Cognex®
(Tacrine Hydrochloride Capsules

INDICATIONS AND USAGE
Cognex® is indicated for the treatment of mild to moderate dementia of the Alzheimer’s type.

CLINICAL TRIAL DATA
Clinical Trial Data show that Cognex® improves 7 or more ADAS cognitive points over tacrine at 160 mg a day or with placebo who attained a particular measure of improvement in patients who do so.

Each 10-, 20-, 30-, and 40-mg Cognex® capsule contains 12.75, 25.50, 30 mg: D&C Yellow #10, FD&C Blue #1, FD&C Red #40, titanium dioxide; 30 mg: D&C Blue #1, FD&C Red #40, titanium dioxide; 40 mg: D&C Blue #1, FD&C Red #40, titanium dioxide; 60 mg: D&C Blue #1, FD&C Red #40. Inactive ingredients are hydrous starch, calcium phosphate dibasic, D&C Blue #1, D&C Red #40, magnesium stearate, starch, titanium dioxide.

Tacrine hydrochloride is a white solid and is freely soluble in distilled water, 0.1N hydrochloric acid, and alcohol.

Twelve-Week Study

The twelve-week study randomized 248 patients to tacrine at 80 mg/day, 120 mg/day, and 160 mg/day, and placebo. In the 160 mg/day group, a substantial number of patients withdrew due to side effects.

In a 30-week study, 221 patients were randomized to placebo, 160 mg/day tacrine, and 80 mg/day tacrine.

FIGURE 1. ADAS Cog Change From Baseline

The results on the CIBI are shown in Figure 3.

The mean drug-placebo ADAS cog difference for the 30-week 160 mg/day completer group was 7.8 unit improvement.

Cognex® treatment was associated with a statistically significant lower mean change in ADAS cog score from baseline at least as large as the ADAS cog change score value given on the Y axis. The variability of response is apparent from the fact that the distribution of response values is skewed to the right.

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64%, respectively.

The events cited in the tables below reflect experience gained under closely monitored conditions. The events were reported in the context of the use of tacrine and are not necessarily causally related to the use of tacrine.

### Adverse Events Reported in Controlled Trials

<table>
<thead>
<tr>
<th>Table</th>
<th>Adverse Event</th>
<th>Placebo</th>
<th>Cognex®</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Rash</td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Hostility</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Thinking Abnormal</td>
<td>17</td>
<td>14</td>
</tr>
</tbody>
</table>

#### Experience with the rechallenge of patients with transaminase elevations following recovery:

- Of the 145 patients rechallenged, 127 (88%) were able to continue at the same dose and monitoring regimen should be modified as described in Table 4.
- For patients with ALT/SGPT >2 X ULN and/or bilirubin >3 mg/dL, monitoring should be done until ALT/SGPT levels return to <1.5 X ULN or bilirubin <2 mg/dL, and then every other week from at least week 4 to week 16 following initiation of treatment, after which monitoring may be decreased to every 3 months. For patients with ALT/SGPT >3 X ULN or that resulted in a change in patient behavior, and the kinds of patients treated may differ.

#### Adverse Events

- **Body As a Whole:** Asthenia, fatigue, malaise, flatulence, lower extremity swelling, edema, sweating.
- **Cardiovascular System:** Palpitations, hypertension, hypotension, tachycardia, arrhythmia, chest pain, angina, syncope, and worsening of congestive heart failure.
- **Digestive System:** Diarrhea, abdominal pain, dyspepsia, flatulence, nausea, vomiting, constipation, dysphagia, flatulence, dyspepsia, and worsening of constipation.
- **Endocrine System:** Diabetes.
- **Gastrointestinal System:** GI bleed, anorexia, gastritis, gastritis, and worsening of peptic ulcer disease.
- **General:** Rash, pruritus, erythema, urticaria, and worsening of pruritus.
- **Hematologic System:** Thrombocytopenia, leukopenia, lymphopenia, neutropenia, and worsening of anemia.
- **Hepatic System:** Hyperbilirubinemia, and worsening of hepatitis.
- **Nervous System:** Seizures, confusion, headache, ataxia, peripheral neuropathy, and worsening of peripheral neuropathy.
- **Respiratory System:** Cough, bronchitis, and worsening of asthma.
- **Skin:** Rash, pruritus, phototoxicity, and worsening of psoriasis.
- **Urogenital System:** Polyuria, nocturia, pyuria, cystitis, urinary retention, and worsening of enuresis.
- **Vascular System:** Edema, peripheral edema, and worsening of peripheral edema.

#### Laboratory Tests

- Total Clinical Experience: More than 12,000 patients were treated with tacrine in controlled clinical trials and a similar number of patients were treated in open-label clinical trials.
- The total clinical experience in more than 12,000 patients does not indicate a clear association with tacrine treatment and serious white blood cell abnormalities.
- Conditions commonly associated with a low ANC; 2 of these patients remained on Cognex.

#### Other Information

- Theophylline: Coadministration of tacrine with theophylline increased theophylline elimination via cytochrome P450 IA2.
- Bilirubin: Patients and caregivers should be advised that the effect of Cognex® (brand of tacrine) on serum bilirubin has not been adequately studied.
- Studies in rats: Tacrine increased the plasma levels of bilirubin in rats, an effect that has not been observed in volunteers treated with tacrine.

### Tacrine Discontinuation

- Cognex® should be used with caution in patients who have a history of cholinergic crisis.
- If a patient experiences any of the following symptoms, Cognex® should be stopped immediately and not be restarted:
  - Severe nausea/vomiting
  - Diarrhea
  - Hypotension
  - Prolonged QT interval
- If a patient experiences any of the following symptoms, Cognex® should be stopped and not be restarted:
  - Seizures
  - Confusion
  - Headache

#### Tacrine Titration

- The recommendations for dose titration are based on experience from clinical trials. The rate of dose titration is approximately 12 times the maximum recommended human dose of 160 mg/day. Dose-related increases in serum transaminase levels have been observed in patients treated with tacrine up to a total daily dose of 160 mg/day. The effect of tacrine on serum bilirubin has not been adequately studied.

#### Precautions

- Patients who have a history of cholinergic crisis should be treated with caution.
- If a patient experiences any of the following symptoms, Cognex® should be stopped immediately and not be restarted:
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- If a patient experiences any of the following symptoms, Cognex® should be stopped and not be restarted:
  - Seizures
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  - Headache

### Tacrine Overdose

- **Symptoms:** Severe nausea/vomiting, diarrhea, hypotension, convulsions, vertigo, syncope, hyperkinesia, paresthesia.
- **Management:** Supportive care, including monitoring of vital signs and symptoms associated with hepatitis and follow ALT/SGPT levels until ALT/SGPT levels return to normal limits.

### Tacrine Administration

- **Indications:** Cognex® is indicated for the treatment of moderate to severe cognitive impairment due to Alzheimer's disease when the diagnosis is confirmed by neurologic and neuroradiologic findings, and in a case basis in 2-12 patients to improve global function scores.
- **Contraindications:** Cognex® is contraindicated in patients with a history of cholinergic crisis, severe bowel obstruction, severe glaucoma, and severe pain.
- **Warnings:** Cognex® is associated with an increased risk of falls and fractures. Patients with a history of falls, fractures, or cognitive impairment due to Alzheimer's disease should be treated with caution.
- **Precautions:** Cognex® should be used with caution in patients who have a history of cholinergic crisis.
- **Dosage and Administration:** The total daily dose (80 mg/day or more) may cause a decline in cognitive function and behavioral changes. Caregivers should be advised that abrupt discontinuation of Cognex® or a large reduction in dose may cause an exacerbation of symptoms associated with Alzheimer's disease.