

Restraint Warranted in Pap Tests for Teenagers

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BOSTON — Regarding Pap smears in adolescents: Don't do them in the first 3 years after their sexual debut, Dr. Michael S. Policar stressed.

Pap testing in this population is no longer recommended "because it can do more harm than good," he said. "High-grade lesions are rare in teenagers, occurring in 3 cases per 1,000 15- to 19-year-olds,

and they take years to develop. For example, it takes 3 years after sexual debut for high-grade squamous intraepithelial lesions to develop and 5 years for invasive cancers to emerge," he said at a conference on contraceptive technology sponsored by Contemporary Forums.

Additionally, "approximately 91% of low-grade lesions in teens, such as cervical intraepithelial neoplasia 1 [CIN 1] often resolve spontaneously, while 6% remain stable and only 3% progress to high-grade

dysplasia." Biopsy-proven CIN 2 lesions in teenagers often regress spontaneously, as well, said Dr. Policar. Recognition of these early cytologic abnormalities on Pap testing could easily lead to unnecessary intervention and consequent risks, said Dr. Policar of the department of obstetrics, gynecology, and reproductive sciences at the University of California, San Francisco.

For these reasons, the American College of Obstetricians and Gynecologists recommends that Pap testing should not be

initiated in young women until age 21 or 3 years after first intercourse, Dr. Policar said. Even so, he noted, many clinicians are still screening virginal 18-year-olds as per the previous guidelines.

Restraint is also warranted in the management of teens whose Pap tests show atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSIL), Dr. Policar stated.

Although consensus guidelines for the

EVISTA® (Raloxifene Hydrochloride) 60 mg tablets

Brief Summary. Consult the package insert for complete prescribing information.

WARNING: INCREASED RISK OF VENOUS THROMBOEMBOLISM AND DEATH FROM STROKE

- Increased risk of deep vein thrombosis and pulmonary embolism have been reported with EVISTA. Women with active or past history of venous thromboembolism should not take EVISTA.
- Increased risk of death due to stroke occurred in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. Consider risk-benefit balance in women at risk for stroke.

INDICATIONS AND USAGE: Treatment and Prevention of Osteoporosis in Postmenopausal Women—EVISTA is indicated for the treatment and prevention of osteoporosis in postmenopausal women [see Clinical Studies].

Reduction in the Risk of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis—EVISTA is indicated for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis [see Clinical Studies].

Reduction in the Risk of Invasive Breast Cancer in Postmenopausal Women at High Risk of Invasive Breast Cancer—EVISTA is indicated for the reduction in risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer [see Clinical Studies].

The effect in the reduction in the incidence of breast cancer was shown in a study of postmenopausal women at high risk for breast cancer with a 5-year planned duration with a median follow-up of 4.3 years [see Clinical Studies]. Twenty-seven percent of the participants received drug for 5 years. The long-term effects and the recommended length of treatment are not known.

High risk of breast cancer is defined as at least one breast biopsy showing lobular carcinoma in situ (LCIS) or atypical hyperplasia, one or more first-degree relatives with breast cancer, or a 5-year predicted risk of breast cancer $\geq 1.66\%$ (based on the modified Gail model). Among the factors included in the modified Gail model are the following: current age, number of first-degree relatives with breast cancer, number of breast biopsies, age at menarche, nulliparity or age of first live birth. Healthcare professionals can obtain a Gail Model Risk Assessment Tool by dialing 1-800-545-5979. Currently, no single clinical finding or test result can quantify risk of breast cancer with certainty.

After an assessment of the risk of developing breast cancer, the decision regarding therapy with EVISTA should be based upon an individual assessment of the benefits and risks.

EVISTA does not eliminate the risk of breast cancer. Patients should have breast exams and mammograms before starting EVISTA and should continue regular breast exams and mammograms in keeping with good medical practice after beginning treatment with EVISTA.

Important Limitations of Use for Breast Cancer Risk Reduction

- There are no data available regarding the effect of EVISTA on invasive breast cancer incidence in women with inherited mutations (BRCA1, BRCA2) to be able to make specific recommendations on the effectiveness of EVISTA.
- EVISTA is not indicated for the treatment of invasive breast cancer or reduction of the risk of recurrence.
- EVISTA is not indicated for the reduction in the risk of noninvasive breast cancer.

DOSE AND ADMINISTRATION: Recommended Dosing—The recommended dosage is one 60 mg EVISTA tablet daily, which may be administered any time of day without regard to meals [see Clinical Pharmacology].

For the indications in risk of invasive breast cancer the optimum duration of treatment is not known [see Clinical Studies].

Recommendations for Calcium and Vitamin D Supplementation—For either osteoporosis treatment or prevention, supplemental calcium and/or vitamin D should be added to the diet if daily intake is inadequate. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Total daily intake of calcium above 1500 mg has not demonstrated additional bone benefits while daily intake above 2000 mg has been associated with increased risk of adverse effects, including hypercalcemia and kidney stones. The recommended intake of vitamin D is 400-800 IU daily. Patients at increased risk for vitamin D insufficiency (e.g., over the age of 70 years, nursing home bound, or chronically ill) may need additional vitamin D supplements. Patients with gastrointestinal malabsorption syndromes may require higher doses of vitamin D supplementation and measurement of 25-hydroxyvitamin D should be considered.

CONTRAINDICATIONS: Venous Thromboembolism—EVISTA is contraindicated in women with active or past history of venous thromboembolism (VTE), including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis [see Warnings and Precautions].

Pregnancy, Women Who May Become Pregnant, and Nursing Mothers—EVISTA is contraindicated in pregnancy, in women who may become pregnant, and in nursing mothers [see Use in Specific Populations]. EVISTA may cause fetal harm when administered to a pregnant woman. If this drug is used during

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pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

In rabbit studies, abortion and a low rate of fetal heart anomalies (ventricular septal defects) occurred in rabbits at doses ≥ 0.1 mg/kg (≥ 0.04 times the human dose based on surface area, mg/m²), and hydrocephaly was observed in fetuses at doses ≥ 10 mg/kg (≥ 4 times the human dose based on surface area, mg/m²). In rat studies, retardation of fetal development and developmental abnormalities (wavy ribs, kidney cavitation) occurred at doses ≥ 1 mg/kg (≥ 0.2 times the human dose based on surface area, mg/m²). Treatment of rats at doses of 0.1 to 10 mg/kg (0.02 to 1.6 times the human dose based on surface area, mg/m²) during gestation and lactation produced effects that included delayed and disrupted parturition; decreased neonatal survival and altered physical development; sex- and age-specific reductions in growth and changes in pituitary hormone content; and decreased lymphoid compartment size in offspring. At 10 mg/kg, raloxifene disrupted parturition, which resulted in maternal and progeny death and morbidity. Effects in adult offspring (4 months of age) included uterine hypoplasia and reduced fertility; however, no ovarian or vaginal pathology was observed.

WARNINGS AND PRECAUTIONS: Venous Thromboembolism—In clinical trials, EVISTA-treated women had an increased risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism). Other venous thromboembolic events also could occur. A less serious event, superficial thrombophlebitis, also has been reported more frequently with EVISTA than with placebo. The greatest risk for deep vein thrombosis and pulmonary embolism occurs during the first 4 months of treatment, and the magnitude of risk appears to be similar to the reported risk associated with use of hormone therapy. Because immobilization increases the risk for venous thromboembolic events independent of therapy, EVISTA should be discontinued at least 72 hours prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest), and EVISTA therapy should be resumed only after the patient is fully ambulatory. In addition, women taking EVISTA should be advised to move about periodically during prolonged travel. The risk-benefit balance should be considered in women at risk of thromboembolic disease for other reasons, such as congestive heart failure, superficial thrombophlebitis, and active malignancy [see Contraindications and Adverse Reactions].

Death Due to Stroke—In a clinical trial of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, an increased risk of death due to stroke was observed after treatment with EVISTA. During an average follow-up of 5.6 years, 59 (1.2%) EVISTA-treated women died due to a stroke compared to 39 (0.8%) placebo-treated women (22 versus 15 per 10,000 women-years; hazard ratio 1.49; 95% confidence interval, 1.00-2.24; $p=0.0499$). There was no statistically significant difference between treatment groups in the incidence of stroke (249 in EVISTA [4.9%] versus 224 placebo [4.4%]). EVISTA had no significant effect on all-cause mortality. The risk-benefit balance should be considered in women at risk for stroke, such as prior stroke or transient ischemic attack (TIA), atrial fibrillation, hypertension, or cigarette smoking [see Clinical Studies].

Cardiovascular Disease—EVISTA should not be used for the primary or secondary prevention of cardiovascular disease. In a clinical trial of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, no cardiovascular benefit was demonstrated after treatment with raloxifene for 5 years [see Clinical Studies].

Premenopausal Use—There is no indication for premenopausal use of EVISTA. Safety of EVISTA in premenopausal women has not been established and its use is not recommended.

Hepatic Impairment—EVISTA should be used with caution in patients with hepatic impairment. Safety and efficacy have not been established in patients with hepatic impairment [see Clinical Pharmacology].

Concomitant Estrogen Therapy—The safety of concomitant use of EVISTA with systemic estrogens has not been established and its use is not recommended.

History of Hypertriglyceridemia when Treated with Estrogens—Limited clinical data suggest that some women with a history of marked hypertriglyceridemia (>5.6 mmol/L or >500 mg/dL) in response to treatment with oral estrogen or estrogen plus progestin may develop increased levels of triglycerides when treated with EVISTA. Women with this medical history should have serum triglycerides monitored when taking EVISTA.

Renal Impairment—EVISTA should be used with caution in patients with moderate or severe renal impairment. Safety and efficacy have not been established in patients with moderate or severe renal impairment [see Clinical Pharmacology].

History of Breast Cancer—EVISTA has not been adequately studied in women with a prior history of breast cancer.

Use in Men—There is no indication for the use of EVISTA in men. EVISTA has not been adequately studied in men and its use is not recommended.

Unexplained Uterine Bleeding—Any unexplained uterine bleeding should be investigated as clinically indicated. EVISTA-treated and placebo-treated groups had similar incidences of endometrial proliferation [see Clinical Studies].

Breast Abnormalities—Any unexplained breast abnormality occurring during EVISTA therapy should be investigated. EVISTA does not eliminate the risk of breast cancer [see Clinical Studies].

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general population call for reflex human papillomavirus (HPV) testing for women with ASC-US and colposcopic examination of the cervix for those with evidence of HPV infection, LSIL, and high-grade squamous intraepithelial lesion (HSIL), these guidelines do not apply to adolescents and young women, he said.

“Colposcopy and reflex HPV triage are no longer recommended as initial options,” he stated, referring to the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for the management of women with abnormal cervical screening tests that were released late last year (Am. J. Obstet. Gynecol.

2007;197:346-55).

Approximately 80% of female adolescents become HPV-DNA positive soon after their first sexual encounters and the majority of these infections clear spontaneously within 2 years.

The identification of abnormal cervical cytology on HPV-DNA testing in adolescents could lead to the unnecessary referral of many teens for colposcopy despite their low cervical cancer risk, Dr. Policar warned.

Rather than immediate colposcopy, adolescents with ASC-US or LSIL on Pap testing should undergo a repeat Pap smear in 12 months. “If the repeat Pap

shows high-grade squamous intraepithelial lesions, the adolescent should be referred for colposcopy,” said Dr. Policar. Those patients with less than HSIL, however, should undergo a repeat Pap in another 12 months, at which point, evidence of ASC-US or greater warrants a colposcopy referral, he said.

While the same 24-month conservative pathway should be followed for adolescent patients with biopsy-proven CIN 1 or CIN 2 to allow for regression, the management options for adolescents and young women with a histologic diagnosis of CIN 2,3 include treatment using either excision or ablation of the T-zone depending on

the adequacy of the colposcopic exam, or colposcopic and cytologic observation at 6-month intervals for 24 months, “as long as colposcopy results are normal and cytology is negative,” said Dr. Policar.

“If colposcopy worsens or high-grade cytology or colposcopy persists, the biopsy should be repeated,” he said. “If, on repeat biopsy, CIN 3 or CIN 2,3 persists for 24 months [the initial diagnosis], treatment should be undertaken to reduce the potential risk of cervical cancer.”

Dr. Michael Policar disclosed that he is a speaker for Graceway Pharmaceuticals LLC, Merck & Co., and TyRx Pharma Inc. ■

ADVERSE REACTIONS: Clinical Trials Experience—Because clinical studies 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 data described below reflect exposure to EVISTA in 8429 patients who were enrolled in placebo-controlled trials, including 6666 exposed for 1 year and 5685 for at least 3 years.

Osteoporosis Treatment Clinical Trial (MORE)—The safety of raloxifene in the treatment of osteoporosis was assessed in a large (7705 patients) multinational, placebo-controlled trial. Duration of treatment was 36 months, and 5129 postmenopausal women were exposed to raloxifene (2557 received 60 mg/day, and 2572 received 120 mg/day). The incidence of all-cause mortality was similar among groups: 23 (0.9%) placebo, 13 (0.5%) EVISTA-treated (raloxifene 60 mg), and 28 (1.1%) raloxifene 120 mg women died. Therapy was discontinued due to an adverse reaction in 10.9% of EVISTA-treated women and 8.8% of placebo-treated women.

Venous Thromboembolism: The most serious adverse reaction related to EVISTA was VTE (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis). During an average of study-drug exposure of 2.6 years, VTE occurred in about 1 out of 100 patients treated with EVISTA. Twenty-six EVISTA-treated women had a VTE compared to 11 placebo-treated women, the hazard ratio was 2.4 (95% confidence interval, 1.2, 4.5), and the highest VTE risk was during the initial months of treatment.

Common adverse reactions considered to be related to EVISTA therapy were hot flashes and leg cramps. Hot flashes occurred in about one in 10 patients on EVISTA and were most commonly reported during the first 6 months of treatment and were not different from placebo thereafter. Leg cramps occurred in about one in 14 patients on EVISTA.

Placebo-Controlled Osteoporosis Prevention Clinical Trials—The safety of raloxifene has been assessed primarily in 12 Phase 2 and Phase 3 studies with placebo, estrogen, and estrogen-progestin therapy control groups. The duration of treatment ranged from 2 to 30 months, and 2036 women were exposed to raloxifene (371 patients received 10 to 50 mg/day, 828 received 60 mg/day, and 837 received from 120 to 600 mg/day).

Therapy was discontinued due to an adverse reaction in 11.4% of 581 EVISTA-treated women and 12.2% of 584 placebo-treated women. Discontinuation rates due to hot flashes did not differ significantly between EVISTA and placebo groups (1.7% and 2.2%, respectively).

Common adverse reactions considered to be drug-related were hot flashes and leg cramps. Hot flashes occurred in about one in four patients on EVISTA versus about one in six on placebo. The first occurrence of hot flashes was most commonly reported during the first 6 months of treatment.

Table 1 lists adverse reactions occurring in either the osteoporosis treatment or in five prevention placebo-controlled clinical trials at a frequency $\geq 2.0\%$ in either group and in more EVISTA-treated women than in placebo-treated women. Adverse reactions are shown without attribution of causality. The majority of adverse reactions occurring during the studies were mild and generally did not require discontinuation of therapy.

Table 1: Adverse Reactions Occurring in Placebo-Controlled Osteoporosis Clinical Trials at a Frequency $\geq 2.0\%$ and in More EVISTA-Treated (60 mg Once Daily) Women than Placebo-Treated Women^a

	Treatment		Prevention	
	EVISTA N=2557 %	Placebo N=2576 %	EVISTA N=581 %	Placebo N=584 %
<i>Body as a Whole</i>				
Infection	A	A	15.1	14.6
Flu Syndrome	13.5	11.4	14.6	13.5
Headache	9.2	8.5	A	A
Leg Cramps	7.0	3.7	5.9	1.9
Chest Pain	A	A	4.0	3.6
Fever	3.9	3.8	3.1	2.6
<i>Cardiovascular System</i>				
Hot Flashes	9.7	6.4	24.6	18.3
Migraine	A	A	2.4	2.1
Syncope	2.3	2.1	B	B
Varicose Vein	2.2	1.5	A	A
<i>Digestive System</i>				
Nausea	8.3	7.8	8.8	8.6
Diarrhea	7.2	6.9	A	A
Dyspepsia	A	A	5.9	5.8
Vomiting	4.8	4.3	3.4	3.3
Flatulence	A	A	3.1	2.4
Gastrointestinal Disorder	A	A	3.3	2.1
Gastroenteritis	B	B	2.6	2.1

(Table 1 continued in next column)

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(Table 1 continued here)

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	Treatment		Prevention	
	EVISTA N=2557 %	Placebo N=2576 %	EVISTA N=581 %	Placebo N=584 %
<i>Metabolic and Nutritional</i>				
Weight Gain	A	A	8.8	6.8
Peripheral Edema	5.2	4.4	3.3	1.9
<i>Musculoskeletal System</i>				
Arthralgia	15.5	14.0	10.7	10.1
Myalgia	A	A	7.7	6.2
Arthritis	A	A	4.0	3.6
Tendon Disorder	3.6	3.1	A	A
<i>Nervous System</i>				
Depression	A	A	6.4	6.0
Insomnia	A	A	5.5	4.3
Vertigo	4.1	3.7	A	A
Neuralgia	2.4	1.9	B	B
Hypesthesia	2.1	2.0	B	B
<i>Respiratory System</i>				
Sinusitis	7.9	7.5	10.3	6.5
Rhinitis	10.2	10.1	A	A
Bronchitis	9.5	8.6	A	A
Pharyngitis	5.3	5.1	7.6	7.2
Cough Increased	9.3	9.2	6.0	5.7
Pneumonia	A	A	2.6	1.5
Laryngitis	B	B	2.2	1.4
<i>Skin and Appendages</i>				
Rash	A	A	5.5	3.8
Sweating	2.5	2.0	3.1	1.7
<i>Special Senses</i>				
Conjunctivitis	2.2	1.7	A	A
<i>Urogenital System</i>				
Vaginitis	A	A	4.3	3.6
Urinary Tract Infection	A	A	4.0	3.9
Cystitis	4.6	4.5	3.3	3.1
Leukorrhea	A	A	3.3	1.7
Uterine Disorder ^{b,c}	3.3	2.3	A	A
Endometrial Disorder ^b	B	B	3.1	1.9
Vaginal Hemorrhage	2.5	2.4	A	A
Urinary Tract Disorder	2.5	2.1	A	A

^a A: Placebo incidence greater than or equal to EVISTA incidence; B: Less than 2% incidence and more frequent with EVISTA.

^b Includes only patients with an intact uterus: Prevention Trials: EVISTA, n=354, Placebo, n=364; Treatment Trial: EVISTA, n=1948, Placebo, n=1999.

^c Actual terms most frequently referred to endometrial fluid.

Breast Pain—Across all placebo-controlled trials, EVISTA was indistinguishable from placebo with regard to frequency and severity of breast pain and tenderness. EVISTA was associated with less breast pain and tenderness than reported by women receiving estrogens with or without added progestin.

Gynecologic Cancers—EVISTA-treated and placebo-treated groups had similar incidences of endometrial cancer and ovarian cancer.

Placebo-Controlled Trial of Postmenopausal Women at Increased Risk for Major Coronary Events (RUTH)—The safety of EVISTA (60 mg once daily) was assessed in a placebo-controlled multinational trial of 10,101 postmenopausal women (age range 55-92) with documented coronary heart disease (CHD) or multiple CHD risk factors. Median study drug exposure was 5.1 years for both treatment groups [see Clinical Studies]. Therapy was discontinued due to an adverse reaction in 25% of 5044 EVISTA-treated women and 24% of 5057 placebo-treated women. The incidence per year of all-cause mortality was similar between the raloxifene (2.07%) and placebo (2.25%) groups.

Adverse reactions reported more frequently in EVISTA-treated women than in placebo-treated women included peripheral edema (14.1% raloxifene versus 11.7% placebo), muscle spasms/leg cramps (12.1% raloxifene versus 8.3% placebo), hot flashes (7.8% raloxifene versus 4.7% placebo), venous thromboembolic events (2.0% raloxifene versus 1.4% placebo), and cholelithiasis (3.3% raloxifene versus 2.6% placebo) [see Clinical Studies].

Tamoxifen-Controlled Trial of Postmenopausal Women at Increased Risk for Invasive Breast Cancer (STAR)—The safety of EVISTA 60 mg/day versus tamoxifen 20 mg/day over 5 years was assessed in 19,747 postmenopausal women (age range 35-83 years) in a randomized, double-blind trial. As of 31 December 2005, the median follow-up was 4.3 years. The safety profile of raloxifene was similar to that in the placebo-controlled raloxifene trials [see Clinical Studies].

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