

# Antibiotic Safety of Concern to Nursing Mothers

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SAN FRANCISCO — Many new mothers are leery of taking antibiotics while breast-feeding, but their fears are unfounded, Dr. Natali Aziz said at a meeting on antepartum and intrapartum management sponsored by the University of California, San Francisco.

Most of the commonly used antimicrobials are safe in breast-feeding and very

few are controversial or contraindicated. Take the time to review the risks and benefits of antibiotics for a new mother who needs the medicine. "Many times we can dispel the fears and rumors that patients might have heard," said Dr. Aziz of the university.

Penicillins, cephalosporins, macrolides, and aminoglycosides all are safe in breast-feeding. The only potential side effects observed in infants who breast-feed from mothers taking these antibiotics are

changes in intestinal flora that may cause loose stools or diarrhea.

Some controversy around whether to take quinolones or metronidazole while breast-feeding has been resolved in favor of the drugs' safety.

The quinolone ofloxacin raised concerns after it was associated with arthropathy in juvenile animals, but the risk of arthropathy in infants breast-feeding from mothers on short courses of the medication is extremely low, she said. In a review

of more than 7,000 children on chronic quinolone therapy, only 10 developed an arthropathy-like syndrome.

The American Academy of Pediatrics has declared ofloxacin safe for breast-feeding, she added.

Metronidazole has been associated with carcinogenesis in rodents, but the drug does not increase the rate of adverse events in breast-fed infants and no studies have found cancer to be associated with breast-feeding in humans. The worst of the data show is a statistical trend toward relatively benign side effects—loose stools or candidal colonization may develop in infants breast-feeding from women on metronidazole.

The American Academy of Pediatrics rates metronidazole safe while breast-feed-

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**CARDIOVASCULAR AND OTHER RISKS**  
Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** in prescribing information and **WARNINGS, Cardiovascular disorders and Dementia**.) The estrogen plus progestin sub-study of the Women's Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) per day, relative to placebo. (See **CLINICAL STUDIES** in prescribing information and **WARNINGS, Cardiovascular disorders and Malignant neoplasms, Breast cancer**.) The estrogen-alone sub-study of the WHI reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 6.8 years and 7.1 years, respectively, of treatment with oral conjugated estrogens (CE 0.625 mg) per day, relative to placebo. (See **CLINICAL STUDIES** in prescribing information and **WARNINGS, Cardiovascular disorders**.) The Women's Health Initiative Memory Study (WHIMS), a sub-study of the WHI study, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with CE 0.625 mg combined with MPA 2.5 mg and during 5.2 years of treatment with CE 0.625 mg alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** in prescribing information and **WARNINGS, Dementia and PRECAUTIONS, Geriatric Use**.) Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

**INDICATIONS AND USAGE** Activella 1.0 mg/0.05 mg and 0.5 mg/0.1 mg are indicated in women who have a uterus for the:

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

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1,500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

Activella 1.0 mg/0.05 mg is also indicated in women who have a uterus for the:

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

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

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism, or history of these conditions.
5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).

**WARNINGS**  
See **BOXED WARNINGS**.

**1. Cardiovascular disorders** Estrogen-plus-progestin therapy has been associated with an increased risk of myocardial infarction as well as stroke, venous thrombosis and pulmonary embolism. Estrogen-alone therapy has been associated with an increased risk of stroke and deep vein thrombosis (DVT). Should any of these events occur or be suspected, estrogens should be discontinued immediately. Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and/or atherosclerosis, a history of stroke, personal history of or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

**a. Stroke** In the estrogen plus progestin sub-study of the Women's Health Initiative (WHI), a statistically significant increased risk of stroke was reported in women receiving CE/MPA 0.625mg/2.5mg daily compared to women receiving placebo (31 vs. 24 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted. (See **CLINICAL STUDIES** in prescribing information.) In the estrogen-alone sub-study of the WHI, a statistically significant increased risk of stroke was reported in women receiving CE 0.625 mg daily compared to women receiving placebo (44 vs. 32 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted.

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

In postmenopausal women with documented heart disease (n=2,763, average age 66.7 years), a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study (HERS)) treatment with CE/MPA (0.625mg/2.5mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Participation in an open-label extension of the original HERS trial (HERS II) was agreed by 2,221 women. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall. Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thromboembolism.

**c. Venous thromboembolism** In the estrogen-plus-progestin sub-study of the Women's Health Initiative (WHI), a statistically significant 2-fold greater rate of VTE (DVT and pulmonary embolism [PE]), was reported in women receiving CE/MPA compared to women receiving placebo (35 vs. 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 vs. 13 per 10,000 women-years) and PE (18 vs. 6 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. (See **CLINICAL STUDIES** in prescribing information.) In the estrogen-alone sub-study of WHI, the risk of VTE was reported to be increased for women taking conjugated estrogens (30 vs. 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 vs. 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first two years. If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

**2. Malignant neoplasms**

**a. Breast cancer** In some studies, the use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the CE/MPA sub-study of the WHI study (See **CLINICAL STUDIES** in prescribing information). The results from observational studies are generally consistent with those of the WHI clinical trial. Observational studies have also reported an increased risk of breast cancer for estrogen-plus-progestin combination therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with estrogen-plus-progestin combination therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen-plus-progestin combinations, doses, or routes of administration. In the estrogen-plus-progestin sub-study, after a mean follow-up of 5.6 years, the WHI sub-study reported an increased risk of breast cancer. In this sub-study, prior use of estrogen alone or estrogen-plus-progestin combination hormone therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24 (95% CI 1.01-1.54), and the absolute risk was 41 vs. 33 cases per 10,000 women-years for estrogen plus progestin therapy compared with placebo, respectively. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years of

estrogen plus progestin compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen-plus-progestin group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups.

In the estrogen-alone sub-study of WHI, after an average of 7.1 years of follow-up, CE (0.625 mg daily) was not associated with an increased risk of invasive breast cancer (RR 0.80, 95% CI 0.62-1.04). In a one-year trial among 1,176 women who received either unopposed 1 mg estradiol or a combination of 1 mg estradiol plus one of three different doses of MPA (0.1, 0.25, and 0.5 mg), seven new cases of breast cancer were diagnosed, two of which occurred among the group of 295 women treated with Activella 1.0 mg/0.05 mg and two of which occurred among the group of 294 women treated with 1 mg estradiol/0.1 mg MPA.

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

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

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Endometrial hyperplasia (a histologic precursor of endometrial cancer) has been reported to occur in approximately 1% of less than one year of treatment with CE 0.625 mg/MPA 2.5 mg combination therapy.

**3. Dementia** In the estrogen-plus-progestin Women's Health Initiative Memory Study (WHIMS), a sub-study of WHI, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo. In the estrogen-alone WHIMS sub-study, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to CE (0.625 mg daily) or placebo. In the estrogen-plus-progestin study, after an average follow-up of four years, 40 women in the estrogen-plus-progestin group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen plus progestin vs. placebo was 2.05 (95% CI 1.21-3.48). The absolute risk of probable dementia for CE/MPA vs. placebo was 45 vs. 22 cases per 10,000 women-years.

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

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

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

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

**6. Visual abnormalities** Retinal vascular thromboses has been reported in patients receiving estrogens. Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

**PRECAUTIONS**

**A. General**

**1. Addition of a progestin when a woman has not had a hysterectomy** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone treatment. These include a possible increased risk of breast cancer.

**2. Elevated blood pressure and past history of cholestatic jaundice** Estrogens may increase blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

**3. Hypertriplomycidemia** In patients with preexisting hypertriplomycidemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

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

**5. Hypothyroidism** Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T<sub>4</sub> and T<sub>3</sub> serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogen may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored to maintain their free thyroid hormone levels in an acceptable range.

**6. Fluid retention** Estrogens may cause some degree of fluid retention. Because of this, patients who have conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

**7. Hypocalcemia** Estrogens should be used with caution in individuals with severe hypocalcemia.

**8. Ovarian cancer** The estrogen-plus-progestin sub-study of WHI reported that after an average follow-up of 5.6 years, the relative risk for ovarian cancer for estrogen plus progestin vs. placebo was 1.58 (95% CI 0.77 - 3.24), but was not statistically significant. The absolute risk for estrogen plus progestin vs. placebo was 4.2 vs. 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, in particular for 10 or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

**9. Exacerbation of endometriosis** Endometriosis may be exacerbated with administration of estrogens. Malignant transformation of residual endometrial implants has been reported in women treated post-hysterectomy with estrogen-alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

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

**B. Patient Information** Physicians are advised to discuss the contents of the Patient Information Leaflet with patients for whom they prescribe Activella 1.0 mg/0.05 mg or Activella 0.5 mg/0.1 mg.

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

**D. Drug/Laboratory Test Interactions**

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII, antigen, VIII coagulant activity, IX, X, XII, VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating thyroid hormone levels as measured by protein-bound iodine (PBI), T<sub>4</sub> levels (by column or by radioimmunoassay), or T<sub>3</sub> levels by radioimmunoassay. T<sub>4</sub> resin uptake is decreased, reflecting the elevated TBG. Free T<sub>4</sub> and free T<sub>3</sub> concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin [CBG], SHBG) leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1 antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL<sub>2</sub>, cholesterol subtraction concentration, reduced LDL cholesterol concentration, increased triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

**E. Carcinogenesis, Mutagenesis, Impairment of Fertility** Long-term continuous administration of estrogen, with or without progestin, in women with or without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNINGS, WARNINGS, and PRECAUTIONS**.)

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

**G. Nursing Mothers** Estrogen administration to nursing mothers has been shown to decrease the

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

**H. Pediatric Use** Activella is not indicated in children.

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

Of the total number of subjects in the estrogen-plus-progestin sub-study of the Women's Health Initiative (WHI) study, 44% (n=7,320) were 65-74 years of age, while 6.8% (n=1,095) were 75 years and over. There was a higher relative risk (CE/MPA vs. placebo) of non-fatal stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age. In women greater than 75, the increased risk of non-fatal stroke and invasive breast cancer observed in the estrogen-plus-progestin combination group compared to the placebo group was 75 vs. 24 per 10,000 women-years and 52 vs. 12 per 10,000 women-years, respectively. Of the total number of subjects in the estrogen-alone sub-study of WHI, 46% (n=4,943) were 65 years and over, while 7.1% (n=767) were 75 years and over. There was a higher relative risk (CE vs. placebo) of stroke in women less than 75 years of age compared to women 75 years and over. In the estrogen-alone WHIMS sub-study, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to CE (0.625 mg daily) or placebo. After an average follow-up of 5.2 years, the relative risk (CE vs. placebo) of probable dementia was 1.49 (95% CI 0.83-2.66). The absolute risk of developing probable dementia with estrogen alone was 37 vs. 25 cases per 10,000 women-years with placebo. Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 for the CE-alone group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CE/MPA group. The most common classification of probable dementia in both the treatment groups and placebo groups was Alzheimer's disease. When data from these two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Since both sub-studies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **WARNINGS, Dementia**.)

**ADVERSE REACTIONS**  
See **BOXED WARNINGS, WARNINGS and PRECAUTIONS**.

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

Adverse events reported with Activella 1.0 mg/0.05 mg by investigators in the Phase 3 studies regardless of causality assessment are shown in Table 6.

**TABLE 6: ALL TREATMENT-EMERGENT ADVERSE EVENTS REGARDLESS OF RELATIONSHIP REPORTED AT A FREQUENCY OF ≥ 5% WITH ACTIVELLA 1.0 MG/0.05 MG**

	Endometrial Hyperplasia Study (12-Months)		Vasomotor Symptoms Study (3-Months)		Osteoporosis Study (2 Years)	
	Activella 1.0 mg/0.05 mg (n=295)	E2 1.0 mg/0.5 mg (n=29)	Placebo (n=34)	Activella 1.0 mg/0.05 mg (n=47)	Placebo (n=48)	
<b>Body as a Whole</b>						
Back Pain	6%	5%	3%	3%	6%	4%
Headache	16%	16%	17%	18%	11%	6%
<b>Digestive System</b>						
Nausea	3%	5%	10%	0%	11%	0%
Gastroenteritis	2%	2%	0%	0%	6%	4%
<b>Nervous System</b>						
Insomnia	6%	4%	3%	3%	0%	8%
Headache	1%	1%	0%	0%	0%	0%
<b>Respiratory System</b>						
Upper Respiratory Tract Infection	18%	15%	10%	6%	15%	19%
Sinusitis	7%	11%	7%	0%	15%	10%
<b>Metabolic and Nutritional</b>						
Weight extremely increased	0%	0%	0%	0%	9%	6%
<b>Urogenital System</b>						
Breast Pain	24%	10%	21%	0%	17%	8%
Post-Menopausal Bleeding	5%	15%	10%	3%	11%	0%
Uterine Fibroid	5%	4%	0%	0%	4%	8%
Ovarian Cyst	3%	2%	7%	0%	0%	0%
<b>Resistance mechanism</b>						
Infection Viral	4%	6%	0%	3%	6%	6%
Molluscias Genital	4%	7%	0%	0%	6%	0%
<b>Secondary Terms</b>						
Injury Accidental	4%	3%	3%	0%	17%*	4%*
Other Events	2%	3%	3%	0%	6%	4%

\*Including one upper extremity fracture in each group. Adverse events reported with Activella 0.5 mg/0.1 mg by investigators during the Phase 3 study regardless of causality assessment are shown in Table 7.

**TABLE 7: ALL TREATMENT-EMERGENT ADVERSE EVENTS REGARDLESS OF RELATIONSHIP REPORTED AT A FREQUENCY OF ≥ 5% WITH ACTIVELLA 0.5 MG/0.1 MG**

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

The following adverse reactions have been reported with estrogen and/or progestin therapy:  
**1. Gastrointestinal system** Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea; increase in size of uterine leiomyomas; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; premenstrual-like syndrome; cystitis-like syndrome; ovarian cancer; endometrial hyperplasia; endometrial cancer.  
**2. Breasts** Tenderness, enlargement, pain, nipple discharge, galactorrhea, fibrocystic breast changes; breast cancer.  
**3. Cardiovascular** Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.  
**4. Gastrointestinal** Nausea, vomiting; changes in appetite; cholestatic jaundice; abdominal pain/cramps; flatulence, bloating; increase incidence of gallbladder disease; pancreatitis; enlargement of hepatic hemangiomas.  
**5. Skin** Oedema or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; seborrhea; hirsutism; itching; skin rash; pruritus.  
**6. Eyes** Retinal vascular thrombosis; intolerance to contact lenses.  
**7. Central nervous system** Headache; migraine; dizziness; mental depression; chorea; insomnia; nervousness; mood disturbances; irritability; exacerbation of epilepsy; probable dementia.  
**8. Musculoskeletal** Increase or decrease in weight; aggravation of porphyria; edema; leg cramps; changes in libido; fatigue; reduced carbohydrate tolerance; anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides; back pain; arthralgia; myalgia.  
**OVERDOSSAGE** Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children. Overdose of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

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