HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ACTIVELLA® safely and effectively. See full prescribing information for ACTIVELLA®.

Activella® (estradiol/norethindrone acetate) tablets, for oral use

Initial U.S. Approval: 1998

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**WARNINGS AND PRECAUTIONS**

- Estrogens increase the risk of gall bladder disease (5.4)
- Discontinue estrogen if severe hypertriglyceridemia, loss of vision, severe hyperglycemia or cholestatic jaundice occurs (5.5, 5.6, 5.9, 5.10)
- Monitor thyroid function in women on thyroid replacement therapy (5.11, 5.18)

**ADVERSE REACTIONS**

Most common adverse reactions (incidence > 5 percent) are back pain, headache, pain in the extremity, nausea, diarrhea, gastroenteritis, insomnia, emotional lability, upper respiratory tract infection, sinusitis, nasopharyngitis, weight increase, breast pain, post-menopausal bleeding, uterine fibroid vaginal hemorrhage, ovarian cyst, endometrial thickening, viral infection, moniliasis, genitai, and accidental injury. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-888-824-4336 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

- Inducers and/or inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)

**USE IN SPECIFIC POPULATIONS**

- Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
- Geriatric Use: An increase risk of probable dementia in women over 65 years of age was reported in the Women’s Health Initiative Memory ancillary studies of Women’s Health Initiative (5.3, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 10/2013
1 INDICATIONS AND USAGE

1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

1.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

2 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.

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogen. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see Warnings and Precautions (5.2)].

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.5, 14.6)].

The WHI estrogen-alone substudy reported increased risks of stroke and DVT in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (0.625 mg) combined with medroxyprogesterone acetate (MPA) (2.5 mg), relative to placebo [see Warnings and Precautions (5.1), and Clinical Studies (14.5)].

The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) and MPA (2.5 mg), relative to placebo. In a 2-year follow-up, women who used estrogen-alone in WHIMS had a statistically non-significant reduction in CHD events (defined as nonfatal MI, silent MI, or CHD death) reported in comparison to the placebo group, with a relative risk of 0.81 (95% CI: 0.63, 1.04) [see Warnings and Precautions (5.1), and Clinical Studies (14.5)].

The WHIMS estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) alone compared to those receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. In the WHI estrogen-alone substudy, a statistically significant increased risk of DVT was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted [see Clinical Studies (14.5)]. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years). Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

In the WHI estrogen plus progesterin substudy, there was a statistically significant reduction in breast cancer (CHD) events (defined as nonfatal MI, silent MI, or CHD death) reported in comparative estrogen-alone plus MPA (2.5 mg) group to the placebo group (41 versus 34 per 10,000 women-years) [see Warnings and Precautions (5.1), and Clinical Studies (14.5)].

In postmenopausal women with documented heart disease (n=2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study (HERS), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established CHD. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II (n=1,970), and an additional 2,000 women, for a total of 6,871 women overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

Vascular Thromboembolism

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and PE), was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17, per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 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 (14.5)]. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately. In the WHI estrogen-alone substudy, the risk of VTE was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years [see Clinical Studies (14.5)]. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately. If feasible, estrogens should be discontinued at 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

5.2 Malignant Neoplasms

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin study
reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this study, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 47 versus 37 cases per 10,000 women-years, for CE plus MPA compared with placebo [see Clinical Studies (14.5)]. 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 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years, for CE plus MPA compared with placebo [see Clinical Studies (14.5)]. 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 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years, for CE plus MPA compared with placebo [see Clinical Studies (14.5)].

5.3 Prohibitive Dementia
In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4.532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) versus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA and 21 women in the placebo group were diagnosed with probable dementia. The absolute risk of probable dementia for the CE plus MPA versus placebo was 0.25 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years [see Use in Specific Populations (8.5), and Clinical Studies (14.6)].

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,519 estrogen-alone women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo. 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 absolute risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.93-2.68). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years [see Use in Specific Populations (8.5), and Clinical Studies (14.6)].

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk of probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see Use in Specific Populations (8.5), and Clinical Studies (14.6)].

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

5.5 Hypocalcemia
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.

5.6 Vision 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 photopsia, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

5.7 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. Associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 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 using estrogen-alone or estrogen plus progestin therapy is important. Appropriate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital 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 in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Ovarian Cancer
The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association.

5.8 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 estrogen therapy on blood pressure was not seen.

5.9 Hypertriglyceridemia
In women with pre-existing hypertriglyceridemia, estrogen therapy may increase triglyceride levels, leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

5.10 Hepatic Impairment and/or Past History of Cholestatic Jaundice
Estrogens may be poorly metabolized in women with impaired liver function. For women 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.

5.11 Hypothyroidism
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women 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. Women dependent on thyroid hormone replacement therapy who are also receiving estrogen may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored to maintain their free thyroid hormone levels in an acceptable range.

5.12 Fluid Retention
Estrogens plus progestins may cause some degree of fluid retention, such as body swelling, which might be influenced by this factor, such as a cardiac or renal impairment, warrant careful observation when estrogens plus progestins are prescribed.

5.13 Hypocalcemia
Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

5.14 Exacerbation of Endometriosis
A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

5.15 Hereditary Angioedema
Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

5.16 Exacerbation of Other Conditions
Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomata and should be used with caution in women with these conditions.

5.17 Laboratory Tests
Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy.

5.18 Drug–Laboratory Test Interactions
Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subtraction concentration, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglyceride levels, impaired glucose tolerance.

6 ADVERSE REACTIONS
The following serious adverse reactions are discussed elsewhere in the labeling.

- Cardiovascular Disorders [see Boxed Warning, Warnings and Precautions (5.1)]
- Malignant Neoplasms [see Boxed Warning, Warnings and Precautions (5.2)]

6.1 Clinical Trials Experience
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.
Adverse reactions reported with Activella® 1 mg/0.5 mg by investigators in the Phase 3 studies regardless of causality assessment are shown in Table 1.

### Table 1: All Treatment-Emergent Adverse Reactions Regardless of Relationship Reported at a Frequency of ≥5 percent with Activella® 1 mg/0.5 mg

<table>
<thead>
<tr>
<th>Endometrial Hyperplasia Study (12-Months)</th>
<th>Vasomotor Symptoms Study (3-Months)</th>
<th>Osteoporosis Study (2-Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activella® 1 mg/0.5 mg (n=295)</strong></td>
<td><strong>Activella® 1 mg/0.5 mg (n=29)</strong></td>
<td><strong>Activella® 1 mg/0.5 mg (n=47)</strong></td>
</tr>
<tr>
<td><strong>1 mg E₂ (n=296)</strong></td>
<td><strong>Placebo (n=34)</strong></td>
<td><strong>Placebo (n=48)</strong></td>
</tr>
<tr>
<td><strong>Body as a Whole</strong></td>
<td><strong>Digestive System</strong></td>
<td><strong>Central Nervous System</strong></td>
</tr>
<tr>
<td>Back Pain</td>
<td>Nausea</td>
<td>Headache</td>
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<td>16%</td>
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<tr>
<td><strong>Nervous System</strong></td>
<td><strong>Respiratory System</strong></td>
<td><strong>Vaginal Bleeding</strong></td>
</tr>
<tr>
<td>Insomnia</td>
<td>Insomnia</td>
<td>Headache</td>
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<td>6%</td>
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<tr>
<td><strong>Metabolic and Nutritional</strong></td>
<td><strong>Urogenital System</strong></td>
<td><strong>Other Events</strong></td>
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<tr>
<td>Weight Increase</td>
<td>Breast Pain</td>
<td><strong>Other Events</strong></td>
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<tr>
<td><strong>Endogenous</strong></td>
<td><strong>Secondary Terms</strong></td>
<td><strong>Norethindrone Acetate</strong></td>
</tr>
<tr>
<td>Nausea</td>
<td>Injury Accidental</td>
<td>Drugs or herbal products that induce or inhibit cytochrome P-450 enzymes, including CYP3A4, may decrease or increase the serum concentrations of norethindrone.</td>
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<tr>
<td><strong>Digestive System</strong></td>
<td><strong>Urogenital System</strong></td>
<td><strong>Other Events</strong></td>
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<td>Diarrhea</td>
<td>Endometrial thickening</td>
<td><strong>Other Events</strong></td>
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<tr>
<td><strong>Other Events</strong></td>
<td><strong>Secondary Terms</strong></td>
<td><strong>Other Events</strong></td>
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<td>Other Events</td>
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</tbody>
</table>

*Including one upper extremity fracture in each group

Adverse reactions reported with Activella® 0.5 mg/0.1 mg by investigators during the Phase 3 study regardless of causality assessment are shown in Table 2.

### Table 2: All Treatment-Emergent Adverse Reactions Regardless of Relationship Reported at a Frequency of ≥5 percent with Activella® 0.5 mg/0.1 mg

<table>
<thead>
<tr>
<th><strong>Activella® 0.5 mg/0.1 mg (n=194)</strong></th>
<th><strong>Placebo (n=200)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td><strong>Digestive System</strong></td>
</tr>
<tr>
<td>Back Pain</td>
<td>Nausea</td>
</tr>
<tr>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>4%</td>
<td>4%</td>
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<tr>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Central Nervous System</strong></td>
<td><strong>Vaginal Bleeding</strong></td>
</tr>
<tr>
<td>Headache</td>
<td>Menorrhagia; oligomenorrhea; spotting; dysmenorrhea, increase in size of uterine leiomyoma; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; pre-menstrual-like syndrome; cystitis-like syndrome; ovarian cancer; endometrial hyperplasia; endometrial cancer.</td>
</tr>
<tr>
<td>22%</td>
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<tr>
<td>19%</td>
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</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td><strong>Other Events</strong></td>
</tr>
<tr>
<td>Headache</td>
<td>Other Events</td>
</tr>
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<td>10%</td>
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</tbody>
</table>

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Activella®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

6.3 Genitourinary System

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

6.4 Breast

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

6.5 Cardiovascular

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction, stroke; increase in blood pressure.

6.6 Gastrointestinal

Nausea, vomiting; changes in appetite; cholestatic jaundice; abdominal pain/cramps, flatulence, bloating; increased incidence of gallbladder disease and pancreatitis.

6.7 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. Eyes Retinal vascular thrombosis, intolerance to contact lenses.

6.8 Other Events

Other adverse reactions occurring at an incidence of ≥1 percent with Activella® 0.5 mg/0.1 mg and not previously listed are shown in Table 2.

8.1 Pregnancy

Activella® should not be used during pregnancy (see Contraindications (4)). There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

8.2 Nursing Mothers

Activella® should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogen and progestin have been identified in the breast milk of women receiving estrogen plus progestin therapy. Caution should be exercised when Activella® is administered to a nursing woman.

8.3 Geriatric Use

There have been insufficient numbers of geriatric women involved in clinical studies utilizing Activella® to determine whether those over 65 years of age differ from younger subjects in their response to Activella®. The Women’s Health Initiative Studies

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg]-alone plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age (see Clinical Studies (14.5)).

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age (see Clinical Studies (14.5)).

The Women’s Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen plus progestin or estrogen-alone when compared to placebo. It is unknown whether this finding applies to younger postmenopausal women (see Warnings and Precautions (5.3), and Clinical Studies (14.6)).

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women (see Warnings and Precautions (5.3), and Clinical Studies (14.6)).

8.4 Pediatric Use

Activella® is not indicated in children. Clinical studies have not been conducted in the pediatric population.

8.5 Pregnancy

8.7 Osteoporosis

8.8 Other Events

The effect of renal impairment on the pharmacokinetics of Activella® has not been studied.
8.7 Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of Activella® has not been studied.

10 OVERDOSAGE
Overdosage of estrogen plus progestin may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of Activella® therapy with institution of appropriate symptomatic care.

11 DESCRIPTION
Activella® 1 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), an estrogen, is a white or almost white crystalline powder. Its chemical name is 17β-estradiol. The structural formula of E₂ is as follows:

\[
\text{Estradiol (E}_2\text{)} \\
\begin{array}{c}
\text{HO} \\
\text{CH_2CH_2O_2} \\
\text{CHOH} \\
\end{array}
\]

Norethindrone acetate (NET), a progestin, is a white or almost white crystalline powder. Its chemical name is 17α-acetoxy-19-nor-17α-pregn-4-en-20-yn-3-ol with the empirical formula of C₂₃H₃₂O₄ and a molecular weight of 340.5. The structural formula of NET is as follows:

\[
\text{Norethindrone Acetate} \\
\begin{array}{c}
\text{OH} \\
\text{CH_2CH_2O_2} \\
\text{CHOH} \\
\end{array}
\]

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
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 in the 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 FSH through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

12.2 Pharmacodynamics
There are no pharmacodynamic data known for Activella® tablets.

12.3 Pharmacokinetics

Absorption
Estradiol
Estradiol is absorbed through the gastrointestinal tract. Following oral administration of Activella® tablets, peak plasma estradiol concentrations are reached within 5 to 8 hours. The oral bioavailability of estradiol following administration of Activella® 1 mg/0.5 mg when compared to a combination oral solution is 53%. Administration of Activella® 1 mg/0.5 mg with food did not modify the bioavailability of estradiol.

Norethindrone Acetate
After oral administration, norethindrone acetate is absorbed and transformed to norethindrone. Norethindrone reaches a peak plasma concentration within 0.5 to 1.5 hours after the administration of Activella® tablets. The oral bioavailability of norethindrone following administration of Activella® 1 mg/0.5 mg when compared to a combination oral solution is 100%. Administration of Activella® 1 mg/0.5 mg with food increases norethindrone AUC0-72 by 19% and decreases Cmax by 36%.

The pharmacokinetic parameters of estradiol (E₂), estrone (E₁), and norethindrone (NET) following oral administration of Activella® 1 mg/0.5 mg or 2 Activella® 0.5 mg/0.1 mg tablet(s) to healthy postmenopausal women are summarized in Table 3.

Table 3: Pharmacokinetic Parameters After Administration of 1 Tablet of Activella® 1 mg/0.5 mg or 2 Tablets of Activella® 0.5 mg/0.1 mg to Healthy Postmenopausal Women

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Activella® 1 mg/0.5 mg (n=24)</th>
<th>Mean (%CV)1</th>
<th>Activella® 0.5 mg/0.1 mg (n=24)</th>
<th>Mean (%CV)2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (E₂)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC0-t (pg/mL*h)</td>
<td>7665.6 (48)</td>
<td>6973.5 (53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (pg/mL)</td>
<td>25.8 (36)</td>
<td>26.5 (37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tmax (h); median (range)</td>
<td>6.0 (0.5-16.0)</td>
<td>6.5 (0.5-16.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t1/2 (h)3</td>
<td>14.0 (29)</td>
<td>14.5 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrone (E₁)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC0-t (pg/mL*h)</td>
<td>4469.1 (48)</td>
<td>4506.4 (44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (pg/mL)</td>
<td>215.5 (37)</td>
<td>199.5 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tmax (h); median (range)</td>
<td>6.0 (1.0-9.0)</td>
<td>6.0 (2.0-9.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t1/2 (h)3</td>
<td>10.7 (44)4</td>
<td>11.8 (25)4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norethindrone (NET)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC0-t (pg/mL*h)</td>
<td>21043 (41)</td>
<td>8407.2 (43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (pg/mL)</td>
<td>5249.5 (47)</td>
<td>2375.4 (41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tmax (h); median (range)</td>
<td>0.7 (0.7-1.25)</td>
<td>0.8 (0.7-1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t1/2 (h)3</td>
<td>9.8 (32)5</td>
<td>11.4 (36)5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 AUC = area under the curve; 0 – last quantifiable sample
2 Cmax = maximum plasma concentration
3 tmax = time at maximum plasma concentration
4 t1/2 = half-life.

Distribution
Estradiol
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.

Norethindrone Acetate
Norethindrone also binds to a similar extent to SHBG (36%) and to albumin (61%).

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 a major urinary metabolite. Estrogens also undergo enterohpatic 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 5α-dihydro-norethindrone and tetrahydro-norethindrone, which are excreted mainly in the urine as sulfate or glucuronide conjugates.

Excretion
Estradiol
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 mg/0.5 mg is 12 to 14 hours.

Norethindrone Acetate
The terminal half-life of norethindrone is about 8 to 11 hours.

Use in Specific Populations
No pharmacokinetic studies were conducted in specific populations, including women with renal or hepatic impairment.

**Figure 1a:** Mean Baseline-Uncorrected Estradiol and Estrone Serum Concentration-Time Profiles Following Multiple Doses of Activella® 1 mg/0.5 mg (N=24)

**Figure 1b:** Mean Baseline-Uncorrected Norethindrone Serum Concentration-Time Profile Following Multiple Doses of Activella® 1 mg/0.5 mg (N=24)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES
14.1 Effects on Vasomotor Symptoms

In a 12-week randomized clinical trial involving 92 subjects, Activella® 1 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 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 Flushes 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 Flushes for Weeks 0 Through 12

14.2 Effects on the Endometrium

Activella® 1 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 + 0.25 mg NETA (n=294), 1 mg E2 + 0.25 mg NETA (n=291), and Activella® 1 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 mg/0.5 mg are shown in Table 4.

Table 4: Incidence of Endometrial Hyperplasia with Unopposed Estradiol and Activella® 1 mg/0.5 mg in a 12-Month Study

14.3 Effects on Uterine Bleeding or Spotting

During the initial months of therapy, irregular bleeding or spotting occurred with Activella® 1 mg/0.5 mg treatment. However, bleeding tended to decrease over time, and after 12 months of treatment with Activella® 1 mg/0.5 mg, about 86 percent of women were amenorrheic (see Figure 4).

Figure 4: Patients Treated with Activella® 1 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 percent of women were amenorrheic after 6 months of treatment (See Figure 5).

Figure 5: Patients Treated with Activella® 0.5 mg/0.1 mg with Cumulative Amenorrhea over Time

Percentage of Women with no Bleeding or Spotting at any Cycle Through Cycle 6, Intent to Treat Population, LOCF

14.4 Effects on Bone Mineral Density

The results of two randomized, multicenter, calcium-supplemented (500-1000 mg per day), placebo-controlled, 2 year clinical trials have shown that Activella® 1 mg/0.5 mg and estradiol 0.5 mg are effective in preventing bone loss in postmenopausal women. A total of 462 postmenopausal women with intact uteri and baseline BMD values for lumbar spine within 2 standard deviations of the mean in healthy young women (T-score > -2.0) 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, 0.5 mg, 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 percent and 67 percent of the randomized subjects in the two clinical trials, respectively, completed the two clinical trials. BMD was measured using dual-energy x-ray absorptiometry (DXA).

A summary of the results comparing Activella® 1 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 mg/0.5 mg and 0.5 mg E2† (Intent to Treat Analysis, Last Observation Carried Forward)

14.5 Women’s Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)/alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nontal MI, silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A “global index” included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other cause. These substudies did not evaluate the effects of CE plus MPA or CE-alone on menopausal symptoms. WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive 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.

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 plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79, 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 6. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.
Table 6: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years.a,b

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk</th>
<th>Absolute Risk per 10,000 Women-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CE/MPA versus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>CHD events</td>
<td>1.23 (0.99-1.53)</td>
<td>34</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1.28 (1.00-1.63)</td>
<td>25</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.10 (0.70-1.75)</td>
<td>8</td>
</tr>
<tr>
<td>All strokes</td>
<td>1.31 (1.03-1.68)</td>
<td>25</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.44 (1.08-1.90)</td>
<td>18</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.95 (1.43-2.67)</td>
<td>13</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2.13 (1.54-3.11)</td>
<td>8</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>1.24 (1.01-1.54)</td>
<td>33</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.61 (0.42-0.87)</td>
<td>16</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>0.81 (0.48-1.63)</td>
<td>7</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>1.44 (0.47-4.42)</td>
<td>2</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.67 (0.47-0.96)</td>
<td>11</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>0.65 (0.46-0.92)</td>
<td>11</td>
</tr>
<tr>
<td>Lower arm/wrist fracture</td>
<td>0.71 (0.59-0.85)</td>
<td>44</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.76 (0.69-0.83)</td>
<td>152</td>
</tr>
<tr>
<td>Overall Mortality</td>
<td>1.00 (0.83-1.19)</td>
<td>52</td>
</tr>
<tr>
<td>Global Index</td>
<td>1.13 (1.02-1.25)</td>
<td>184</td>
</tr>
</tbody>
</table>

a Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
b Results are based on centrally adjudicated data.
c Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
d Not included in “global index”.
e Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.
f All deaths, except from breast or colorectal cancer, definite or probable CHD, PE, or cerebrovascular disease.
g A subset of the events was combined in a “global index” defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, 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 CE-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures. The absolute excess risk of events included in the “global index” was a significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk/benefit profile. The WHI estrogen plus progestin substudy, stratified by age, showed in women 50 to 59 years of age a non-significant trend toward reduced risk for overall mortality [hazard ratio (HR) 0.69 (95 percent CI, 0.44-1.07)].

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was 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 63 years of age, range 50 to 79), 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other, after an average follow-up of 7.1 years, are presented in Table 7.

Table 7: Relative and Absolute Risk Seen in the Estrogen Alone Substudy of WHI

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk</th>
<th>Absolute Risk per 10,000 Women-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CE versus Placebo (95% CI)</td>
<td></td>
</tr>
<tr>
<td>CHD events</td>
<td>0.95 (0.78-1.19)</td>
<td>54</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.91 (0.73-1.14)</td>
<td>40</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.01 (0.77-1.36)</td>
<td>16</td>
</tr>
<tr>
<td>All strokes</td>
<td>1.33 (1.05-1.68)</td>
<td>45</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.55 (1.19-2.01)</td>
<td>38</td>
</tr>
</tbody>
</table>

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Activilena® 1 mg/0.5 mg is a white, film-coated tablet, engraved with NOVO 298 on one side and the APIS bull on the other. It is round, 6mm in diameter and bi-convex. (NDC 0169-5174-02). It is supplied as 28 tablets in a calendar dial pack dispenser.

Activilena® 0.5 mg/0.1 mg is a white, film-coated tablet, engraved with NOVO 299 on one side and the APIS bull on the other. It is round, 6mm in diameter and bi-convex. (NDC 0169-5175-10). It is supplied as 28 tablets in a calendar dial pack dispenser.

16.2 Storage and Handling

Store in a dry place protected from light. Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)
17.2 Possible Serious Adverse Reactions with Estrogen Plus Progestin Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen plus progestin therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia (see Warnings and Precautions (5.1, 5.2, 5.3)).

17.3 Possible Less Serious but Common Adverse Reactions with Estrogen Plus Progestin Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen plus progestin therapy such as headache, breast pain and tenderness, nausea and vomiting.
Activella® (estradiol/norethindrone acetate) Tablets

Read this Patient Information before you start taking Activella® and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

What is the most important information I should know about Activella® (a combination of estrogen and progestin)?

- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes, or dementia (decline of brain function).
- Taking estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Taking estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years of age or older.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia.
- Taking estrogen-alone may increase your chance of getting cancer of the uterus (womb).
- Taking estrogen-alone may increase your chances of getting strokes or blood clots.
- Taking estrogen-alone may increase your chance of getting dementia, based on a study of women 65 years of age or older.
- You and your healthcare provider should talk regularly about whether you still need treatment with Activella®.

What is Activella®?
Activella® is a prescription medicine that contains two kinds of hormones, an estrogen and a progestin.

What is Activella® used for?
Activella® is used after menopause to:

- reduce moderate to severe hot flushes
  Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 yrs old. This drop in body estrogen levels causes the “change of life” or menopause, the end of 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 get very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden, intense episodes of heat and sweating (“hot flashes” or “hot flushes”). In some women, the symptoms are mild, and they will not need to take estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether or not you still need treatment with Activella®.

- treat moderate to severe menopausal changes in and around the vagina
  You and your healthcare provider should talk regularly about whether you still need treatment with Activella®.

- help reduce your chances of getting osteoporosis (thin weak bones)
  If you use Activella® only to prevent osteoporosis from menopause, talk to your healthcare provider about whether a different treatment or medicine without estrogens might be better for you.

- You and your healthcare provider should talk regularly about whether you still need treatment with Activella®.

Who should not take Activella®?
Do not take Activella® if you have had your uterus (womb) removed (hysterectomy).
Activella® contains a progestin to decrease the chance 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 take Activella® if you:
- have unusual vaginal bleeding
  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- 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 healthcare provider about whether you should take Activella®.
- had a stroke or heart attack
- have been diagnosed with a bleeding disorder
- are allergic to Activella® or any of its ingredients

What should I tell my healthcare provider before taking Activella®?
Before you take Activella®, tell your healthcare provider if you:
- have any unusual vaginal bleeding
  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- have any other medical conditions
  Your healthcare provider may need to check you more carefully if you have some certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, angioedema (swelling of face and tongue), or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- are going to have surgery or will be on bed rest
  Your healthcare provider will let you know if you need to stop taking Activella®.
- are breast feeding

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Activella® works. Activella® may also affect how your other medicines work. Keep a list of your medicines and show them to your healthcare provider and pharmacist when you get a new medicine.

How should I take Activella®?
- Take Activella® exactly as your healthcare provider tells you to take it.
- Take 1 Activella® at the same time each day.
- You and your healthcare provider should talk regularly (every 3 to 6 months) about the dose you are taking and whether you still need treatment with Activella®.

Follow the instructions below to use your 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.

What are the possible side effects of Activella®?
Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:
- heart attack
- stroke
- blood clots
- dementia
- breast cancer
- cancer of the lining of the uterus (womb)
- cancer of the ovary
- high blood pressure
- high blood sugar
- gallbladder disease
- liver problems

changes in your thyroid hormone levels
enlargement of benign tumors (“fibroids”)
Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- new breast lumps
- unusual vaginal bleeding
- changes in vision or speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness and fatigue

Less serious, but common side effects include:

- headache
- breast pain
- irregular vaginal bleeding or spotting
- stomach or abdominal cramps, bloating
- nausea and vomiting
- hair loss
- fluid retention
- vaginal yeast infection

These are not all the possible side effects of Activella®. For more information, ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effect that bothers you or does not go away. You may report side effects to Novo Nordisk at 1-888-824-4336 or to FDA at 1-800-FDA-1088.

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

- Talk with your healthcare provider regularly about whether you should continue taking Activella®.
- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you.
- The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus (womb).
- See your healthcare provider right away if you get vaginal bleeding while taking Activella®.
- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else.
- If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), 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 healthcare provider for ways to lower your chances for getting heart disease.

How should I store Activella®?

- Store Activella® at room temperature between 68°F to 77°F (20°C to 25°C).
- Store Activella® in a dry place protected from light.

KEEP ACTIVELLA® and all medicines out of the reach of children.

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.

This leaflet summarizes the most important information about Activella®. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about Activella® that is written for health professionals.

For more information go to www.activella.com or call 1-866-668-6336.