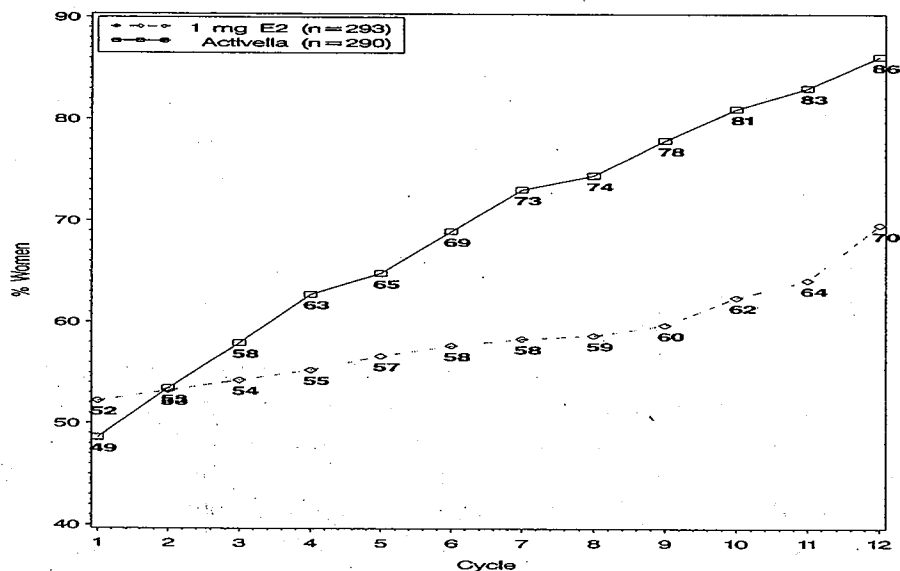
TABLE 2
INCIDENCE OF ENDOMETRIAL HYPERPLASIA
WITH UNOPPOSED ESTRADIOL AND ACTIVELLA 1.0 MG/0.5 MG
IN A 12-MONTH STUDY

	1 mg E ₂ (n=296)	Activella 1 mg E ₂ /0.50mg NETA (n=295)	1 mg E ₂ /0.25 mg NETA (n=291)	1 mg E ₂ /0.1 mg NETA (n=294)
No. of subjects with histological evaluation at the end of the study	247	241	251	249
No. (%) of subjects with endometrial hyperplasia at the end of the study	36 (14.6%)	1 (0.4%)	1 (0.4%)	2 (0.8%)

Effects on Uterine Bleeding or Spotting

During the initial months of therapy, irregular bleeding or spotting occurred with Activella 1.0 mg/0.5 mg treatment. However, bleeding tended to decrease over time, and after 12 months of treatment with Activella 1.0 mg/0.5 mg, about 86% of women were amenorrheic (see Figure 4).

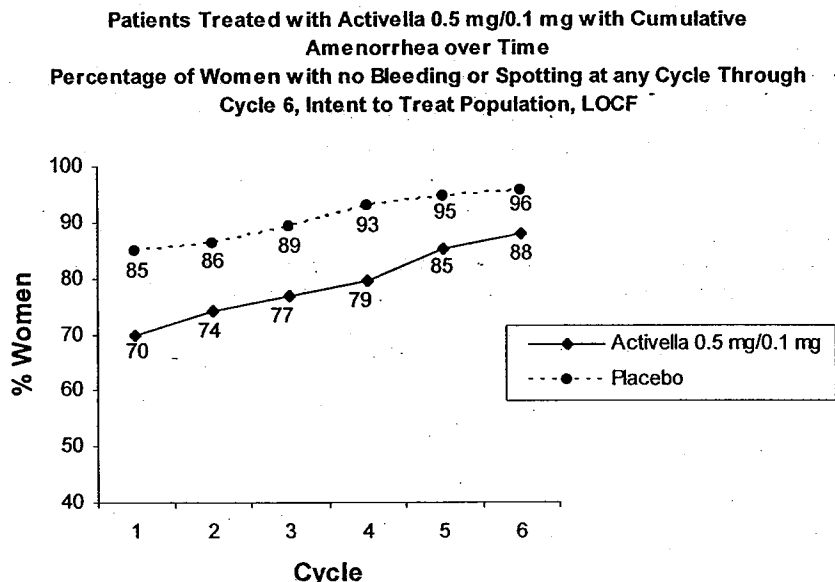
Figure 4
Patients Treated with Activella 1.0 mg/0.5 mg with Cumulative Amenorrhea over Time
Percentage of Women with no Bleeding or Spotting
at any Cycle Through Cycle 13
Intent to Treat Population, LOCF



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).

In the clinical trial with Activella 0.5 mg/0.1 mg, 88% of women were amenorrheic after 6 months of treatment (See Figure 5).

Figure 5



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 1.0 mg/0.5 mg and estradiol 0.5 mg are effective in preventing bone loss in postmenopausal women. While Activella 0.5mg/0.1mg was not directly studied in these trials, the US trial showed that addition of NETA to estradiol enhances the effect on BMD, therefore the BMD changes expected from treatment with Activella 0.5mg/0.1mg should be at least as great as observed with estradiol 0.5mg. 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 (EU 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 1.0 mg/0.5 mg and estradiol 0.5 mg to placebo from the two prevention trials is shown in Table 5.

TABLE 5
PERCENTAGE CHANGE (MEAN ± SD) IN BONE MINERAL DENSITY (BMD)
FOR ACTIVELLA 1.0 MG/0.5 MG AND 0.5 MG E₂ †
(Intent to Treat Analysis, Last Observation Carried Forward)

	US Trial			EU Trial	
	Placebo (n=37)	0.5 mg E ₂ † (n=31)	Activella 1.0 mg/0.5 mg (n=37)	Placebo (n=40)	Activella 1.0 mg/0.5 mg (n=38)
Lumbar spine	-2.1 ± 2.9	2.3 ± 2.8 *	3.8 ± 3.0 *	-0.9 ± 4.0	5.4 ± 4.8 *
Femoral neck	-2.3 ± 3.4	0.3 ± 2.9 **	1.8 ± 4.1 *	-1.0 ± 4.6	0.7 ± 6.1
Femoral trochanter	-2.0 ± 4.3	1.7 ± 4.1 ***	3.7 ± 4.3 *	0.8 ± 6.9	6.3 ± 7.6 *

US= United States, EU = European

†While Activella 0.5mg/0.1mg was not directly studied in these trials, the US trial showed that addition of NETA to estradiol enhances the effect on BMD, therefore the BMD changes expected from treatment with Activella 0.5mg/0.1mg should be at least as great as observed with estradiol 0.5mg.

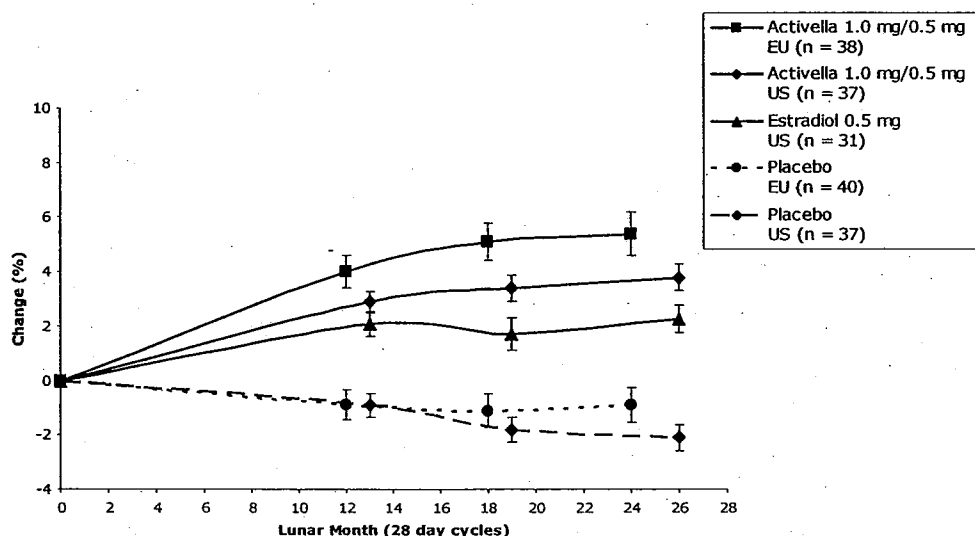
* Significantly (p<0.001) different from placebo

** Significantly (p<0.007) different from placebo

***Significantly (p<0.002) different from placebo

The overall difference in mean percentage change in BMD at the lumbar spine in the US trial (1000 mg/day calcium) between Activella 1.0 mg/0.5 mg and placebo was 5.9% and between estradiol 0.5 mg and placebo was 4.4%. In the European trial (500 mg/day calcium), the overall difference in mean percentage change in BMD at the lumbar spine was 6.3%. Activella 1.0 mg/0.5 mg and estradiol 0.5 mg 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 for Activella 1.0 mg/0.5 mg and estradiol 0.5 mg is displayed in Figure 6.

Figure 6
Percentage Change in Bone Mineral Density (BMD) $\pm$ SEM of the Lumbar Spine (L1-L4) for Activella 1.0 mg/0.5 mg and Estradiol 0.5 mg†
(Intent to Treat Analysis with Last Observation Carried Forward)



†While Activella 0.5mg/0.1mg was not directly studied in these trials, the US trial showed that addition of NETA to estradiol enhances the effect on BMD, therefore the BMD changes expected from treatment with Activella 0.5mg/0.1mg should be at least as great as observed with estradiol 0.5mg.

Effect on Bone Turnover

Activella 1.0 mg/0.5 mg 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.

Treatment with 0.5 mg estradiol decreased biochemical markers of bone resorption (urinary pyridinoline, urinary deoxypyridinoline) and bone formation (bone-specific alkaline phosphatase) compared to placebo. These decreases occurred by 6 months of treatment after which the levels were maintained throughout the 24 months.

Women's Health Initiative Studies

The WHI enrolled a total of 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of either the use of oral conjugated estrogens (CE 0.625 mg per day) alone or the use of oral conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg 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 (MI), silent MI 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.

The estrogen-plus-progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.2 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years (RR 1.15, 95% nCI 1.03-1.28).

For those outcomes included in the WHI "global index," that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were six more CHD events, seven more strokes, ten more PEs, and eight more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were seven fewer colorectal cancers and five fewer hip fractures. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Results of the estrogen-plus-progestin substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9 % White, 6.8 % Black, 5.4 % Hispanic, 3.9% Other) are presented in Table 5 below:

TABLE 5. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-PLUS-PROGESTIN SUBSTUDY OF WHI AT AN AVERAGE OF 5.6 YEARS^a

Event	Relative Risk CE/MPA vs. Placebo (95% nCI ^b)	Absolute Risk per 10,000 Women- years	
		CE/MPA n = 8,506	Placebo n = 8,102
CHD events	1.24 (1.00-1.54)	39	33
<i>Non-fatal MI</i>	<i>1.28 (1.00-1.63)</i>	<i>31</i>	<i>25</i>
<i>CHD death</i>	<i>1.10 (0.70-1.75)</i>	<i>8</i>	<i>8</i>
All strokes	1.31 (1.02-1.68)	31	24
<i>Ischemic stroke</i>	<i>1.44 (1.09-1.90)</i>	<i>26</i>	<i>18</i>
Deep vein thrombosis	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer ^c	1.24 (1.01-1.54)	41	33
Invasive colorectal cancer	0.56 (0.38-0.81)	9	16

TABLE 5. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-PLUS-PROGESTIN SUBSTUDY OF WHI AT AN AVERAGE OF 5.6 YEARS^a

Event	Relative Risk CE/MPA vs. Placebo (95% nCI ^b)	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-years	
Endometrial cancer	0.81 (0.48–1.36)	6	7
Cervical cancer	1.44 (0.47–4.42)	2	1
Hip fracture	0.67 (0.47–0.96)	11	16
Vertebral fractures	0.65 (0.46–0.92)	11	17
Lower arm/wrist fractures	0.71 (0.59–0.85)	44	62
Total fractures	0.76 (0.69–0.83)	152	199

^aResults are based on centrally adjudicated data. Mortality data was not part of the adjudicated data; however, data at 5.2 years of follow-up showed no difference between the groups in terms of all-cause mortality (RR 0.98, 95% nCI 0.82–1.18).

^bNominal confidence intervals unadjusted for multiple looks and multiple comparisons.

^cIncludes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.

The estrogen-alone substudy was also stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints. Results of the estrogen-alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3 % White, 15.1 % Black, 6.1 % Hispanic, 3.6% Other), after an average follow-up of 6.8 years are presented in Table 6 below.

TABLE 6. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-ALONE SUBSTUDY OF WHI^a

Event	Relative Risk CE vs. Placebo (95% nCI ^a)	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-years	
CHD events ^b	0.95 (0.79–1.16)	53	56
Non-fatal MI ^b	0.91 (0.73–1.14)	40	43
CHD death ^b	1.01 (0.71–1.43)	16	16

TABLE 6. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-ALONE SUBSTUDY OF WHI^a

Event	Relative Risk CE vs. Placebo (95% nCI ^a)	CE n = 5,310 Absolute Risk per 10,000 Women-years	Placebo n = 5,429
Stroke ^c	1.39 (1.10-1.77)	44	32
Deep vein thrombosis ^{b,d}	1.47 (1.06-2.06)	23	15
Pulmonary embolism ^b	1.37 (0.90-2.07)	14	10
Invasive breast cancer ^b	0.80 (0.62-1.04)	28	34
Colorectal cancer ^c	1.08 (0.75-1.55)	17	16
Hip fracture ^c	0.61 (0.41-0.91)	11	17
Vertebral fractures ^{c,d}	0.62 (0.42-0.93)	11	17
Total fractures ^{c,d}	0.70 (0.63-0.79)	139	195
Death due to other causes ^{c,e}	1.08 (0.88-1.32)	53	50
Overall mortality ^{c,d}	1.04 (0.88-1.22)	81	78
Global Index ^{c,f}	1.01 (0.91-1.12)	192	190

^aNominal confidence intervals unadjusted for multiple looks and multiple comparisons.

^bResults are based on centrally adjudicated data for an average follow-up of 7.1 years.

^cResults are based on an average follow-up of 6.8 years.

^dNot included in Global Index.

^eAll deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.

^fA subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with estrogen-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was six fewer hip fractures. The absolute excess risk of events included in the "global index" was a nonsignificant two events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Final adjudicated results for CHD events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) in women receiving CE alone compared with placebo (see Table 6)

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.

Activella 1.0 mg/0.5 mg is also indicated in women who have a uterus for the:

3. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When used solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

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. Known hypersensitivity to the ingredients of Activella 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg.
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-plus-progestin therapy has been associated with an increased risk of myocardial infarction as well as stroke, venous thrombosis and pulmonary embolism.

Estrogen-alone therapy has been associated with an increased risk of stroke and deep vein thrombosis (DVT). Should any of these events 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. Stroke

In the estrogen plus progestin substudy of the Women's Health Initiative (WHI), a statistically significant increased risk of stroke was reported in women receiving CE/MPA 0.625mg/2.5mg daily compared to woman receiving placebo (31 vs. 24 per 10,000 women years). The increase in risk was demonstrated after the first year and persisted. (See **CLINICAL STUDIES**.)

In the estrogen-alone substudy of the WHI, a statistically significant increased risk of stroke was reported in women receiving CE 0.625 mg daily compared to women receiving placebo (44 vs. 32 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted.

b. Coronary heart disease

In the estrogen-plus progestin sub-study of WHI, no statistically significant increase in CHD events (defined as non-fatal, MI, silent MI, or death, due to CHD) was reported in women receiving CE/MPA compared to women receiving placebo (39 vs. 33 per 10,000 women years). An increase in relative risk was demonstrated in year one, and a trend toward decreasing relative risk was reported in years 2 through 5. (See **CLINICAL STUDIES**.)

In the estrogen-alone substudy of WHI, no overall effect on coronary disease (CHD) events was reported in women receiving estrogen alone compared to placebo. (See **CLINICAL STUDIES**.)

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. Participation in an open-label extension of the original HERS trial (HERS II) was agreed to by 2,321 women. 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.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

c. Venous thromboembolism

In the estrogen-plus-progestin substudy of the Women's Health Initiative (WHI), a statistically significant 2-fold greater rate of VTE (DVT and pulmonary embolism [PE]), was reported in women receiving CE/MPA compared to women receiving placebo (35 vs. 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 vs. 13 per 10,000 women-years) and PE (18 vs. 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. (See **CLINICAL STUDIES**.)

In the estrogen-alone substudy of WHI, the risk of VTE was reported to be increased for women taking conjugated estrogens (30 vs. 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 vs. 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first two years.

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. Breast cancer

In some studies, 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 CE/MPA substudy of the WHI study (see **CLINICAL STUDIES**). The results from observational studies are generally consistent with those of the WHI clinical trial.

Observational studies have also reported an increased risk of breast cancer for estrogen-plus-progestin combination therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with estrogen-plus-progestin combination therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen-plus-progestin combinations, doses, or routes of administration.

In the estrogen-plus-progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of breast cancer. In this substudy, prior use of estrogen alone or estrogen-plus-progestin combination hormone therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24 (95% nCI 1.01-1.54), and the absolute risk was 41 vs 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo, respectively. 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 estrogen plus progestin 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 of estrogen plus progestin compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen-plus-progestin-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.

In the estrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, CE (0.625 mg daily) was not associated with an increased risk of invasive breast cancer (RR 0.80, 95% nCI 0.62-1.04).

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 women treated with Activella 1.0 mg/0.5 mg and two of which occurred among the group of 294 women treated with 1 mg estradiol/0.1 mg NETA.

The use of estrogen alone and 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.

b. 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 nonusers, 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 an increased risk of 15- to 24-fold for five to ten years or more. 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.

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur in approximately 1% or less in with Activella in one large clinical trial.

3. Dementia

In the estrogen-plus-progestin Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo. In the estrogen-alone WHIMS substudy, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to CE (0.625 mg daily) or placebo.

In the estrogen-plus-progestin substudy, after an average follow-up of four years, 40 women in the estrogen-plus-progestin group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen plus progestin vs. placebo was 2.05 (95% CI 1.21-3.48). The absolute risk of probable dementia for CE/MPA vs. placebo was 45 vs. 22 cases per 10,000 women-years.

In the estrogen-alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE alone vs. placebo was 1.49 (95% CI 0.83-2.66). The absolute risk of probable dementia for CE alone vs. placebo was 37 vs. 25 cases per 10,000 women-years.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk of probable dementia was 1.76 (95% CI 1.19-2.60). Since both substudies were conducted in women ages 65 to 79, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **PRECAUTIONS, Geriatric Use.**)

4. Gallbladder disease

A two-to four 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 preexisting 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 to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention

Estrogens may cause some degree of fluid retention. Because of this, patients who have 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 estrogen-plus-progestin substudy of WHI reported that after an average follow-up of 5.6 years, the relative risk for ovarian cancer for estrogen plus progestin vs. placebo was 1.58 (95% CI 0.77 – 3.24), but was not statistically significant. The absolute risk for estrogen plus progestin vs. placebo was 4.2 vs. 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, in particular for 10 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.

Malignant transformation of residual endometrial implants has 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 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg.

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

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity, increased levels of fibrinogen and fibrinogen activity; increased Plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T₄ levels (by column or by radioimmunoassay), or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), 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. Increased plasma HDL and HDL₂ cholesterol subfraction concentration, reduced LDL cholesterol concentration, increased triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of estrogen, with or without progestin, in women with or without a uterus, has shown an increased risk of endometrial cancer, breast cancer, 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 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.

Of the total number of subjects in the estrogen-plus-progestin substudy of the Women's Health Initiative (WHI) study, 44% (n=7,320) were 65–74 years of age, while 6.6% (n=1,095) were 75 years and over. There was a higher relative risk (CE/MPA vs. placebo) of non-fatal stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age. In women greater than 75, the increased risk of non-fatal stroke and invasive breast cancer observed in the estrogen-plus-progestin combination group compared to the placebo group was 75 vs. 24 per 10,000 women-years and 52 vs. 12 per 10,000 women-years, respectively.

In the estrogen-plus-progestin Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 4,532 hysterectomized women, aged 65 to 79 years, was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo. In the estrogen-plus-progestin group, after an average follow-up of four years, the relative risk (CE/MPA vs. placebo) of probable dementia was 2.05 (95% CI 1.21-3.48). The absolute risk of developing probable dementia with CE/MPA was 45 vs. 22 cases per 10,000 women-years with placebo.

Of the total number of subjects in the estrogen-alone substudy of WHI, 46% (n=4,943) were 65 years and over, while 7.1% (n=767) were 75 years and over. There was a higher relative risk (CE vs. placebo) of stroke in women less than 75 years of age compared to women 75 years and over. In the estrogen-alone WHIMS substudy, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to CE (0.625 mg daily) or placebo. After an average follow-up of 5.2 years, the relative risk (CE vs. placebo) of probable dementia was 1.49 (95% CI 0.83-2.66). The absolute risk of developing probable dementia with estrogen alone was 37 vs. 25 cases per 10,000 women-years with placebo.

Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 for the CE-alone group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CE/MPA group. The most common classification of probable dementia in both the treatment groups and placebo groups was Alzheimer's disease.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **WARNINGS, Dementia.**)

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 with Activella 1.0 mg/0.5 mg by investigators in the Phase 3 studies regardless of causality assessment are shown in Table 7.

TABLE 7
ALL TREATMENT-EMERGENT ADVERSE EVENTS REGARDLESS OF RELATIONSHIP REPORTED
AT A FREQUENCY OF $\geq 5\%$ WITH ACTIVELLA 1.0 MG/0.5 MG

	Endometrial Hyperplasia Study (12-Months)		Vasomotor Symptoms Study (3-Months)		Osteoporosis Study (2 years)	
	Activella 1.0 mg/0.5 mg (n=295)	1 mg E2 (n=296)	Activella 1.0 mg/0.5 mg (n=29)	Placebo (n=34)	Activella 1.0 mg/0.5 mg (n=47)	Placebo (n=48)
<i>Body as a Whole</i>						
Back Pain	6%	5%	3%	3%	6%	4%
Headache	16%	16%	17%	18%	11%	6%
<i>Digestive System</i>						
Nausea	3%	5%	10%	0%	11%	0%
Gastroenteritis	2%	2%	0%	0%	6%	4%
<i>Nervous System</i>						
Insomnia	6%	4%	3%	3%	0%	8%
Emotional Lability	1%	1%	0%	0%	6%	0%
<i>Respiratory System</i>						
Upper Respiratory Tract Infection	18%	15%	10%	6%	15%	19%
Sinusitis	7%	11%	7%	0%	15%	10%
<i>Metabolic and Nutritional</i>						
Weight Increase	0%	0%	0%	0%	9%	6%
<i>Urogenital System</i>						
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%
<i>Resistance mechanism</i>						
Infection Viral	4%	6%	0%	3%	6%	6%
Moniliasis Genital	4%	7%	0%	0%	6%	0%
<i>Secondary Terms</i>						
Injury Accidental	4%	3%	3%	0%	17%*	4%*
Other Events	2%	3%	3%	0%	6%	4%

* including one upper extremity fracture in each group

Adverse events reported with Activella 0.5 mg/0.1 mg by investigators during the Phase 3 study regardless of causality assessment are shown in Table 8.

TABLE 8
ALL TREATMENT-EMERGENT ADVERSE EVENTS REGARDLESS OF RELATIONSHIP REPORTED
AT A FREQUENCY OF $\geq 5\%$ WITH ACTIVELLA 0.5 MG/0.1 MG

	Activella 0.5 mg/0.1 mg (n=194)	-Placebo (n=200)
<i>Body as a Whole</i>		
Back Pain	10%	4%
Headache	22%	19%
Pain in extremity	5%	4%
<i>Digestive System</i>		
Nausea	5%	4%
Diarrhea	6%	6%
<i>Respiratory System</i>		
Nasopharyngitis	21%	18%
<i>Urogenital System</i>		
Endometrial thickening	10%	4%
Vaginal hemorrhage	26%	12%

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; change in amount of cervical secretion; changes in cervical ectropion; premenstrual-like syndrome; cystitis-like syndrome; ovarian cancer; endometrial hyperplasia; endometrial cancer.

2. Breasts

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

3. Cardiovascular

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; 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

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 re-evaluated 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.

1. For the treatment of moderate to severe vasomotor symptoms associated with menopause, and the 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.

- Activella 1.0 mg/0.5 mg
 - Activella 0.5 mg/0.1 mg
2. For the treatment of moderate to severe symptoms of vulvar and vaginal atrophy. When used solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
- Activella 1.0 mg/0.5 mg

Patients should be started at the lowest dose.

HOW SUPPLIED

Activella 1.0 mg/0.5 mg 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. (NDC 0169-5174-02).

Activella 0.5 mg/0.1 mg is a white, film-coated tablet, engraved with NOVO 291 on one side and the APIS bull on the other. It is round, 6mm in diameter and bi-convex. (NDC 0169-XXXX-XX).

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

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.]

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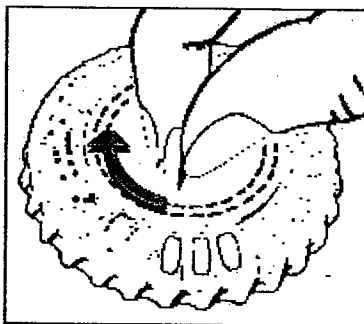
Rx Only

Activella is a trademark owned by Novo Nordisk FemCare AG

Revised December 2006
Version 7

Novo Nordisk Inc.
Princeton, NJ 08540
1-866-668-6336
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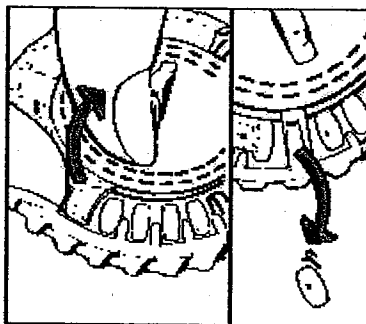
Manufactured by
Novo Nordisk A/S
2880 Bagsvaerd, Denmark



How to use the ACTIVELLA® Dispenser

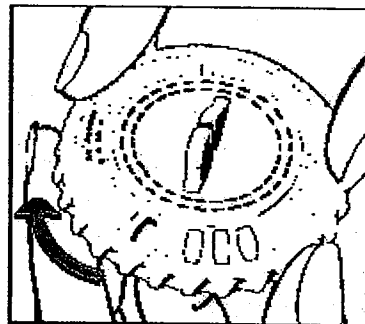
1. Set the Day Reminder

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
(December 2006)

Activella®
(estradiol/norethindrone acetate) tablets
1.0 mg/0.5 mg
0.5 mg/ 0.1 mg

Read this Patient Information leaflet 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 health care 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)?**

- Estrogens increase the chance of getting cancer of the uterus.

Report any unusual vaginal bleeding right away while you are taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your health care provider should check any unusual vaginal bleeding to find out the cause.

- Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes.

Using estrogens with or without progestins may increase your chance of getting heart attacks, strokes, breast cancer, and blood clots.

- Do not use estrogens with or without progestins to prevent dementia.

Using estrogens with or without progestins may increase your risk of dementia.

You and your health care provider should talk regularly about whether you still need treatment with Activella.

What is Activella?

Activella is a medicine that contains estrogen and progestin hormones.

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 health care provider should talk regularly about whether you still need treatment with Activella.

- **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 health care provider about whether a different treatment or medicine without estrogens might be better for you. You and your health care 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 health care provider before starting them.

Activella 1.0 mg/0.5 mg is also used after menopause to:

- **Treat moderate to severe dryness, itching, and burning in or around the vagina**

You and your health care provider should talk regularly about whether you still need treatment with Activella 1.0 mg/0.5 mg to control these problems. If you use Activella 1.0 mg/0.5 mg only to treat your dryness, itching, and burning in and around your vagina, talk with your health care provider about whether a topical vaginal product would be better for you.

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 chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your health care provider about whether you should take Activella 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg.

- **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 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg or any of their ingredients**

See section entitled, "What are the ingredients in Activella?" for a list of ingredients in Activella 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg.

- **Think you may be pregnant**

Tell your health care provider:

- **If you are breastfeeding**

The hormones in Activella can pass into your milk.

- **About all of your medical problems**

Your health care provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing); epilepsy (seizures); migraine; endometriosis; lupus; problems with your heart, liver, thyroid, or kidneys; or have high calcium levels in your blood.

- **About all the medicines you take**

This includes 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.

How should I take Activella 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg?

1. Take one Activella 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg tablet once a day
2. Estrogens should be used at the lowest dose possible for your treatment only as long as needed. You and your health care provider should talk regularly (e.g., every 3 to 6 months) about the dose you are taking and 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**

Some of the warning signs of serious side effects include:

- **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 health care 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**
- **Mental depression**

These are not all the possible side effects of Activella 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg. For more information, ask your health care provider or pharmacist.

What can I do to lower my chances of a serious side effect with Activella 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg?

- Talk with your health care provider regularly about whether you should continue taking Activella.
- See your health care provider right away if you get vaginal bleeding while taking Activella.
- Have a breast exam and mammogram (breast X-ray) every year unless your health care provider tells you otherwise. 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 provider for ways to lower your chances for getting heart disease.

Have an annual gynecologic exam

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 health care 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 1-866-668-6336.

What are the ingredients in Activella 1.0 mg/0.5 mg?

Each tablet contains 1.0 mg estradiol and 0.5 mg norethindrone acetate. Each 1.0/0.5 mg tablet also contains lactose monohydrate, starch (corn), copovidone, talc, magnesium stearate, hypromellose, and triacetin for oral administration.

What are the ingredients in Activella 0.5 mg/0.1 mg?

Each tablet contains 0.5 mg estradiol and 0.1 mg norethindrone acetate. Each 0.5/0.1 mg tablet also contains lactose monohydrate, starch (corn), hydroxypropylcellulose, talc, magnesium stearate, hypromellose, and triacetin for oral administration.

Activella 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg is supplied in a calendar dial pack dispenser containing 28 tablets.

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

Rx only

Activella is a trademark owned by Novo Nordisk FemCare AG

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

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