MRI Is More Accurate for Finding Breast Cancers

BY BRUCE K. DIXON Chicago Bureau

CHICAGO — Magnetic resonance imaging done prior to treatment for breast cancer can reveal cancer missed by mammography and ultrasonography, yielding more accurate information about the extent of disease, according to a poster presented at the annual meeting of the Radiological Society of North America.

We found almost 29% more cancer by



EVOXAC® Capsules (cevimeline hydrochloride)

Brief Summary Consult package insert for full prescribing information.

INDICATIONS AND USAGE: Cevimeline is indicated for the treatment of symptoms of dry mouth in patients with

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

WARNINGS: Cardiovascular Disease: Cevimeline can potentially alter cardiac conduction and/or heart rate. Patients with sig-mificant 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: Cevimeline can potentially increase airway resistance, bronchial smooth muscle tone, and bronchial secretions. Cevimeline should be administered with caution and with close medical supervision to patients with controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease. *Coular:* Ophthalmic formulations of muscarinic agonists have been reported to cause visual blurring which may result in decreased visual acuity, escalial 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 activi-ties in reduced lighting. PBECAITIONS: PRECAUTIONS:

General: Cevimeline 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 tremore.

consolin, can be a mything, and information to patients with a history of nephrolithiasis or cholelithiasis. Contractions of the galibladder 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.

water and consult a health care provider. Drug Interactions: Cevimeline 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. Cevimeline might interfere with desirable antimuscarine effects of drugs used concomitantly. Drugs which inhibit CYP2D6 and CYP3A3/4 also inhibit the metabolism of cevimeline. Cevimeline 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 ware not inhibited by exposure to cevimeline.

Carcinogenesis, Mutagenesis and Impairment of Fetility: 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 inci-dence were observed in either mice or rats.

Cevimeline 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.

Gevimeline 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.

Pregnancy: Pregnancy Category C. Cevimeline 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. Cevimeline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During Mathers: It is not known whather 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 EV0XAC® 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.

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 exer-cised 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:** Cevimeline 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 doese 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 accorded with muscardic aponiem were observed in the clinical trials for eximpling the following 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 Nausea Rhinitis Diarrhea Excessive Salivation	18.7% 13.8% 11.2% 10.3% 2.2%	2.4% 7.9% 5.4% 10.3% 0.6%	Urinary Frequency Asthenia Flushing Polyuria	0.9% 0.5% 0.3% 0.1%	1.8% 0.0% 0.6% 0.6%

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

References: 1. Data on file, Daiichi Pharmaceutical Corporation. NDA #20-989. 2. Fife RS, Chase WF, Dore RK, I. Cevimeline for the treatment of xerostomia in patients with Sjögren syndrome: a randomized trial. Arch arn Med. 2002;162:1293-1300. 3. Petrone D, Condemi JJ, 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.

doing the magnetic resonance imaging before surgery or radiation therapy than we thought we had diagnosed with standard mammography, ultrasound, and clinical examination," said Dr. Gillian Newstead of the University of Chicago in an interview. Identifying more cancer up front will influence the course of treatment and ideally produce a more positive long-term outcome, she said.

The researchers classified newly diagnosed breast cancers in 140 women (mean age 56.5 years), of which 53.5% were invasive ductal carcinoma (IDC) with extensive intraductal component (EIC). Additional lesions identified by MRI in 40 women included 26 in the same quadrant, 11 in a different quadrant, and 3 in the contralateral breast. Specifically, 23 of the lesions were identified as IDC with EIC, 6 as IDC, 6 as ductal carcinoma in situ, and 5 as invasive lobular cancer.

Clinical management was changed in 31 of the 40 women: 20 underwent more ex-

In addition, the following Adverse Event	adverse events (; Cevimeline 30 mg (tid) 	≥3% incidence Placebo (tid) n = 164	e) were reported in the Sjög Adverse Event	ren's clinical trials: Cevimeline 3D 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			Bronchitis	4.1%	1.2%
Tract Infection	11.4%	9.1%	Arthralgia	3.7%	1.8%
Dyspepsia	7.8%	8.5%	Surgical Intervention	3.3%	3.0%
Abdominal Pain	7.6%	6.7%	Fatique	3.3%	1.2%
Urinary Tract Infection	6.1%	3.0%	Pain	3.3%	3.0%
Couahina	6.1%	3.0%	Skeletal Pain	2.8%	1.8%
Pharyngitis	5.2%	5.4%	Insomnia	2.4%	1.2%
Vomítina	4.6%	2.4%	Hot Flushes	2.4%	0.0%
Injury	4.5%	2.4%	Rigors	1.3%	1.2%
Back Pain	4.5%	4.2%	Anxiety	1.3%	1.2%
Rash	4.3%	6.0%	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 43% and 21%: 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, trupal infection, sialoadanitis, ottis media, erythematous rash, pneumonia, edema, salivary gland enlargement, allergy, gastroasophageal reflux, eye abnormality, migraine, tooth disorder, epistaxis, flatulence, toothache, ulcerative stomatitis, anemia, hypoesthesia, cystitis, leg cramps, abscass, encutation, monihasis, palpitation, increased amylase, xerophthalmia, altergic reaction.

auscess, erocuador, monimais, paphatori, increaso amyaes, exoprimainte, ane ge reactori. The following events were reported rarely in treade Sjögrer's patients (<m/s, 'Causa' 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, substemal chest pain Cardiovascular Disorders: abnormal EGS, heart itsorder, heart murrur, agravated hypertension, hypotension, arrhythmia, extrasystoles, t wave inversion, tachycardia, supraventricular tachycardia, angina pectoris, myocardial infarction, pericarditis, pulmonary embolism, perpheral ischemia, superficial phlebitis, purpura, deep thrombo-phlebitis, vascular disorder, vascullits, hypertension

Digestive Disorder: appendicitis, increased appdite, ulcerative colitis, diverticulitis, duodenitis, dysphagia, entero colitis, gastric ulcer, gastritis, gastroenteritis, gastrointestinal hemorrhage, gingivitis, glossitis, rectum hemorr-rhage, hemorrhoids, lieus, irritable bowel syndrome, melena, mucositis, esophageal stricture, esophagitis, oral hemorrhage, peptic ulcer, periodontal destruction; or cella disorder, stomatilis, tenesmus, tongue discoloration, tongue disorder, geographic tongue, tongue ulceration, dental caries

Endocrine Disorders: increased glucocorticoids, goiter, hypothyroidism

Hematologic Disorders: thrombocytopenic purpira, thrombocythemia, thrombocytopenia, hypochromic anemia, eosinophilia, granulocytopenia, leucopenia, leukosytosis, cervical lymphadenopathy, lymphadenopathy Liver and Biliary System Disorders: cholelthiais, increased gamma-glutamy transferase, increased hepatic enzymes, abnormal hepatic function, viral hepatilis, increased gamma-glutamy transferase, increased hepatic (also called AST-aspartate aminotransferase), increased serum glutamate oxaloacetic 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, hyp glycemia, hyperlipemia, 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,

ns: basal cell carcinoma, squamous carcino

Nervous Disorders: carpal tunnel syndrome, cona, abnormal coordination, dysesthesia, dyskinesia, dysphonia aggravated multiple sclerosis, involuntary muscle contractions, neuralgia, neuropathy, paresthesia, speech dis-order, agitation, confusion, depersonalization, aggravated depression, abnormal dreaming, emotional lability, manic reaction, paroniria, 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 asis, sepsis

Respiratory Disorders: asthma, bronchospasm, chronic obstructive airway disease, dyspnea, hemoptysis, laryn-gibs, 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 Disarders: acne, alopecia, burn, dermatitis, contact dermatitis, lichenoid dermatitis, eczema, furunculosis, hyperkeratosis, lichen plarus, nail discoloration, nail discorder, onychia, onychomyco paronychia, photosensitivity reaction, rosacea, sderoderma, seborrhea, skin discoloration, dry skin, skin ekoliation, skin hypertrophy, skin ulceration, uritaria, verruca, bullous eruption, cold clammy skin

exfoliation, skin hypertrophy, skin ulceration, urtitaria, verruca, bullous eruption, cold clammy skin Special Senses Disorders: deafness, decreased haring, motion sickness, parosmia, taste perversion, blepharitis, cataract, conneal opacity, corneal ulceration, diplopia, glaucoma, anterior chamber eye hemorrhage, keraths, kerato-conjunctivitis, mydriasis, myopia, photopsia, retinit deposits, retinal disorder, soleritis, vitreous detachment, tinnitus, Iurogenital Disorders: ejoldymitis, prostatic disorder, anormal sexual function, amenorrhea, female breast neoplasm, malignant female breast neoplasm, female breast pain, positive cervical smear test, dysmenorrhea, endometrial disorder, intermenstrual bleeding, leakorthea, menorrhagia, etrophic vaginitis, albuminuria, bladder dis-comfort, increased blood urea nitrogen, dysuina, lematuria, miciturition disorder, nephrosis, nocuriar, increased nonprotein mitorgen, pyelonephritis, renal calculus, abnormal rena function, renal pain, strangury, urethral disorder, order, abnormal unine, urinary incontinence, decreased urine flow, pyuria In one subiect with luous exvihematous: receivino concomitant multipide druo therany, a biohly elevated ALT level.

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 tri als, 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: 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 bhanch block, increased creatine phosphokinase, electrolyte abnormality, glycosuria, gout, hyperkalemia, hyperpoteniemia, increased lactic dehydrogenase (LDH), increased alkaline phosphatase, failure to firive, abnormal platelets, aggressive reaction, amnesia, apathy, delirium, delu-sion, dementi, illusion, impotence, neurois, paanoli reaction, personality disorder, hyperhemoglobinemia, apnea, atelectasis, yawning, oliguria, urinary retention, distended vein, lymphocytosis

Post-Marketing Adverse Events: cholecystitis

Prost-marketing Auverse Events: cholecystils MANAGEMENT OF OVERDOSE: Management of the signs and symptoms of acute overdosage should be landled 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 DOSAGE 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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EVOXAC is a registered trademark of Dalichi Pharmaceutical Co., Ltd. © 2005 Dalichi Pharmaceutical Corporation EV-201-242 Printed in USA 8/05 tensive surgery, 8 were converted from breast conservation to mastectomy, and 3 were given additional neoadjuvant chemotherapy.

Although mammography and ultrasonography are still the primary imaging methods for breast cancer screening and diagnosis, the higher soft tissue contrast and gadolinium-enhanced images obtained by MRI improve the sensitivity of detection and allow more accurate evaluation of the cancer. Most breast cancers enhance rapidly after IV injection of contrast agents because of higher vascularity and the angiogenic factors that produce an increase in capillary permeability, changes in osmolar pressure, and expansion of the interstitial space, the investigators said.



'We see lesions that may not show up on mammograms, especially in dense breasts.'

DR. NEWSTEAD

"The MR is looking at the new blood vessel growth, or angiogenesis, in tumors and it's a functional test in that sense, so we see lesions that may not show up on mammograms, especially in dense breasts. And there are some tumors that grow in such a way that makes them more difficult to perceive on a mammogram," Dr. Newstead added.

"Patients underwent imaging in the prone position with the breasts gently immobilized within lateral compression plates. Contrast injection was made with IV administration of 0.1 mmol/kg gadodiamide followed by a 20-mL saline flush at the rate of 2.0 mL per second. MR images were acquired using a 1.5-T scanner with use of a dedicated breast coil," the investigators said. The resolution on the MRI machine was 1.6 mm.

Hospitals have been slow to assimilate MRI into clinical practice because there have been a lot of different techniques proposed by academic centers, Dr. Newstead said. "That's becoming less of an issue as our magnets are getting faster and we don't have to make as many compromises; so I would say that any person with a fairly modern magnet and a modern breast coil should be able to achieve satisfactory resolution both spatially and temporally," she said.

MRI has found a home at the University of Chicago's breast imaging section, not only for pretreatment assessment but also to detect cancer recurrence post treatment and to screen high-risk women.

"Early detection of local recurrence improves long-term survival, but postoperative mammographic and ultrasound evaluation often is limited, especially in patients with dense, fibroglandular tissue and postsurgical or postradiation fibrosis," the authors wrote, noting that residual or recurrent tumor exhibits early enhancement.

Continued on following page

VTE Risk Tied to Metastatic Disease in Breast Ca

BY BRUCE JANCIN Denver Bureau

SAN ANTONIO — The incidence of venous thromboembolism in the year following breast cancer diagnosis is roughly 1%, Dr. Helen K. Chew reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

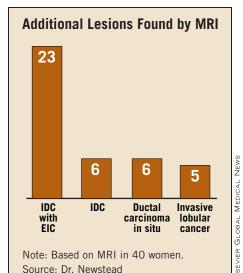
That's a lower figure than previously reported in some clinical trials. But the trials typically feature lengthy exclusion criteria and involve hundreds of patients, whereas Dr. Chew's data carry the authority of big numbers: to be exact, all 108,255 women with breast cancer diagnosed in California during a 4-year period and followed through the California Cancer Registry and California Patient Discharge Data set.

By far the strongest predictor of venous thromboembolism (VTE) in this cohort was the presence of metastatic disease at breast cancer diagnosis. It was associated with a 6.3-fold increased risk, compared

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"MR is a sensitive modality for detection of early recurrent tumor, and breast cancer recurrence must be differentiated from acute and subacute posttreatment changes. Most recurrent tumor, unlike unrecognized residual tumor, usually presents at least 2 years following breast conservation treatment. Normal parenchymal enhancement usually is diminished after breast irradiation. Recurrent tumor may therefore be readily visible in the postradiation breast," they said.

False-positive findings are not a problem with high-resolution MRI and correct procedure, according to Dr. Newstead. "When we find something on MR that wasn't seen before on mammography or ultrasound, typically we'll bring the patient back for a repeat ultrasound and mammogram. If we see something, we'll do a biopsy right then. But if we can't find anything [with conventional imaging]which happens in about 40% of our cases-and MR is the only finding, then we'll bring the patient back and repeat the MRI study. If it still looks worrisome, we'll go ahead and biopsy at the same time, so she only has to come back once," Dr. Newstead explained.



with patients who had localized cancer, said Dr. Chew, director of the breast cancer program at the University of California, Davis, cancer center.

The incidence of VTE was 0.6% in the first 6 months following breast cancer diagnosis and a cumulative 0.9% at the 12-month mark. It fell off thereafter such that the cumulative 2-year incidence was 1.2%.

In a multivariate analysis, regional disease at the time of breast cancer diagnosis—present in 31% of patients—was associated with a 2.2-fold increased risk of subsequent VTE, compared with localized disease, which was present in 61% of the women. Women age 65 or older had an 80% greater risk than those younger than 45.

The presence of a single comorbidity was associated with a 2.2-fold greater risk of VTE than in women with no comorbid conditions; patients with three comorbid conditions had a 3.3-fold increased risk, compared with those who had none. Women of Asian heritage were 70% less likely to experience VTE than whites. Patients who underwent major surgery were half as likely to develop VTE as those who didn't, although Dr. Chew suspects the association isn't causal and more likely reflects localized disease and overall good health. "Patients with metastatic disease generally wouldn't undergo breast cancer surgery," she noted.

Breast cancer histology wasn't predictive of VTE risk.

