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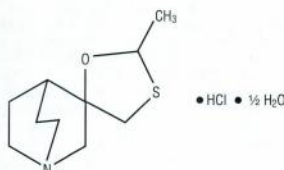


Daiichi-Sankyo

EVOXAC® Capsules (cevimeline hydrochloride)

DESCRIPTION

Cevimeline is cis-2'-methylspiro [1-azabicyclo [2.2.2] octane-3, 5'-[1,3] oxathiolane] hydrochloride, hydrate (2:1). Its empirical formula is $C_{10}H_{17}NOS \cdot HCl \cdot \frac{1}{2}H_2O$, and its structural formula is:



Cevimeline has a molecular weight of 244.79. It is a white to off white crystalline powder with a melting point range of 201 to 203°C. It is freely soluble in alcohol and chloroform, very soluble in water, and virtually insoluble in ether. The pH of a 1% solution ranges from 4.6 to 5.6. Inactive ingredients include lactose monohydrate, hydroxypropyl cellulose, and magnesium stearate.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Cevimeline is a cholinergic agonist which binds to muscarinic receptors. Muscarinic agonists in sufficient dosage can increase secretion of exocrine glands, such as salivary and sweat glands and increase tone of the smooth muscle in the gastrointestinal and urinary tracts.

Pharmacokinetics

Absorption: After administration of a single 30 mg capsule, cevimeline was rapidly absorbed with a mean time to peak concentration of 1.5 to 2 hours. No accumulation of active drug or its metabolites was observed following multiple dose administration. When administered with food, there is a decrease in the rate of absorption, with a fasting T_{max} of 1.53 hours and a T_{max} of 2.86 hours after a meal; the peak concentration is reduced by 17.3%. Single oral doses across the clinical dose range are dose proportional.

Distribution: Cevimeline has a volume of distribution of approximately 6L/kg and is <20% bound to human plasma proteins. This suggests that cevimeline is extensively bound to tissues; however, the specific binding sites are unknown.

Metabolism: Isozymes CYP2D6 and CYP3A4 are responsible for the metabolism of cevimeline. After 24 hours, 86.7% of the dose was recovered (16.0% unchanged, 44.5% as cis and trans-sulfoxide, 22.3% of the dose as glucuronic acid conjugate and 4% of the dose as N-oxide of cevimeline). Approximately 8% of the trans-sulfoxide metabolite is then converted into the corresponding glucuronic acid conjugate and eliminated. Cevimeline did not inhibit cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4.

Excretion: The mean half-life of cevimeline is 5+/-1 hours. After 24 hours, 84% of a 30 mg dose of cevimeline was excreted in urine. After seven days, 97% of the dose was recovered in the urine and 0.5% was recovered in the feces.

Special Populations: The effects of renal impairment, hepatic impairment, or ethnicity on the pharmacokinetics of cevimeline have not been investigated.

Clinical Studies

Cevimeline has been shown to improve the symptoms of dry mouth in patients with Sjögren's Syndrome.

A 6-week, randomized, double blind, placebo-controlled study was conducted in 75 patients (10 men, 65 women) with a mean age of 53.6 years (range 33-75). The racial distribution was Caucasian 92%, Black 1% and other 7%. The effects of cevimeline at 30 mg tid (90 mg/day) and 60 mg tid (180 mg/day) were compared to those of placebo. Patients were evaluated by a measure called global improvement, which is defined as a response of "better" to the question, "Please rate the overall condition of your dry mouth now compared with how you felt before starting treatment in this study." Patients also had the option of selecting "worse" or "no change" as answers. Seventy-six percent of the patients in the 30 mg tid group reported a global improvement in their dry mouth symptoms compared to 35% of the patients in the placebo group. This difference was statistically significant at $p=0.0043$. There was no evidence that patients in the 60 mg tid group had better global evaluation scores than the patients in the 30 mg tid group.

A 12-week, randomized, double-blind, placebo-controlled study was conducted in 197 patients (10 men, 187 women) with a mean age of 54.5 years (range 23-74). The racial distribution was Caucasian 91.4%, Black 3% and other 5.6%. The effects of cevimeline at 15 mg tid (45 mg/day) and 30 mg tid (90 mg/day) were compared to those of placebo. Statistically significant global improvement in the symptoms of dry mouth ($p=0.0004$) was seen for the 30 mg tid group compared to placebo, but not for the 15 mg group compared to placebo. Salivary flow showed statistically significant increases at both doses of cevimeline during the study compared to placebo.

A second 12-week, randomized, double-blind, placebo-controlled study was conducted in 212 patients (11 men, 201 women) with a mean age of 55.3 years (range 24-75). The racial distribution was Caucasian 88.7%, Black 1.9% and other 9.4%. The effects of cevimeline at 15 mg tid (45 mg/day) and 30 mg tid (90 mg/day) were compared to those of placebo. No statistically significant differences were noted in the patient global evaluations. However, there was a higher placebo response rate in this study compared to the aforementioned studies. The 30 mg tid group showed a statistically significant increase in salivary flow from pre-dose to post-dose compared to placebo ($p=0.0017$).

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.

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:

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, 14.6% 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
Excessive Sweating	18.7%	2.4%
Nausea	13.8%	7.9%
Rhinitis	11.2%	5.4%
Diarrhea	10.3%	10.3%
Excessive Salivation	2.2%	0.6%
Urinary Frequency	0.9%	1.8%
Asthenia	0.5%	0.0%
Flushing	0.3%	0.6%
Polyuria	0.1%	0.6%

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

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

Adverse Event	Cevimeline 30 mg (tid) n=533	Placebo (tid) n=164
Headache	14.4%	20.1%
Sinusitis	12.3%	10.9%
Upper Respiratory Tract Infection	11.4%	9.1%
Dyspepsia	7.8%	8.5%
Abdominal Pain	7.6%	6.7%
Urinary Tract Infection	6.1%	3.0%
Coughing	6.1%	3.0%
Pharyngitis	5.2%	5.4%
Vomiting	4.6%	2.4%
Injury	4.5%	2.4%
Back Pain	4.5%	4.2%
Rash	4.3%	6.0%
Conjunctivitis	4.3%	3.6%
Dizziness	4.1%	7.3%
Bronchitis	4.1%	1.2%
Arthralgia	3.7%	1.8%
Surgical Intervention	3.2%	3.0%
Fatigue	3.3%	1.2%
Pain	3.3%	3.0%
Skeletal Pain	2.8%	1.8%
Insomnia	2.4%	1.2%
Hot Flashes	2.4%	0.0%
Rhinitis	1.3%	1.2%
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 $\geq 1\%$: constipation, tremor, abnormal vision, hypertension, 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, eructation, 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 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, thrombocythemia, 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 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, 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, 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 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

The following adverse reaction has been identified during post-approval use of EVOXAC®. Because post-marketing adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Post-Marketing Adverse Events: Liver and Biliary System Disorders: cholecystitis

MANAGEMENT OF OVERDOSE

Management of the signs and symptoms of acute overdosage 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.

HOW SUPPLIED

EVOXAC® is available as white, hard gelatin capsules containing 30 mg of cevimeline hydrochloride. EVOXAC® capsules have a white opaque cap and a white opaque body. The capsules are imprinted with "EVOXAC" on the cap and "30 mg" on the body with a black bar above "30 mg". It is supplied in child resistant bottles of:

100 capsules (NDC 63395-201-13)

Store at 25°C (77°F) excursion permitted to 15°-30°C (59°-86°F)

B Only

Distributed and Marketed by:

Daiichi Sankyo Pharma Development, a Division of Daiichi Sankyo, Inc.
Edison, NJ 08837

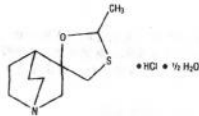
愛我津[®]膠囊 30公絲

EVOXAC[®] capsules 30 mg

本藥須由醫師處方使用

說明

Evoxac[®]膠囊含有主成份Cevimeline hydrochloride 30mg，為一種可與muscarinic receptors結合的cholinergic agonist。
Cevimeline hydrochloride化學名：cis-2'-methylspiro[1-azabicyclo[2.2.2]octane-3,5'-[1,3] oxathiolane]hydrochloride, hydrate(2:1)。
構造式：



分子式：C₁₀H₁₇NOS.HCl.½H₂O

分子量：244.79

性狀：白色至米白色的結晶粉末，熔點範圍為201°C-203°C，可完全溶於酒精與氯仿中。水溶性也很高，但不溶於乙醚。其1%溶液的pH值範圍為4.6至5.6。非活性成分包括lactose monohydrate、hydroxypropyl cellulose與magnesium stearate。

臨床藥理學

藥效學

cevimeline是一種可與muscarinic receptors結合的cholinergic agonist。足量的muscarinic agonist可增加唾液腺與汗腺等外分泌腺體的分泌，並可增加腸胃道與尿道中平滑肌的緊張度。

藥物動力學

吸收：服用一顆30mg膠囊後，cevimeline可被迅速吸收，達到最高濃度的平均時間為1.5到2小時。服用多劑之後，未發現其藥物活性成分或代謝物有蓄積情形。與食物一起服用時，吸收速率會降低，其空腹時的T_{MAX}為1.53小時，飯後服用時的T_{MAX}則為2.86小時；其最高濃度下降17.3%。在臨床劑量範圍內使用單一口服劑量，藥物血中濃度呈現與劑量呈正比關係。

分佈：cevimeline的分佈體積約為6L/kg，與人體血漿蛋白結合的比率小於20%，顯示cevimeline可廣泛地與組織結合，不過，還不清楚其結合位置。

代謝：同位標本(isozymes) CYP2D6與CYP3A3/4負責cevimeline的代謝。服用24小時之後，總劑量的86.7%會代謝掉(包括16.0%原型、44.5%為cis與trans-sulfoxide代謝物、22.3%與葡萄糖醛酸(glucuronic acid)結合、4%為cevimeline的N-氧化物)。

約有8%的trans-sulfoxide代謝物會轉化為葡萄糖醛酸(glucuronic acid)結合後排除。cevimeline不會抑制細胞色素P450(cytochrome P450)同位標本1A2、2A6、2C9、2C19、2D6、2E1與3A4的活性。

排泄：cevimeline的半衰期為5±1小時。服用24小時後，30mg cevimeline有84%會從尿液排泄。服用七天之後，於尿液有97%的劑量被回收，於糞便有0.5%的劑量被回收。

特殊族群：尚未針對腎、肝臟不良患者或不同種族間之病患進行cevimeline的藥物動力學研究。

對老年人的投藥

一般而言，大部分的老年人肝、腎機能皆下降，於是可能持續發生血中濃度偏高的情況，因此需慎重投藥。

肝或腎功能不良患者〔持續維持藥物血中濃度，而可能提高副作用的發生率〕。

臨床試驗

cevimeline已被證明可以改善 Sjögren Syndrome 病患的口乾症狀。

有一臨床試驗針對平均年齡53.6歲(33-75歲)的75名病人(10位男性、65位女性)進行一個為期6週隨機雙盲、對照試驗。受試病人中92%為白種人、黑人1%、其他人種則佔7%。該臨床試驗將一天服用三次cevimeline 30mg(90 mg/天)及一天服用三次60 mg(180 mg/天)的效果與服用安慰劑組作比較。效果的評估是以「整體改善度」(global improvement)作為評量，「整體改善度」(global improvement)的定義是病人對以下問題：「請對您現在口乾症狀相較於治療開始前的感覺進行比較」的回答，病人可選擇回答「較佳」、「較差」或「無變化」。一天服用三次cevimeline 30mg的病人有76%指出其口乾症狀有「整體改善度」，而服用安慰劑病人只有35%改善。此結果具有統計上的差異(p=0.0043)，但沒有證據顯示一天服用三次60mg的病人其效果優於一天服用三次30mg的病人。

有一臨床試驗納入平均年齡為54.5歲(23-74歲)的197名病人(10位男性、187位女性)進行一個為期12週隨機雙盲、對照試驗。受試病人中91.4%為白種人、黑人3%、其他人種則佔5.6%。該臨床試驗將一天服用三次cevimeline 15mg(45mg/天)及30mg(90mg/天)的效果與服用安慰劑組作比較。與服用安慰劑組：一天服用三次30mg的病人其口乾症狀具有統計上顯著的改善(p=0.0004)，但一天服用三次15mg組則與服用安慰劑組無顯著差異。與服用安慰劑組比較，研究期間兩種劑量的cevimeline都可使唾液流量出現統計上顯著的增加。

另一針對平均年齡55.3歲(24-75歲)的212名病人(11名男性、201名女性)之第二個為期12週隨機雙盲、對照試驗。受試病人中88.7%為白種人、黑人1.9%、其他人種則佔9.4%。該試驗將一天服用三次cevimeline 15mg(45mg/天)及30mg(90mg/天)的效果與服用安慰劑組作比較。病人的效果整體評估並未發現有統計上的差異。不過，相較於上面提到的試驗，本臨床試驗有較高的效果反應，即相較於安慰劑組，服用藥物後與服用前比較，一天服用三次30mg的病人其唾液流量有統計上顯著的增加(p=0.0017)。

適應症

治療 Sjögren's Syndrome 所引起的口乾症狀

禁忌

cevimeline不可用於氣管控制不良或已知對cevimeline過敏的病人，而且不宜用在發生膽孔收縮的病患，例如，發生急性紅膜炎與狹角型青光眼患者不宜使用。

警語

心血管疾病：

cevimeline可能會改變心臟傳導作用或心跳速率，有嚴重心血管病疾患者可能無法代償cevimeline引發的血流動力學或心律上暫時的改變，所以曾有心肌梗塞或心臟衰竭病史的心血管病疾患者應在醫師的嚴密監控下謹慎使用cevimeline。

肺病疾病：

cevimeline可能會增加呼吸道的阻力，支氣管的肌肉緊張度與支氣管分泌物，對控制良好的氣喘、慢性支氣管炎或慢性阻塞性肺病疾病的病患應在醫師的嚴密監控下謹慎使用cevimeline。

眼睛：

有報告指出含muscarinic agonist的眼藥水可能引發視網膜剝離，因而造成視覺敏銳度降低，特別是在晚上或中央區域有病患的病人，有可能造成深度敏感度降低。應告知病人後閉眼或在光線不足下從事危險性活動時，必須特別小心。

注意事項

一般：

cevimeline的毒性特點：可能會促進副交感神經作用。這可能包括：頭痛、視力干擾、流淚、出汗、呼吸窘迫、腸胃痙攣、噁心、嘔吐、腹瀉、心房室傳導阻滯、心跳過快、心跳過慢、低血壓、高血壓、眩暈、精神昏亂、心律不整、以及顫抖。

有腎結石或膽結石病史者使用cevimeline時應特別謹慎。膽囊或膽管平滑肌的收縮可能促使膽囊炎、膽管炎與膽管阻塞等併發症的發生。理論上輸尿管平滑肌張力的增加會促使腎結石病人出現腎絞痛或輸尿管回流情形。

病患用藥禁忌：應告知病患cevimeline可能引發視覺干擾而影響駕駛的安全性，尤其在夜間。若病人服用cevimeline時大量出汗，有可能出現脫水現象，此時病人應飲用大量開水，並與醫師商量。

藥物交互作用：

服用β₂-腎上腺素拮抗劑的病人使用cevimeline時應謹慎，因為可能會出現神經傳導障礙。cevimeline與副交感神經作用的藥物同時使用時，可能會出現加成效果，cevimeline可能會干擾併用藥物的抗毒作用。

抑制CYP2D6與CYP3A3/4的藥物也會抑制cevimeline的代謝。根據以往的經驗，已知或疑似CYP2D6缺乏的病患在使用cevimeline時應謹慎，因為出現副作用的危險性可能較高。在一個in vitro試驗中發現，cevimeline不會抑制細胞色素(cytochrome) P450同位標本1A2、2A6、2C9、2C19、2D6、2E1與3A4的活性。

與下列藥物併用時之注意事項

藥物名稱等	可能之影響	機 轉
Cholinergic藥物(Acetylcholine chloride) (Bethanechol chloride)等、Cholinesterase抑制劑(Neostigmine、Ambenonium Chloride等)、會促進釋放acetylcholine作用的藥物(Cisapride、Mosapride等)	可能會增強本劑或這些藥劑的作用	因併用藥物而增強類muscarine作用
Anti-Cholinergic藥物(atropine sulfate、scopolamine hydrobromide等)	可能會減弱本劑或這些藥劑的作用	會與本劑產生拮抗作用
具Anti-Cholinergic作用的藥物Phenothiazine類抗精神病藥(Chlorpromazine等)、三環抗憂鬱藥(Amitriptyline hydrochloride、Imipramine hydrochloride等)	會減弱本劑的作用	
cytochrome P450CYP2D6抑制劑(Quinidine sulfate等)、cytochrome P450CYP3A4抑制劑(Itraconazole、Erythromycin等)、cytochrome P450非特異性抑制劑(Cimetidine等)	可能會增強本劑作用	會因這些藥劑的併用，而發生代謝本劑的酵素發生受阻，於是本劑的血中濃度上升
cytochrome P450誘導藥(Phenobarbital、Rifampicin等)	可能會減弱本劑作用	會因這些藥劑而誘導本劑的代謝酶發生，而降低本劑血中濃度

藥物過量的處理

急性藥物過量的處理應比照其他muscarinic agonist，依其中毒徵候與情況緊急處理，進行一般性的措施。若醫療上有緊急給與解毒劑的必要，可以抗膽鹼藥物atropine作為急救時的解毒劑，對cevimeline用藥過量的病人可能有幫助。對出現嚴重心血管抑制或支氣管收縮的病患，可使用epinephrine加以急救。目前尚未知道cevimeline是否可由人工洗胃清除。

致毒性、致突變性與生育力受損試驗：

在CD-1小鼠與F-344大鼠身上進行致毒試驗中發現，投與100mg/kg/天(從AUC數據得知，該劑量相當於人體最大劑量的8倍)的雌性大鼠，其子宮腺瘤的發生率具有統計上有意義的增加。發生在小鼠或大鼠的腫瘤發生率則不具統計上的差異。

在一系列的試驗中，包括一個Ames試驗、一個in vitro的哺乳類細胞染色體畸變試驗、一個在L5178Y細胞株進行的老鼠淋巴瘤試驗研究與一個在ICR老鼠進行的in vivo微核試驗，都無證據顯示cevimeline會促使基因突變或染色體斷裂。

從交配63天之前開始投與最高劑量cevimeline 45mg/kg/day(相當於以體表面積校正後，體重60公斤的成人之最大劑量的5倍)，對雄性Sprague-Dawley大鼠的繁殖力或生育力並沒有不良影響。從交配之前14天開始投與並經過7天妊娠期，使用最高劑量為45mg/kg/day cevimeline的母鼠，其受孕率與產數目有意義的少於對照組。

懷孕：

孕婦安全級數C。

對Sprague-Dawley母鼠從交配前14天開始投與並經過7天妊娠期，投與最高劑量45mg/kg/day cevimeline(此劑量相當於以體表面積校正後，體重60公斤的成人最高劑量的5倍)，其平均產數目減少。這種影響可能是由於藥物對母體的毒性所造成，但目前尚未針對懷孕婦女進行臨床試驗，所以其安全性未知。對懷孕期間是否可以服用，應衡量其治療益大於對胎兒之危險時，才可使用cevimeline。

授乳婦女：

目前還尚未知此藥物是否會分泌到乳汁中。但因為許多藥物都可能分泌至乳汁中，所以cevimeline可能會對哺乳中的嬰兒引發嚴重的副作用，因此必須先考量此藥物對母親的重要性再決定是否要停止授乳或停藥。

兒童：

cevimeline用於兒童病患的安全性與有效性尚未確立。

老年病患：

雖然cevimeline的臨床試驗有納入65歲以上的受試者，但其人數不足以判定他們對藥物的反應是否異於較年輕的受試者。由於老年人較容易出現肝臟、腎臟或心臟功能下降的情況，而且常患有其他疾病並同時使用他種藥物，所以開始以cevimeline來治療老年病患時，應特別小心。

副作用

在全球進行之臨床試驗中，總共有1777名病人服用過cevimeline，包括Sjögren Syndrome病患與其他病症患者。在美國進行、對照的安慰劑 Sjögren Syndrome 病患臨床試驗中，共有320名病人每天服用三次15mg到60mg不等的cevimeline，其中93%為女性，7%為男性。種族分佈白人佔90%、西班牙裔佔5%、黑人佔3%、其他人種則有2%。在這些臨床試驗中，有14.6%的病患因出現副作用而中斷cevimeline的服用。

在Sjögren Syndrome病患進行的cevimeline臨床試驗中，出現下列與 muscarinic agonism 相關的副作用：

	cevimeline 30mg (一天三次) n=533	安慰劑 (一天三次) n=164
大量出汗	18.7%	2.4%
噁心	13.8%	7.9%
鼻炎	11.2%	5.4%
腹瀉	10.3%	10.3%
唾液過多	2.2%	0.6%
頻尿	0.9%	1.8%
無力	0.5%	0.0%
臉發紅	0.3%	0.6%
多尿症	0.1%	0.6%

*n為病患總數。

此外，Sjögren Syndrome病患臨床試驗中出現以下副作用(發生率≥3%)：

	cevimeline 30mg (一天三次) n=533	安慰劑 (一天三次) n=164
頭痛	14.4%	20.1%
胃炎	12.3%	10.9%
上呼吸道感染	11.4%	9.1%
消化不良	7.8%	8.5%
腹痛	7.6%	6.7%
尿道感染	6.1%	3.0%
咳嗽	6.1%	3.0%
咽喉炎	5.2%	5.4%
嘔吐	4.6%	2.4%
受傷	4.5%	2.4%
背痛	4.5%	4.2%
皮疹	4.3%	6.0%
結膜炎	4.3%	3.6%
頭暈	4.1%	7.3%
支氣管炎	4.1%	1.2%
關節痛	3.7%	1.8%
手銜	3.3%	3.0%
疲勞	3.3%	1.2%
疼痛	3.3%	3.0%
骨節痛	2.8%	1.8%
失眠	2.4%	1.2%
熱潮紅	2.4%	0.0%
寒顫	1.3%	1.2%
焦慮	1.3%	1.2%

*n為病患總數。

以下是發生在 Sjögren Syndrome 病患治療中，副作用發生率<3%，但≥1%的不良事件：便秘、顫抖、視力異常、肌肉張力過高、周邊水腫、胸痛、肌肉痛、發熱、缺乏食慾、眼睛痛、耳痛、口乾、眩暈、唾液腺痛、搔癢、類似感冒症狀、眼睛感染、術後疼痛、陰道炎、皮膚病、憂鬱症、打噴嚏、反射減弱、感染、細菌感染、唾液腺炎、中耳炎、紅斑性疹子、肺炎、水腫、唾液腺腫大、過敏症、胃食道逆流、眼睛異常、偏頭痛、牙痛、鼻出血、胃腸脹氣、牙痛、潰瘍性口腔炎、貧血、感覺遲鈍、膀胱炎、腿抽筋、腰痛、打噴嚏、念珠菌病、心悸、澱粉分解酶增加、乾眼病、過敏反應，有少數接受治療的Sjögren Syndrome病患通報下列不良事件(<1%)：但其與藥物之相關性未知：

全身性病症：過敏症惡化、心前胸痛、異常哭泣、血腫、腿部疼痛、水腫、眼眶周圍水腫、外傷疼痛增加、臉色蒼白、溫度感覺改變、體重下降、體重上升、噁心、口腔水腫、昏厥、身體不適、臉部水腫、胸骨下胸痛。

心血管疾病：心電圖異常、心臟病、心雜音、高血壓惡化、低血壓、心律不整、過早搏動、T波反轉、頻脈、上室性頻脈、心絞痛、心肌梗塞、心包膜炎、肺栓塞、周邊血管缺血症、表層靜脈炎、紫斑症、血栓靜脈炎、血管疾病、脈管炎、高血壓。

消化道疾病：盲腸炎、食慾增加、潰瘍性大腸炎、憩室炎、十二指腸炎、吞嚥困難、腸炎、胃痛、胃炎、腸胃炎、腸胃出血、齒齦炎、舌炎、直腸出血、痔瘡、腸阻塞、大腸炎、便秘、黏膜炎、食道狹窄、食道炎、口腔出血、消化性潰瘍、牙周破壞、直腸疾病、口腔炎、裡急後重、舌頭變色、舌部疾病、地圖樣舌、舌頭潰瘍、齦齒

內分泌疾病：皮質類固醇增加、甲狀腺腫、甲狀腺機能不足疾病。

血液疾病：血小板減少紫斑症、血小板增多症、血小板減少症、低量性貧血、嗜伊紅血球過多、顆粒性細胞減少、白血球減少症、白血球增多、子宮頸淋巴腺病變、淋巴腺病變。

肝膽系統疾病：膽石病、 γ -羧基轉氨酶(γ -glutamyl transferase)增加、肝膽酵素增加、肝功能異常、病毒性肝炎、SGOT(亦稱為AST-天門冬氨酸轉氨酶)增加、SGPT(亦稱為ALT-丙氨酸轉氨酶)增加。

代謝與營養不良疾病：脫水、糖尿、高血鈣症、高膽固醇血症、高血糖、高血脂、高三酸甘油酯血症、高尿酸血症、低血鈣症、低鉀血症、低鈉血症、口渴。

肌肉骨骼疾病：關節炎、關節炎惡化、關節病變、股骨頭壞死、骨節疾病、黏液囊炎、肋軟骨炎、足底筋膜炎、肌肉無力、骨髓炎、骨質疏鬆症、滑膜炎、腱炎、腱鞘炎、腫瘤：基底細胞癌、鱗狀細胞癌。

神經系統疾病：手腳道綜合病徵、昏迷、協調異常、感覺遲鈍、運動困難、發音困難、多發性硬化症惡化、不隨意肌收縮、神經痛、神經病變、感覺異常、言語障礙、精神激昂、困惑、人格解體、憂鬱症惡化、異常的作夢、情緒不穩、躁狂反應、作惡夢、嗜睡、想法異常、運動過度、幻覺。

其他疾病：摔倒、食物中毒、中暑、關節脫臼、銜後出血。

與感染抗藥性有關的疾病：蜂窩組織炎、單純皰疹、帶狀皰疹、細菌感染、病毒感染、生殖道念珠菌感染、敗血症。

呼吸道疾病：氣喘、支氣管痙攣、慢性阻塞性呼吸道疾病、呼吸困難、咳嗽、喉炎、鼻部潰瘍、胸腺積液、胸膜炎、肺炎、肺充血、肺纖維化、呼吸道疾病。

風濕免疫疾病：類風濕性關節炎惡化、紅斑性狼瘡紅疹、紅斑性狼瘡症候群。

皮膚疾病：粉刺、禿髮、燒傷、皮膚炎、接觸性皮膚炎、苔蘚樣皮膚炎、濕疹、癬病、表皮角化症、扁平苔蘚、指甲脫色、指甲疾病、甲床炎、甲癬、甲溝炎、光線敏感、酒渣鼻、硬皮病、皮膚癌、皮膚變色、皮膚乾燥、皮膚剝落、皮膚肥大、皮膚潰瘍、痔瘡、疣、大水皰瘡、濕冷皮膚。

感官疾病：耳聾、聽力變差、癱瘓症、嗅覺異常、味覺錯亂、驗光、白內障、角膜炎、角膜炎、複視、青光眼、前房眼出血、角膜炎、角膜炎、瞳孔放大、近視、幻視、視網膜沉積、視網膜疾病、掌膜炎、玻璃體剝離、耳鳴。

生殖泌尿道疾病：附睾炎、前列腺炎、性功能異常、無月經症、女性乳房腫痛、惡性女性乳房腫痛、女性乳房疼痛、子宮頸抹片檢查呈陽性、經痛、子宮內膜疾病、經期間不規則出血、白帶、月經過多、月經痛症、卵巢囊腫、卵巢病、生殖器腫痛、子宮出血、陰道出血、萎縮性陰道炎、白帶、膀胱不適、血液尿素氮增加、排尿困難、血尿、排尿障礙、腎病、夜尿症、非蛋白氮增加、腎盂腎炎、腎結石、腎功能異常、腎病、尿毒症、尿道疾病、尿尿異常、尿失禁、尿量減少、尿痛。

在臨床試驗中，一位接受多種藥物治療的紅斑性狼瘡病人在服用cevimeline四週後，其ALT值大幅升高。另有兩名病人服用cevimeline後出現非常高的AST值。這些異常值的意義未知。

其他臨床試驗(Sjögren Syndrome以外的病患)中發生的副作用(相關原因不明)如下：體酸性症候群、血壓變動、心臟肥大、體位性低血壓、失語症、抽搐、步態異常、感覺過敏、麻痺、性功能異常、腹部膨大、排便習慣改變、牙齦增生、腸阻塞、房室束枝傳導阻滯、磷酸肌酸酶增加、電解質異常、糖尿、痛風、高血鉀症、高蛋白質血症、LDH增加、鹼性磷酸鹽酶增加、生長遲緩、血小板異常、攻擊反應、健忘症、神經衰弱、精神錯亂、憂鬱症、癱瘓、幻覺、陽萎、神經官能病、類過敏反應、人格違常、重紅血球素血症、窒息、肺部膨脹不全、打呵欠、尿量過多、尿滯留、靜脈擴張、淋巴球過多症。

上市後之副作用：體酸性

用法與用量

cevimeline hydrochloride的建議用量為每次30mg，一天服用三次。沒有足夠的安全性資訊支持高於一天三次30mg劑量，也沒有足夠證據顯示的高於一天三次30mg的cevimeline hydrochloride能產生更大的療效。

外觀、包裝與儲存

EVOXAC[®]是一種白色硬膠囊，含有cevimeline hydrochloride 30mg，有白色不透明膠囊帽與白色不透明的膠囊體。膠囊帽上印有「EVOXAC」字樣，膠囊體上則印有「30mg」字樣。「30mg」上方並有一條黑色橫槓，使用防止孩童開啟的藥瓶。

包裝：一瓶100顆膠囊，一瓶50顆膠囊。

儲存：儲存於15°-30°C (59°-86°F)。

保存期限：36個月

原文件訂日期：2006年5月



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