

# Topical Tamoxifen Benefits Cyclic Mastalgia

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SAN ANTONIO — Afimoxifene, a novel tamoxifen gel applied directly to the breasts, performed favorably as topical therapy for moderate to severe cyclic mastalgia in premenopausal women in a phase II clinical trial.

Although the topical antiestrogen's developer, ASCEND Therapeutics Inc., plans to seek an initial indication for cyclic mastalgia, there also is strong interest in developing afimoxifene as a treatment for male gynecomastia as well as for breast cancer chemoprevention, Dr. Amit Goyal said at the San Antonio Breast Cancer Symposium.

Afimoxifene is 4-hydroxytamoxifen, a highly potent metabolite of tamoxifen, in a proprietary hydroalcoholic gel. Its binding affinity for the alpha and beta estrogen receptors is two- to threefold greater than that of estradiol, explained Dr. Goyal, a surgical oncologist at Cardiff (Wales) University.

Oral tamoxifen, bromocriptine, danazol, and progestins have demonstrated efficacy in treating cyclic mastalgia; however, their systemic side effects ren-

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DR. GOYAL

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In contrast, transdermal afimoxifene is highly effective within the breast yet has very low systemic levels, thus reducing the risk of systemic toxicities, he continued.

In a pharmacokinetic study, 16 healthy premenopausal women applied 4 mg of afimoxifene to their breasts daily for 21 days.

At steady state, achieved after 2 weeks of therapy, mean plasma 4-hydroxytamoxifen levels were just 1/18 of those measured in 19 healthy controls taking 20 mg/day of oral tamoxifen.

Based upon those encouraging findings, Dr. Goyal and his coinvestigators next carried out the phase II trial involving 127 premenopausal women with moderate to severe cyclic mastalgia. They were randomized to placebo or either 2 mg or 4 mg of afimoxifene daily for four menstrual cycles.

Significant differences in efficacy between the 4-mg dose and placebo were documented after two cycles.

After four cycles, mean pain intensity measured on a visual analog scale for the 7 worst days per cycle was 64% lower in women on 4 mg/day of afimoxifene than in the placebo group.

Physician global assessments of breast nodularity and tenderness showed reductions of 70% and 67%, respectively,

relative to placebo. The 2-mg dose showed less robust albeit favorable trends on all end points, he continued.

In an interview, Dr. Goyal said he has had some success in using oral tamoxifen in men with gynecomastia, a condition for which the only established therapy at present is surgery.

Dr. Goyal said he plans to study topical afimoxifene for this condition in a placebo-controlled trial.

Chemoprevention of breast cancer is a particularly exciting potential application for the topical selective estrogen-receptor modulator.

"The main reason why some women and some physicians are reluctant to use oral tamoxifen, even though we know from the National Surgical Adjuvant Breast and Bowel Project study that it works, is because of side effects. If we can show afimoxifene works to prevent

breast cancer as well as oral tamoxifen, I think that would be an important advance," Dr. Goyal said.

That will require a large, lengthy, and costly phase III clinical trial, he noted.

The mastalgia trial was supported by ASCEND Therapeutics.

Dr. Goyal indicated that he has received research funds from the company but has no other financial involvement with ASCEND. ■

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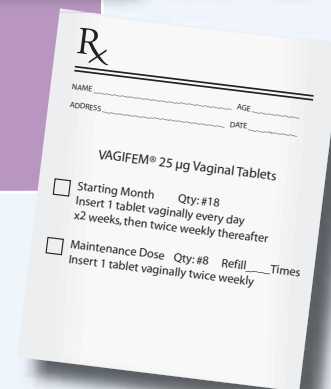


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#### Important Safety Information

#### ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent, case-controlled studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incident rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer-reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.

The three case-controlled studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be re-assessed, on at least a semiannual basis, to determine the need for continued therapy.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or reoccurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.

Other warnings include: induction of malignant neoplasms, gallbladder disease, effects similar to those caused by estrogen-progestogen oral contraceptives (such as thromboembolic disease, hepatic adenoma, elevated blood pressure, worsening of glucose tolerance), hypercalcemia, and rarely, trauma induced by the Vagifem® applicator.

In a placebo-controlled clinical trial, the most commonly reported adverse events included: headache (9%), abdominal pain (7%), upper respiratory tract infection (5%), genital moniliasis (5%), and back pain (7%).

The use of Vagifem® is contraindicated in women who exhibit one or more of the following: known or suspected breast carcinoma, known or suspected estrogen-dependent neoplasia (e.g., endometrial carcinoma), abnormal genital bleeding of unknown etiology, known or suspected pregnancy, porphyria, hypersensitivity to any Vagifem® constituents, active thrombophlebitis or thromboembolic disorders, or a past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast malignancy).

Please see brief summary of Prescribing Information on adjacent page.



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References: 1. Data on file. Development report 448-2794 Vagifem. Novo Nordisk Inc, Princeton, NJ.  
2. Data on file. Study report/VAG/PD/5/CAN. Novo Nordisk Inc, Princeton, NJ.  
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