AP 11-18-98

ACTIVELLE™

(estradiol/norethindrone acetate tablets)

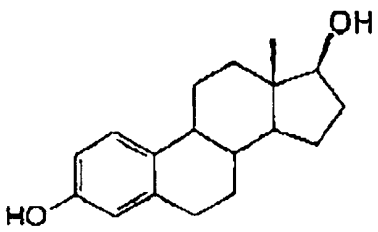
1mg/0.5mg

Rx only

DESCRIPTION

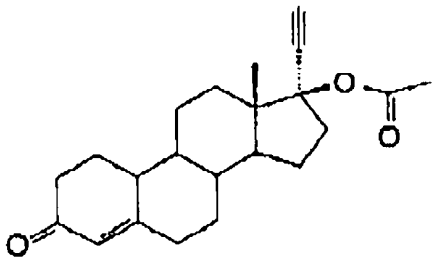
Activelle™ is a single tablet containing an estrogen, estradiol (E_2), and a progestin, norethindrone acetate (NETA), for oral administration. Each tablet contains 1 mg estradiol and 0.5 mg norethindrone acetate and the following excipients: lactose monohydrate, starch (corn), copovidone, talc, magnesium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

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



Estradiol

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



Norethindrone Acetate

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

PHARMACOKINETICS

ABSORPTION

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

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

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

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

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

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

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

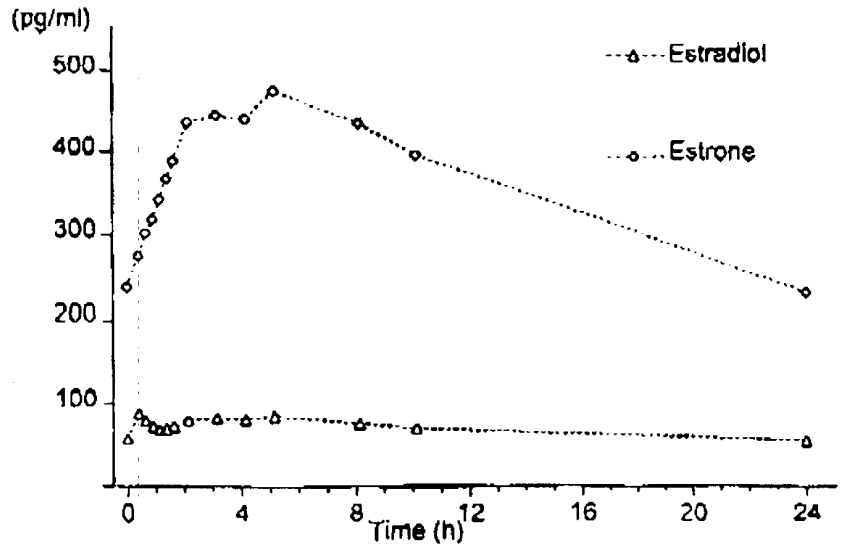
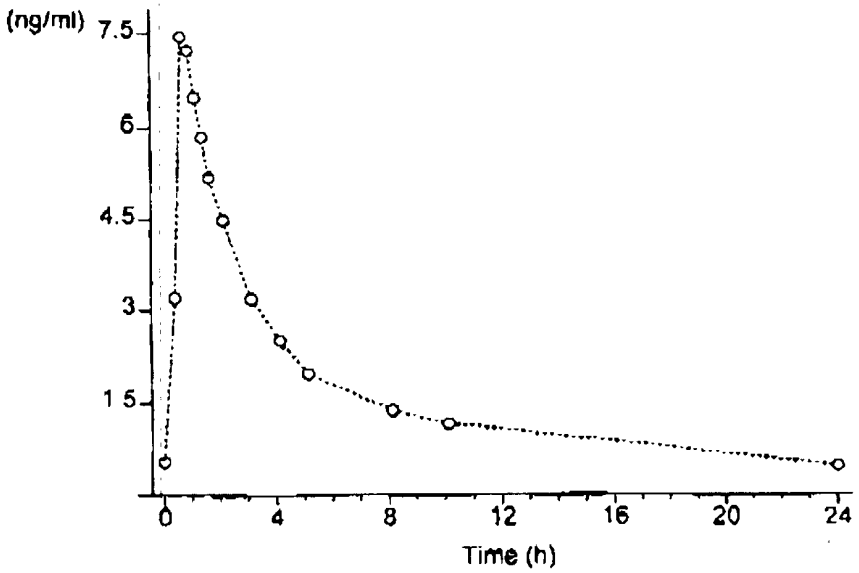


Figure 1b
Levels of Norethindrone at Steady State during Continuous Dosing with Activelle™ (n=24)



DISTRIBUTION

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

METABOLISM AND EXCRETION

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

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

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

DRUG-DRUG INTERACTIONS

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

FOOD-DRUG INTERACTIONS

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

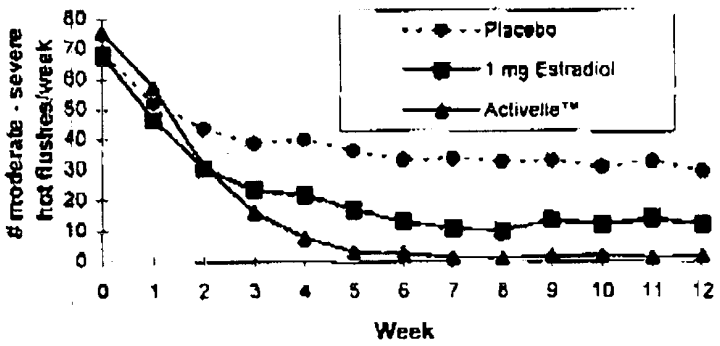
were seen.

CLINICAL STUDIES

VASOMOTOR SYMPTOMS

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

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



ENDOMETRIAL HYPERPLASIA

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

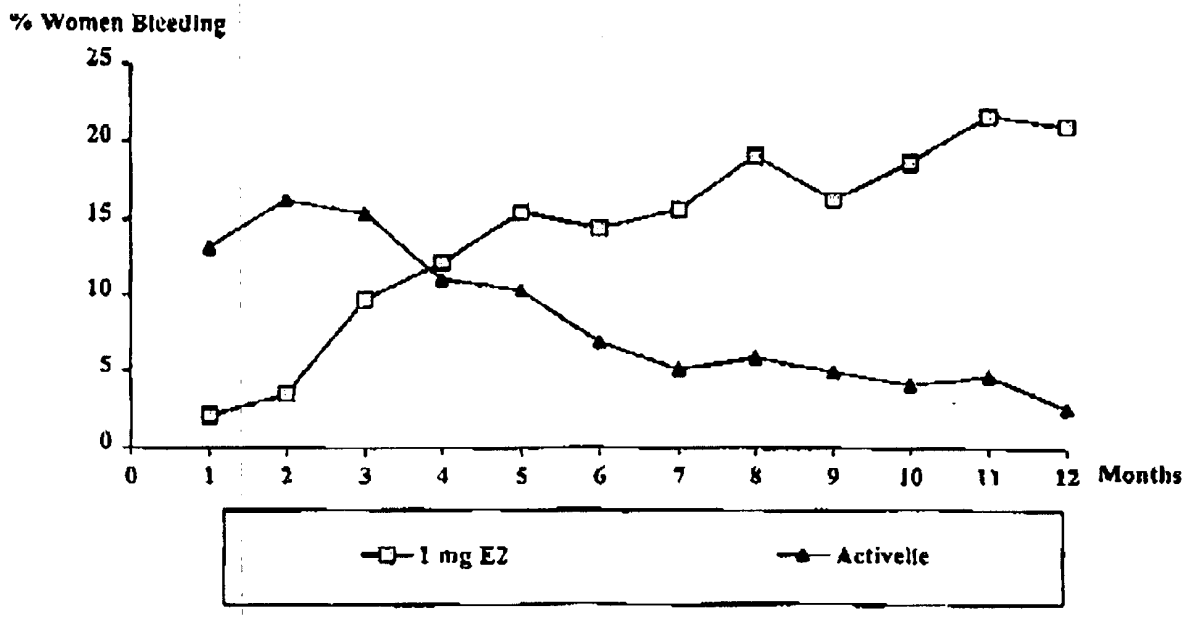
in a randomized, controlled clinical trial. This trial enrolled 1,176 subjects who were randomized to one of 4 arms: 1 mg estradiol unopposed (n=296), 1 mg E_2 + 0.1 mg NETA (n=294), 1 mg E_2 + 0.25 mg NETA (n=291), and Activelle™ [1 mg E_2 + 0.5 mg NETA] (n=295). At the end of the study, endometrial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

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

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

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

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



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

INFORMATION REGARDING LIPID EFFECTS

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

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

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

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

INDICATIONS AND USAGE

Activelle™ therapy is indicated in women with an intact uterus for the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. There is no adequate evidence that estrogens are effective for nervous symptoms or depression that might occur during menopause and they should not be used to treat these conditions.

2. Treatment of vulvar and vaginal atrophy.

CONTRAINDICATIONS

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

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

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

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

4. Abnormal genital bleeding of unknown etiology.

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

6. Liver dysfunction or disease.

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

WARNINGS

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

Based on experience with estrogens and/or progestins:

1. Induction of malignant neoplasms

Endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. There is no significant increased risk

associated with the use of estrogens for less than one year. The greatest risk appears to be associated with prolonged use with increased risks of 15- to 24-fold with five or more years of use. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study, a significant decrease in the incidence of endometrial cancer occurred six months after withdrawal.
Progestins taken with estrogens have been shown to significantly reduce, but not eliminate, the risk of endometrial cancer associated with estrogen use. In a large clinical trial, the incidence of endometrial hyperplasia with Activelle™ was 0.4% (one simple hyperplasia without atypia) compared to 14.6% with 1 mg estradiol unopposed (see CLINICAL STUDIES).

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equivalent estrogen doses.

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

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

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

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

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

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

3. *Cardiovascular disease.* Large doses of estrogens (5 mg conjugated estrogen per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women or from unopposed estrogen to combination estrogen/progestin therapy. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

4. *Hypercalcemia.* Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drugs should be stopped and appropriate measures taken to reduce the serum calcium level.

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

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

7. *Elevated blood pressure*. Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than non-users. Two other studies showed slightly lower blood pressure among estrogen users compared to non-users. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.

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

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

PRECAUTIONS

GENERAL

Based on experience with estrogens and/or progestins:

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

In recent years, many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy without added progestins and a decrease in cardiovascular disease in women. Although most of the observational studies that assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports.
Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits

suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.

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

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

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

3. *Physical examination.* A complete medical and family history should be taken prior to the initiation of any estrogen/progestin therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen,

and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed.

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

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

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

Based on experience with estrogens:

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

2. *Hypercoagulability.* Some studies have shown that women taking estrogen replacement therapy have hypercoagulability primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have changes in levels of coagulation parameters at baseline compared to premenopausal women. Epidemiological studies have suggested that estrogen use is associated with a higher relative risk of developing venous thromboembolism, i.e., deep vein thrombosis or pulmonary embolism. The studies found a 2-3 fold higher risk for estrogen users

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

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

Based on experience with progestins:

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

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

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

INFORMATION FOR THE PATIENT

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

DRUG/LABORATORY TEST INTERACTIONS

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

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

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

3. Estrogen therapy may elevate other binding proteins in serum i.e., corticosteroid-binding globulin (CBG), sex-hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin). In a 12-month clinical trial, SHBG (sex-hormone-binding globulin) was found to increase with Activelle™.

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

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

an hyperinsulinemic euglycemic clamp.

6. Estrogen therapy reduces response to metyrapone test.

7. Estrogen therapy reduces serum folate concentration.

CARCINOGENESIS, MUTAGENESIS, and IMPAIRMENT OF INFERTILITY

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. (See CONTRAINDICATIONS and WARNINGS.)

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

Breasts: tenderness, enlargement.

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

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

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

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

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

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

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

HOW SUPPLIED

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

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

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

ACTIVELLE™
(estradiol/norethindrone acetate tablets)

INFORMATION FOR THE PATIENT

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

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

Progestin-containing drugs taken with estrogen-containing drugs significantly reduce but do not eliminate this risk completely. If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

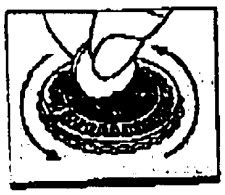
If you take ACTIVELLE™, and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible.

How to use the ACTIVELLE™ Dispenser

1. Set the Day Reminder

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

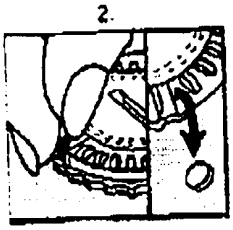
1.



2. How to Take the First Tablet

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

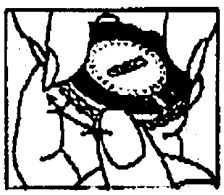
2.



3. Every Day

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

3.



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

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

Estrogen Drugs

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

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

Uses of Estrogen

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

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

When Estrogen Should Not be Used

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

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

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

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

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

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

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

Risks of Estrogens and/or Progestins

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

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

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

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

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

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

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

system, thereby increasing the risk of clots to form in your blood. By cutting off blood supply to vital organs, these clots can cause a stroke, heart attack, or lung clot, any of which may cause death or serious long-term disability. However, most studies of low-dose estrogen usage by women do not show an increased risk of these complications.

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

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

Side Effects with Estrogens and/or Progestins

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

- Nausea, vomiting, pain, cramps, swelling, or tenderness in the abdomen.
- Breast tenderness or enlargement.
- Enlargement of benign tumors (fibroids) of the uterus.
- Yellowing of the skin and/or whites of the eyes.
- Irregular bleeding or spotting.
- Change in amount of cervical secretion.
- Vaginal yeast infections.
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spotty darkening of the skin, particularly on the face; reddening of the skin; skin rashes.
- Worsening of porphyria.

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

Reducing Risk of Estrogen/Progestin Use

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

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

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

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

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

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

Other Information

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

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

- Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.
- Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital, or poison control center immediately.
- This leaflet provides the most important information about ACTIVELLE™. If you have any questions about you and ACTIVELLE™, please speak to your doctor or pharmacist.

How Supplied

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

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

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

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

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