

CLINICAL CAPSULES

Limiting Tunnel Widening in ACL Repair

A novel hamstring anterior cruciate ligament reconstruction technique that uses a shorter, more rigidly fixed graft prevents the tunnel widening that can lead to a bungee-cord effect following ACL repair.

Dr. Peter Fauno of Randers (Denmark) Central Hospital and colleagues randomly assigned 100 patients to undergo either the new technique using a transfemoral fixation implant with an interference screw in the tibial tunnel, or extracortical fixation in the femur with a bicortical screw and washer distal to the tibial tun-

nel. A total of 87 patients were available for assessment at 1-year follow-up.

Patients who underwent the new technique had a lower incidence of tunnel widening, compared with those in the conventional technique group (Arthroscopy 2005;21:1337-41.)

A total of 7 of 41 patients (17%) undergoing transfemoral fixation implantation with an interference screw in the tibial tunnel experienced femoral tunnel widening; 5 patients (12%) in that group experienced tibial tunnel widening.

By comparison, 20 of 46 patients (44%)

who received extracortical fixation had femoral tunnel widening; 16 patients (35%) in that group had tibial tunnel widening.

Despite the similarity in clinical outcome at 1 year and assuming tunnel widening has no clinical implications, Dr. Fauno believes the risk of tunnel widening should be kept as low as possible.

Vitamin D Beats Calcium for Bones

Vitamin D sufficiency appears to be more important for bone health than is high calcium intake, according to Laufey Steingrimsdottir, Ph.D., of the Public Health Institute of Iceland, Reykjavik, and associates.

Both nutrients are known to influence

calcium homeostasis, but the relative contributions of each haven't been studied before, they said (JAMA 2005;294:2336-41).

Vitamin D supplements should be recommended "when sun exposure and dietary sources are insufficient," Dr. Steingrimsdottir and associates said.

The researchers assessed the relative importance of calcium intake and serum levels of 25-hydroxyvitamin D for maintaining calcium homeostasis in a study of 944 healthy white adult residents of Iceland. The 491 women and 453 men were aged 30-85 years.

Most Icelanders take vitamin supplements or cod liver oil to supply vitamin D because there isn't sufficient sunshine there throughout the year for adequate biosynthesis of vitamin D. Most also have a relatively high calcium intake, chiefly through the consumption of dairy products. In this study, the mean intake of both vitamin D and calcium were well above recommended levels in all age groups, although there was great variation.

Vitamin D status was found to ensure ideal values for serum parathyroid hormone, a marker of bone health, even when calcium intake was not sufficient to maintain those PTH levels. In contrast, high calcium intake did not make up for decreased vitamin D.

In addition, mean serum ionized calcium levels, a more precise marker of calcium homeostasis and thus of bone health, were found to be dependent on serum 25-hydroxyvitamin D levels, but not on calcium intake.

"Our study indicates that as long as vitamin D status is secured by vitamin D, supplements or sufficient sunshine calcium intake levels of more than 800 mg [per day] may be unnecessary," the investigators noted.

Botox Effective for Tennis Elbow Pain

Botulinum toxin injections may provide short-term pain relief for patients with lateral epicondylitis, Chinese researchers have reported.

A randomized, placebo-controlled trial of botulinum toxin in 60 patients with lateral epicondylitis was conducted at Prince of Wales Hospital in Hong Kong. Dr. Shiu Man Wong and colleagues administered either a single 60-unit injection of botulinum toxin type A or an equivalent volume of normal saline to patients.

Baseline pain scores, using a 100-mm visual analog scale (VAS) of 65.5 mm at baseline, improved to a score of 25.4 mm at 4 weeks in patients receiving botulinum toxin. In controls, the VAS score was 66 mm at baseline and 51 mm at 4 weeks (Ann. Intern. Med. 2005;143:793-7).

Twelve weeks after injection, VAS scores were 23.5 mm for the study group and 43.5 mm for controls.

Mild paresis of the fingers was found at the 4-week check in four patients in the study group, with symptoms persisting in one patient through 12 weeks of follow-up. No patient in the placebo group developed finger paresis. Weak finger extension in the affected limb was noted in 10 patients who received botulinum toxin and in 6 patients in the placebo group.

There was no significant difference in grip strength between the two groups during the study period.

—Martha Kerr and Mary Ann Moon



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 Sjögren's Syndrome.

CONTRAINDICATIONS: Cevimeline 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: Cevimeline can 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: 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.

Caution: 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: 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 tremors.

Cevimeline 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: 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 antimuscarinic effects of drugs used concomitantly.

Drugs which inhibit CYP2D6 and CYP3A4 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 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.

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.

Cevimeline 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.

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.

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: 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 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, 14.0% 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	Placebo	Adverse Event	Cevimeline	Placebo
	30 mg (tid) n = 533	(tid) n = 164		30 mg (tid) n = 533	(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%	4.4%	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	Placebo	Adverse Event	Cevimeline	Placebo
	30 mg (tid) n = 533	(tid) n = 164		30 mg (tid) n = 533	(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%	1.8%
Abdominal Pain	7.6%	6.7%	Surgical Intervention	3.3%	3.0%
Urinary Tract Infection	6.1%	3.0%	Fatigue	3.3%	1.2%
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, hyperopia, 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, sialadenitis, otitis media, erythematous rash, pneumonia, edema, salivary gland enlargement, allergy, gastroesophageal reflux, eye abnormality, migraine, tooth disorder, epistaxis, flatulence, toothache, ulcerative stomatitis, anemia, hypoesthesia, cystitis, leg cramps, abscess, eruption, moniliasis, palpitation, increased amylase, 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 gluco-corticoids, goiter, hypothyroidism

Hematologic Disorders: thrombocytopenic purpura, thrombocytopenia, thrombocytopenia, hypochromic anemia, eosinophilia, granulocytopenia, leucopenia, 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, 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, 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, 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, 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, scleroderma, seborrhea, skin discoloration, dry skin, skin exfoliation, skin hypertrophy, skin ulceration, urticaria, verruca, bulbous 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 discomfort, increased blood urea nitrogen, dysuria, hematuria, micturition disorder, nephrosis, nocturia, increased nonprotein 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.

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

Distributed and Marketed by: Daiichi Pharmaceutical Corporation, Montvale, NJ 07645

Revised 6/2005 Printed in U.S.A.

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EV-201-242

Printed in USA

8/05

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