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 53.5 years (range 33-75). The racial distribution was Caucasian 88.7%, Black 1.9% and other 9.4%. The effects of cevimeline on the 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 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.

### 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
Cevimeline toxicity is characterized by an exaggeration of its parasympathomimetic effects. These may include: headache, visual disturbance, lacrimation, sweating, respiratory distress, gastrointestinal, spinal, cardiac arrhythmia, and tremors. Cevimeline should be administered with caution to patients with a history of nephrolithiasis or cholecystitis. Constrictions 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:
Pregnancy:
Cevimeline was associated with a reduction in the number of implantations than did control animals. Females that were treated with cevimeline at dosages up to 100 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.

### INDICATIONS AND USAGE
Cevimeline is indicated for the treatment of symptoms of dry mouth in patients with Sjögren's Syndrome.
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 36% patients and patients with other conditions. In placebo-controlled clinical trials 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 continued treatment with cevimeline due to adverse events.

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cevimeline 30 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(tid)</td>
<td>(tid)</td>
</tr>
<tr>
<td>n</td>
<td>n=164</td>
<td>n=154</td>
</tr>
<tr>
<td>Excessive Sweating</td>
<td>18.7%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13.8%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>11.2%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.3%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Excessive Salivation</td>
<td>2.2%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Urinary Frequency</td>
<td>0.9%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0.5%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Flushing</td>
<td>0.3%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Polyuria</td>
<td>0.1%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cevimeline 30 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(tid)</td>
<td>(tid)</td>
</tr>
<tr>
<td>n</td>
<td>n=164</td>
<td>n=154</td>
</tr>
<tr>
<td>Headache</td>
<td>14.4%</td>
<td>20.1%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>12.3%</td>
<td>10.9%</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>11.4%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>7.8%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>7.6%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>6.1%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Coughing</td>
<td>6.1%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>5.2%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.6%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Injury</td>
<td>4.5%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>4.5%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Rash</td>
<td>4.3%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>4.3%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4.1%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4.1%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3.7%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Surgical Intervention</td>
<td>3.3%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Fainting</td>
<td>3.3%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Pain</td>
<td>3.3%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Skeletal Pain</td>
<td>2.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.4%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Hot Flashes</td>
<td>2.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Rigs</td>
<td>1.3%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1.3%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

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

The following events were reported in Sjogren’s patients at incidences of <3% and ≥1%: constipation, tremor, abnormal vision, hyperventilation, 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, pain, hiccups, hypoflexia, infection, fungal infection, sialoadenitis, lymphocytosis, impaired athletic performance, dyspnea, hemoptysis, laryngitis, nasal ulcer, pleural effusion, pleurisy, pulmonary congestion, pulmonary fibrosis, respiratory disorder.

Liver and Biliary System Disorders:
- Hepatomegaly
- Increased serum alkaline phosphatase
- Increased serum gamma-glutamyl transferase
- Increased hepatic enzymes

Respiratory Disorders:
- Asthma
- Bronchospasm
- Chronic obstructive airway disease
- Diaphragmatic hernia
- Increased blood urea nitrogen
- Dyspnea
- Tachypnea

Cardiovascular Disorders:
- Raynaud’s phenomenon
- Chest pain
- High blood pressure
- Angina pectoris
- Myocardial infarction

Endocrine Disorders:
- Hyperglycemia
- Hypoglycemia

Gastrointestinal Disorders:
- Anorexia
- Abdominal pain
- Flatulence
- Diarrhea
- Hemorrhoids

Excessive sweating, leg pain, edema, periorbital edema, activated pain trauma, pallor, changed sensorium, anemia, neutropenia, granulocytopenia, leucopenia, leukocytosis, cervical lymphadenopathy.

Musculoskeletal Disorders:
- Arthritis
- Aggravated arthritis
- Arthralgia
- Femoral head avascular necrosis

Nervous Disorders:
- Carpal tunnel syndrome
- Paresthesia
- Hyperesthesia
- Dysesthesia

Miscellaneous Disorders:
- Fall
- Food poisoning
- Joint pain

Respiration Resistance Mechanism Disorders:
- Cellulitis

Skin and Appendages Disorders:
- Acne
- Dermatitis
- Contact dermatitis
- Lichenoid dermatitis
- Eczema

Special Senses Disorders:
- Deafness

Urogenital Disorders:
- Pyelonephritis

Digestive Disorders:
- Anorexia
- Abdominal pain
- Flatulence
- Diarrhea

Rheumatologic Disorders:
- Rheumatoid arthritis
- Lupus erythematosus

Psychiatric Disorders:
- Anxiety
- Rigors
- Insomnia
- Fatigue
- Arthralgia

Respiratory Disorders:
- Dyspnea
- Hemoptysis

Cardiovascular Disorders:
- Tachycardia
- Angina pectoris
- Myocardial infarction

Body as a Whole Disorders:
- Malaise

Central Nervous System Disorders:
- Convulsions

Endocrine Disorders:
- Diabetes mellitus

Hematologic Disorders:
- Thrombocytopenia

Lymphatic Disorders:
- Lymphadenopathy

Neoplasms:
- Basal cell carcinoma

Other Disorders:
- Motion sickness

Vascular Disorders:
- Hypotension

Infections:
- Bacterial infection

Other Adverse Events:
- Increased serum alkaline phosphatase
- Increased serum gamma-glutamyl transferase

Management of OVERDOSE:
- A specific antidote for cevimeline is not available. In case of overdose, supportive and symptomatic therapy should be given.

DOSAGE AND ADMINISTRATION:

Dosage:

- The recommended dose of cevimeline hydrochloride is 30 mg taken three times a day.
- 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.

Management of overdosage:

- The administration of atropine should be at a dosage that produces dry mouth, bradycardia, or both. The dosage should be adjusted to produce these signs and symptoms.

Post-Marketing Adverse Events:

LIVER AND BILIARY SYSTEM DISORDERS:
- Cholestatics

MANAGEMENT OF OVERDOSE:

- Management of 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.

DISTRIBUTED AND MARKETED BY:

- Daiichi Pharmaceutical Co., Ltd.

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