ADASUVE®
(LOXAPINE) INHALATION POWDER

EDUCATION PROGRAM for
HEALTHCARE PROFESSIONALS

August 2013
ADASUVE® Risk Evaluation and Mitigation Strategy (REMS) Education Program Content

At the end of this education program, you should understand:

• ADASUVE REMS Program Requirements

• ADASUVE Product Information
  – Indication
  – Dose

• Important safety information
  – Risk of bronchospasm with ADASUVE
  – Use of albuterol rescue treatment to treat bronchospasm in asthma and COPD patients
  – Decreased Forced Expiratory Volume in 1 second (FEV₁) in asthma and COPD patients
  – Safety of ADASUVE in agitation trials
  – Administer only a single dose of ADASUVE per patient within any 24-hour period

For complete safety profile, see the Full Prescribing Information including Boxed Warning.
ADASUVE® Risk Evaluation and Mitigation Strategy (REMS) Education Program Content

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• How to use ADASUVE safely
  – Appropriate patient selection
  – Dosage and administration
  – Observation and management of patient

• How to enroll in the ADASUVE REMS Program
ADASUVE® REMS Program

• The purpose of the ADASUVE REMS Program is to mitigate the risk of bronchospasm that has the potential to lead to respiratory distress and respiratory arrest.

• To mitigate the risk, the ADASUVE REMS requires that ADASUVE is only administered in enrolled healthcare facilities:
  – With immediate, on-site resources to manage bronchospasm and/or respiratory distress

• The REMS will inform healthcare professionals about:
  – The risk of bronchospasm after ADASUVE administration
  – Appropriate patient selection
  – Monitoring patients after ADASUVE administration
  – Management of ADASUVE induced bronchospasm
Risk of Bronchospasm

• ADASUVE® can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest.

• Administer ADASUVE only in an enrolled healthcare facility that has:
  – Immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation)

• Prior to administering ADASUVE, ask patients regarding:
  – A history or symptoms of asthma, COPD and other lung diseases
  – Examine (including chest auscultation) patients for respiratory abnormalities (eg, wheezing)

• Following treatment with ADASUVE, monitor for signs and symptoms of bronchospasm
Contraindications

• ADASUVE® is contraindicated in patients with the following:
  - Current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm
  - Acute respiratory signs or symptoms (eg, wheezing)
  - Current use of medications to treat airways disease, such as asthma or COPD
  - History of bronchospasm following ADASUVE treatment
  - Hypersensitivity to loxapine or amoxapine (eg, serious skin reaction)
ADASUVE®: Product Information

ADASUVE is a typical antipsychotic indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.

- The efficacy of ADASUVE was established in one study of acute agitation in patients with schizophrenia and one study of acute agitation in patients with bipolar I disorder

Dosing and Administration

- ADASUVE is a single-use disposable product that delivers an aerosol of loxapine in a single inhalation
  
  - ADASUVE is administered only by oral inhalation
  - ADASUVE must be administered only by a healthcare professional, in an enrolled healthcare facility
  - Recommended dose of ADASUVE is 10 mg
  - Only a single dose per patient should be administered in any 24-hour period
Pulmonary Safety Studies in Patients with Asthma and COPD

Albuterol Rescue Treatment after Administration of ADASUVE®

- Dedicated pulmonary safety studies were performed in subjects with mild-to-moderate persistent asthma or mainly moderate-to-severe COPD

- After receiving ADASUVE (Dose 1 and Dose 2):
  - 54% of patients with asthma required treatment with albuterol to treat pulmonary adverse events
  - 23% of patients with COPD required treatment with albuterol

Do not use in patients with acute respiratory signs and symptoms; with a current diagnosis or history of asthma, COPD and other lung disease associated with bronchospasm; or with current use of medications to treat airways disease, such as asthma or COPD.
## Pulmonary Safety Studies in Patients with Asthma and COPD – Use of Rescue Albuterol

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo (N = 26)</th>
<th>ADASUVE® (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects receiving albuterol rescue at any time</td>
<td>3/26 (12%)</td>
<td>14/26 (54%)</td>
</tr>
<tr>
<td>Number receiving rescue after Dose 1</td>
<td>1/26 (4%)</td>
<td>7/26 (27%)</td>
</tr>
<tr>
<td>Number receiving rescue after Dose 2</td>
<td>2/25 (8%)</td>
<td>7/17 (41%)</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects receiving albuterol rescue at any time</td>
<td>4/27 (15%)</td>
<td>6/26 (23%)</td>
</tr>
<tr>
<td>Number receiving rescue after Dose 1</td>
<td>1/27 (4%)</td>
<td>2/26 (8%)</td>
</tr>
<tr>
<td>Number receiving rescue after Dose 2</td>
<td>3/26 (12%)</td>
<td>4/19 (21%)</td>
</tr>
</tbody>
</table>
Pulmonary Safety Studies in Patients with Asthma and COPD

Decreased Forced Expiratory Volume in One Second (FEV₁) after ADASUVE® Administration

• Dedicated pulmonary safety studies were performed in subjects with mild-to-moderate persistent asthma or mainly moderate-to-severe COPD

• There were significantly more asthma and COPD patients who experienced a decrease in FEV₁ of >10%, >15%, and >20% in the ADASUVE treated patients compared to the placebo treated patients

Do not use in patients with acute respiratory signs and symptoms; with a current diagnosis or history of asthma, COPD and other lung disease associated with bronchospasm; or with current use of medications to treat airways disease, such as asthma or COPD.
# Maximum Decrease in FEV\(_1\) from Baseline in Healthy Volunteer, Asthma and COPD Trials

<table>
<thead>
<tr>
<th>FEV(_1) Categories</th>
<th>Healthy Volunteer</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N (%)</td>
<td>ADASUVE N (%)</td>
<td>Placebo N (%)</td>
</tr>
<tr>
<td>After any Dose</td>
<td>N=26</td>
<td>N=26</td>
<td>N=26</td>
</tr>
<tr>
<td>≥10</td>
<td>7 (27%)</td>
<td>7 (27%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>≥15</td>
<td>1 (4%)</td>
<td>5 (19%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>≥20</td>
<td>0</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>After Dose 1</td>
<td>N=26</td>
<td>N=26</td>
<td>N=26</td>
</tr>
<tr>
<td>≥10</td>
<td>4 (15%)</td>
<td>5 (19%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>≥15</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>≥20</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>After Dose 2</td>
<td>N=26</td>
<td>N=25</td>
<td>N=25</td>
</tr>
<tr>
<td>≥10</td>
<td>5 (19%)</td>
<td>6 (24%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>≥15</td>
<td>0</td>
<td>5 (20%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>≥20</td>
<td>0</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

FEV\(_1\) categories are cumulative, i.e. a subject with a maximum decrease of 21% is included in all 3 categories. Patients with a >20% decrease in FEV\(_1\) did not receive a second dose of study drug.

Dose 1 = time 0, Dose 2 = 10 hours after time 0

Reference ID: 3419276
Pulmonary Safety Studies in Patients with Asthma and COPD

Increased Pulmonary Adverse Events after Dose 2 of ADASUVE®

• A higher percentage of patients required albuterol treatment after Dose 2 compared to Dose 1 (Slide 9)

• A higher percentage of patients treated with ADASUVE had a decrease in $FEV_1$ after Dose 2 compared to Dose 1 (Slide 11)

• $FEV_1$s did not return to baseline up to 24 hours after administration of the second dose of ADASUVE (Slide 13)

ADASUVE may only be administered to a patient once in 24 hours.

Healthcare facilities must have policies in place to limit administration of ADASUVE to a single dose per patient in a 24-hour period.

Reference ID: 3419276
Mean Change from Baseline in FEV$_1$ in Patients with Asthma

Subjects in the ADASUVE group who had a >20% decrease in FEV$_1$ or developed respiratory symptoms after the first dose did not receive a second dose of ADASUVE in the pulmonary safety studies. Therefore 9 of 26 (35%) subjects in the asthma study did not receive a second dose.
Profile of Bronchospasm Occurring after a First Dose of ADASUVE® in Subjects with Asthma or COPD

In subjects who developed bronchospasm after a first dose of ADASUVE:

- **Timing:**
  - Symptoms occurred with a median time of 4 minutes in asthma subjects and 10 minutes in COPD subjects
  - In 11/12 subjects with asthma or COPD, symptoms began within 25 minutes

- **Outcome:**
  - When treatment was required, bronchospasm resolved with use of an inhaled bronchodilator (via metered-dose inhaler or nebulizer), without sequelae
Profile of Bronchospasm Occurring after a First Dose\textsuperscript{a} of ADASUVE® in Subjects with Asthma or COPD

-continued-

In subjects who developed bronchospasm after a first dose of ADASUVE:

• Albuterol was used by:
  – 7/26 (26.9\%) asthma subjects after ADASUVE 10 mg, compared with 1/26 (3.8\%) after placebo
  – 2/26 (7.7\%) COPD subjects after ADASUVE 10 mg, compared with 1/27 (3.7\%) after placebo

• After albuterol treatment, FEV1\textsuperscript{b} was documented to return to within 10\% of baseline in ≤ 1 hour
  – Asthma subjects: in 7/8 (87.5\%) instances
  – COPD subjects: in 2/3 (66.7\%) instances
  – At later, scheduled spirometry time points in the remaining 2 instances

\textsuperscript{a} And before Dose 2 in those who received it at the 10-hour time point
\textsuperscript{b} Forced expiratory volume in 1 second, as measured by spirometry

Reference ID: 3419276
Bronchospasm in Agitation Trials

- Bronchospasm (including reports of wheezing, shortness of breath, or cough) was reported in premarketing Phase 2 and 3 trials in patients with agitation associated with Schizophrenia or Bipolar I Disorder.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Frequency</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADASUVE® 10 mg</td>
<td>0.8%</td>
<td>2/259</td>
</tr>
<tr>
<td>Placebo</td>
<td>0%</td>
<td>0/263</td>
</tr>
</tbody>
</table>

- One episode of bronchospasm was treated with albuterol via metered-dose inhaler and oxygen via nasal cannula, and responded promptly.
  - The other event resolved without intervention.
**ADASUVE® Adverse Reactions\textsuperscript{a} in Premarketing Agitation Trials**

### Adverse Reactions in Short Term, Placebo-Controlled Phase 2 and 3 Trials

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (n = 263)</th>
<th>10 mg ADASUVE (n = 259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgeusia</td>
<td>5%</td>
<td>14%</td>
</tr>
<tr>
<td>Sedation</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Throat Irritation</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Adverse reactions (incidence > 2% and greater than placebo) for ADASUVE 10 mg
Steps to Reduce Risk of Bronchospasm

This poster is available to enrolled healthcare facilities to reinforce how to use ADASUVE® safely.

Healthcare facilities are encouraged to post this where ADASUVE will be administered.

Additional copies can be ordered at www.adasuverems.com or by calling 855-755-0492.