

# Many Uninformed on External Anogenital Warts

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CHARLESTON, S.C. — Most clinicians counsel patients appropriately about the cause and prevention of external anogenital warts, but many—including some ob.gyns.—are unaware of the difference between oncogenic and wart-related human papillomavirus types, Zsakeba Henderson, M.D., reported in a poster at the annual meeting of the Infec-

tious Diseases Society for Obstetrics and Gynecology.

Of 4,305 clinicians who responded to a 2004 survey, 90% said they have diagnosed anogenital warts in patients. Of the ob.gyns. who responded, 96% have diagnosed anogenital warts in patients, 97% tell patients the warts are sexually transmitted, 97% tell patients that their sex partners can acquire the warts, 96% tell patients they may have been infected long ago, and 86% tell patients not much is

known about the duration of human papillomavirus (HPV) infection, said Dr. Henderson of the Centers for Disease Control and Prevention, Atlanta.

Also, 86% of the ob.gyns. said they discuss ways to prevent HPV transmission, and 81% usually or always ask about sexual behaviors to assess risk.

As for recommended methods for preventing transmission, 90% recommend condoms, 79% recommend monogamy, 61% recommend avoiding contact with

warts, and 43% recommend abstinence.

Of the respondents, 89% knew that HPV causes anogenital warts, but only 70% knew that HPV types associated with cancer differ from those associated with warts, Dr. Henderson said in an interview.

Although ob.gyns. are doing better than the overall survey population with regard to knowledge about oncogenic vs. wart-related HPV types (48% overall knew cancer- and wart-related types differ), 44% of ob.gyns. (38% overall), knew warts do not increase the risk of cancer at the wart site.

Of particular concern is the relationship between clinician knowledge of how HPV types differ and recommendations for Pap testing. A total of 87% of the ob.gyns. who don't know that oncogenic and wart-related HPV types differ and 78% of those who do know they differ recommend prompt Pap smears in patients presenting with warts. And 57% of those who don't know, and 47% of those who do know recommend more frequent Pap smears.

"It really didn't matter what their knowledge was—about half are recommending more frequent Pap smears in patients with warts, which is not in accordance with current clinical guidelines," Dr. Henderson said.

Anecdotal speaking, some respondents recommend Pap smears because of concerns about increased risk for HPV exposure, but there is no evidence that prompt or more frequent Pap testing is warranted in patients with anogenital warts, she added.

Also of concern based on the survey responses is that while most ob.gyns. are counseling patients appropriately about the cause and prevention of anogenital warts, they also reported many barriers to counseling, including difficulty dealing with patients' emotional and relationship issues, inadequate reimbursement for patient counseling, difficulty motivating patients to adopt prevention measures, and lack of time for patient counseling. Such barriers were reported by more than half of the respondents.

The findings of this survey, which are still being analyzed, will be used to develop training materials to promote appropriate counseling methods, Dr. Henderson noted.



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(cevimeline hydrochloride)

#### Brief Summary

Consult package insert for full prescribing information.

**INDICATIONS AND USAGE:** EVOXAC is indicated for the treatment of symptoms of dry mouth in patients with Sjögren's Syndrome.

**CONTRAINDICATIONS:** EVOXAC is contraindicated in patients with uncontrolled asthma, known hypersensitivity to cevimeline, and when miosis is undesirable, e.g., in acute iritis and in narrow-angle (angle-closure) glaucoma.

#### WARNINGS:

**Cardiovascular Disease:** EVOXAC may potentially alter cardiac conduction and/or heart rate. Patients with significant cardiovascular disease may potentially be unable to compensate for transient changes in hemodynamics or rhythm induced by EVOXAC. EVOXAC should be used with caution and under close medical supervision in patients with a history of cardiovascular disease evidenced by angina pectoris or myocardial infarction.

**Pulmonary Disease:** EVOXAC may potentially increase airway resistance, bronchial smooth muscle tone, and bronchial secretions. EVOXAC should be administered with caution and with close medical supervision to patients with controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease.

**Ocular:** Ophthalmic formulations of muscarinic agonists have been reported to cause visual blurring which may result in decreased visual acuity, especially at night and in patients with central lens changes, and to cause impairment of depth perception. Caution should be advised while driving at night or performing hazardous activities in reduced lighting.

#### PRECAUTIONS:

**General:** EVOXAC toxicity is characterized by an exaggeration of its parasympathomimetic effects. These may include: headache, visual disturbance, lacrimation, sweating, respiratory distress, gastrointestinal spasm, nausea, vomiting, diarrhea, atrioventricular block, tachycardia, bradycardia, hypotension, hypertension, shock, mental confusion, cardiac arrhythmia, and tremors.

EVOXAC should be administered with caution to patients with a history of nephrolithiasis or cholelithiasis. Contractions of the gallbladder or biliary smooth muscle could precipitate complications such as cholecystitis, cholangitis and biliary obstruction. An increase in the ureteral smooth muscle tone could theoretically precipitate renal colic or ureteral reflux in patients with nephrolithiasis.

**Information for Patients:** Patients should be informed that cevimeline may cause visual disturbances, especially at night, that could impair their ability to drive safely.

If a patient sweats excessively while taking cevimeline, dehydration may develop. The patient should drink extra water and consult a health care provider.

**Drug Interactions:** EVOXAC should be administered with caution to patients taking beta adrenergic antagonists, because of the possibility of conduction disturbances. Drugs with parasympathomimetic effects administered concurrently with cevimeline can be expected to have additive effects. EVOXAC might interfere with desirable antimuscarinic effects of drugs used concomitantly.

Drugs which inhibit CYP2D6 and CYP3A4 also inhibit the metabolism of cevimeline. EVOXAC should be used with caution in individuals known or suspected to be deficient in CYP2D6 activity, based on previous experience, as they may be at a higher risk of adverse events. In an *in vitro* study, cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 were not inhibited by exposure to cevimeline.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** Lifetime carcinogenicity studies were conducted in CD-1 mice and F-344 rats. A statistically significant increase in the incidence of adenocarcinomas of the uterus was observed in female rats that received cevimeline at a dosage of 100 mg/kg/day (approximately 8 times the maximum human exposure based on comparison of AUC data). No other significant differences in tumor incidence were observed in either mice or rats.

EVOXAC exhibited no evidence of mutagenicity or clastogenicity in a battery of assays that included an Ames test, an *in vitro* chromosomal aberration study in mammalian cells, a mouse lymphoma study in L5178Y cells, or a micronucleus assay conducted *in vivo* in ICR mice.

EVOXAC did not adversely affect the reproductive performance or fertility of male Sprague-Dawley rats when administered for 63 days prior to mating and throughout the period of mating at dosages up to 45 mg/kg/day (approximately 5 times the maximum recommended dose for a 60 kg human following normalization of the data on the basis of body surface area estimates). Females that were treated with cevimeline at dosages up to 45 mg/kg/day from 14 days prior to mating through day seven of gestation exhibited a statistically significantly smaller number of implantations than did control animals.

**Pregnancy:** Pregnancy Category C.

EVOXAC was associated with a reduction in the mean number of implantations when given to pregnant Sprague-Dawley rats from 14 days prior to mating through day seven of gestation at a dosage of 45 mg/kg/day (approximately 5 times the maximum recommended dose for a 60 kg human when compared on the basis of body surface area estimates). This effect may have been secondary to maternal toxicity. There are no adequate and well-controlled studies in pregnant women. EVOXAC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether this drug is secreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from EVOXAC, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use:** Although clinical studies of cevimeline included subjects over the age of 65, the numbers were not sufficient to determine whether they respond differently from younger subjects. Special care should be exercised when cevimeline treatment is initiated in an elderly patient, considering the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in the elderly.

**ADVERSE REACTIONS:** EVOXAC was administered to 1777 patients during clinical trials worldwide, including Sjögren's patients and patients with other conditions. In placebo-controlled Sjögren's studies in the U.S., 320 patients received cevimeline doses ranging from 15 mg tid to 60 mg tid, of whom 93% were women and 7% were men. Demographic distribution was 90% Caucasian, 5% Hispanic, 3% Black, and 2% of other origin. In these studies, 14.6% of patients discontinued treatment with cevimeline due to adverse events.

The following adverse events associated with muscarinic agonism were observed in the clinical trials of cevimeline in Sjögren's syndrome patients:

Adverse Event	Cevimeline 30 mg (tid) n = 533	Placebo (tid) n = 164	Adverse Event	Cevimeline 30 mg (tid) n = 533	Placebo (tid) n = 164
Excessive Sweating	18.7%	2.4%	Urinary Frequency	0.9%	1.8%
Nausea	13.8%	7.9%	Asthenia	0.5%	0.0%
Rhinitis	11.2%	5.4%	Flushing	0.3%	0.6%
Diarrhea	10.3%	10.3%	Polyuria	0.1%	0.6%
Excessive Salivation	2.2%	0.6%			

\*n is the total number of patients exposed to the dose at any time during the study

#### EVOXAC® Capsules (cevimeline hydrochloride)

In addition, the following adverse events (≥3% incidence) were reported in the Sjögren's clinical trials:

Adverse Event	Cevimeline 30 mg (tid) n = 533	Placebo (tid) n = 164	Adverse Event	Cevimeline 30 mg (tid) n = 533	Placebo (tid) n = 164
Headache	14.4%	20.1%	Conjunctivitis	4.3%	3.6%
Sinusitis	12.3%	10.9%	Dizziness	4.1%	7.3%
Upper Respiratory Tract Infection	11.4%	9.1%	Bronchitis	4.1%	1.2%
Dyspepsia	7.8%	8.5%	Arthralgia	3.7%	3.0%
Abdominal Pain	7.6%	6.7%	Surgical Intervention	3.3%	1.2%
Urinary Tract Infection	6.1%	3.0%	Fatigue	3.3%	3.0%
Coughing	6.1%	3.0%	Pain	3.3%	3.0%
Pharyngitis	5.2%	5.4%	Skeletal Pain	2.8%	1.8%
Vomiting	4.6%	2.4%	Insomnia	2.4%	1.2%
Injury	4.5%	2.4%	Hot Flashes	2.4%	0.0%
Back Pain	4.5%	4.2%	Rigors	1.3%	1.2%
Rash	4.3%	6.0%	Anxiety	1.3%	1.2%

\*n is the total number of patients exposed to the dose at any time during the study

The following events were reported in Sjögren's patients at incidences of <3% and ≥1%: constipation, tremor, abnormal vision, hypertonia, peripheral edema, chest pain, myalgia, fever, anorexia, eye pain, earache, dry mouth, vertigo, salivary gland pain, pruritus, influenza-like symptoms, eye infection, post-operative pain, vaginitis, skin disorder, depression, hiccup, hyporeflexia, infection, fungal infection, sialoadenitis, otitis media, erythematous rash, pneumonia, edema, salivary gland enlargement, angina, gastroesophageal reflux, eye abnormality, migraine, tooth disorder, epistaxis, flatulence, toothache, ulcerative stomatitis, anemia, hyposthesia, cystitis, leg cramps, abscess, erection, moniliasis, palpitation, increased amyase, xerophthalmia, allergic reaction.

The following events were reported rarely in treated Sjögren's patients (<1%): Causal relation is unknown:

**Body as a Whole Disorders:** aggravated allergy, precordial chest pain, abnormal crying, hematoma, leg pain, edema, periorbital edema, activated pain trauma, pallor, changed sensation to temperature, weight decrease, weight increase, choking, mouth edema, syncope, malaise, face edema, substernal chest pain

**Cardiovascular Disorders:** abnormal ECG, heart disorder, heart murmur, aggravated hypertension, hypotension, arrhythmia, extrasystoles, T wave inversion, tachycardia, supraventricular tachycardia, angina pectoris, myocardial infarction, pericarditis, pulmonary embolism, peripheral ischemia, superficial phlebitis, purpura, deep thrombophlebitis, vascular disorder, vasculitis, hypertension

**Digestive Disorders:** appendicitis, increased appetite, ulcerative colitis, diverticulitis, duodenitis, dysphagia, enterocolitis, gastric ulcer, gastritis, gastroenteritis, gastrointestinal hemorrhage, gingivitis, glossitis, rectum hemorrhage, hemorrhoids, ileus, irritable bowel syndrome, melena, mucositis, esophageal stricture, esophagitis, oral hemorrhage, peptic ulcer, periodontal destruction, rectal disorder, stomatitis, tenesmus, tongue discoloration, tongue disorder, geographic tongue, tongue ulceration, dental caries

**Endocrine Disorders:** increased glucocorticoids, goiter, hypothyroidism

**Hematologic Disorders:** thrombocytopenic purpura, thrombocytopenia, thrombocytopenia, hypochromic anemia, eosinophilia, granulocytopenia, leukopenia, leukocytosis, cervical lymphadenopathy, lymphadenopathy

**Liver and Biliary System Disorders:** cholelithiasis, increased gamma-glutamyl transferase, increased hepatic enzymes, abnormal hepatic function, viral hepatitis, increased serum glutamate oxaloacetate transaminase (SGOT) (also called AST-aspartate aminotransferase), increased serum glutamate pyruvate transaminase (SGPT) (also called ALT-alanine aminotransferase)

**Metabolic and Nutritional Disorders:** dehydration, diabetes mellitus, hypercalcemia, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, thirst

**Musculoskeletal Disorders:** arthritis, aggravated arthritis, arthropathy, femoral head avascular necrosis, bone disorder, bursitis, costochondritis, plantar fasciitis, muscle weakness, osteomyelitis, osteoporosis, synovitis, tendinitis, tenosynovitis

**Neoplasms:** basal cell carcinoma, squamous carcinoma

**Nervous Disorders:** carpal tunnel syndrome, coma, abnormal coordination, dysesthesia, dyskinesia, dysphonia, aggravated multiple sclerosis, involuntary muscle contractions, neuralgia, neuropathy, paresthesia, speech disorder, agitation, confusion, depersonalization, aggravated depression, abnormal dreaming, emotional lability, manic reaction, paranoia, somnolence, abnormal thinking, hyperkinesia, hallucination

**Miscellaneous Disorders:** fall, food poisoning, heat stroke, joint dislocation, post-operative hemorrhage

**Resistance Mechanism Disorders:** cellulitis, herpes simplex, herpes zoster, bacterial infection, viral infection, genital moniliasis, sepsis

**Respiratory Disorders:** asthma, bronchospasm, chronic obstructive airway disease, dyspnea, hemoptysis, laryngitis, nasal ulcer, pleural effusion, pleurisy, pulmonary congestion, pulmonary fibrosis, respiratory disorder

**Rheumatologic Disorders:** aggravated rheumatoid arthritis, lupus erythematosus rash, lupus erythematosus syndrome

**Skin and Appendages Disorders:** acne, alopecia, burn, dermatitis, contact dermatitis, lichenoid dermatitis, eczema, furunculosis, hyperkeratosis, lichen planus, nail discoloration, nail disorder, onychia, onychomycosis, paronychia, photosensitivity reaction, rosacea, sderoderma, seborrhea, skin discoloration, dry skin, skin exfoliation, skin hypertrophy, skin ulceration, urticaria, verruca, bullous eruption, cold clammy skin

**Special Senses Disorders:** deafness, decreased hearing, motion sickness, parosmia, taste perversion, blepharitis, cataract, corneal opacity, corneal ulceration, diplopia, glaucoma, anterior chamber eye hemorrhage, keratitis, keratoconjunctivitis, mydriasis, myopia, photopsia, retinal deposits, retinal disorder, scleritis, vitreous detachment, tinnitus

**Urogenital Disorders:** epididymitis, prostatic disorder, abnormal sexual function, amenorrhea, female breast neoplasm, malignant female breast neoplasm, female breast pain, positive cervical smear test, dysmenorrhea, endometrial disorder, intermenstrual bleeding, leukorrhea, menorrhagia, menstrual disorder, ovarian cyst, ovarian disorder, genital pruritus, uterine hemorrhage, vaginal hemorrhage, atrophic vaginitis, albuminuria, bladder disorder, increased blood urea nitrogen, dysuria, hematuria, micturition disorder, nephrosis, nocturia, increased non-protein nitrogen, pyelonephritis, renal calculus, abnormal renal function, renal pain, stranguary, urethral disorder, abnormal urine, urinary incontinence, decreased urine flow, pyuria

In one subject with lupus erythematosus receiving concomitant multiple drug therapy, a highly elevated ALT level was noted after the fourth week of cevimeline therapy. In two other subjects receiving cevimeline in the clinical trials, very high AST levels were noted. The significance of these findings is unknown.

Additional adverse events (relationship unknown) which occurred in other clinical studies (patient population different from Sjögren's patients) are as follows:

cholinergic syndrome, blood pressure fluctuation, cardiomegaly, postural hypotension, aphasia, convulsions, abnormal gait, hyperesthesia, paralysis, abnormal sexual function, enlarged abdomen, change in bowel habits, gum hyperplasia, intestinal obstruction, bundle branch block, increased creatine phosphokinase, electrolyte abnormality, glycosuria, gout, hyperkalemia, hyperproteinemia, increased lactic dehydrogenase (LDH), increased alkaline phosphatase, failure to thrive, abnormal platelets, aggressive reaction, amnesia, apathy, delirium, delusion, dementia, illusion, impotence, neurosis, paranoid reaction, personality disorder, hyperhemoglobinemia, apnea, atelectasis, yawning, oliguria, urinary retention, distended vein, lymphocytosis

**Post-Marketing Adverse Events:** cholecystitis

**MANAGEMENT OF OVERDOSE:** Management of the signs and symptoms of acute overdose should be handled in a manner consistent with that indicated for other muscarinic agonists: general supportive measures should be instituted. If medically indicated, atropine, an anti-cholinergic agent may be of value as an antidote for emergency use in patients who have had an overdose of cevimeline. If medically indicated, epinephrine may also be of value in the presence of severe cardiovascular depression or bronchoconstriction. It is not known if cevimeline is dialyzable.

**DOSE AND ADMINISTRATION:** The recommended dose of cevimeline hydrochloride is 30 mg taken three times a day. There is insufficient safety information to support doses greater than 30 mg tid. There is also insufficient evidence for additional efficacy of cevimeline hydrochloride at doses greater than 30 mg tid.

#### Rx Only

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**References:** 1. Data on file, Daichi Pharmaceutical Corporation, NDA #20-989. 2. Fife RS, Chase WF, Dore RK, et al. Cevimeline for the treatment of xerostomia in patients with Sjögren syndrome: a randomized trial. *Arch Intern Med.* 2002;162:1293-1300. 3. Petrone D, Cordemii J, Fife R, Gluck O, Cohen S, Dalgin P. A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. *Arthritis Rheum.* 2002;46:748-754.

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