

Initial REMS Approval: 12/21/2012

NDA 022549

ADASUVE® (loxapine) Inhalation Powder

Teva Select Brands,

A division of Teva Pharmaceuticals USA, Inc.

Horsham, PA 19044

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S)

The goal of the ADASUVE® REMS is to mitigate the negative outcomes associated with ADASUVE-induced bronchospasm by:

- Ensuring that ADASUVE is dispensed only in certified healthcare settings that have immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation.
- Informing healthcare professionals in these settings that ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest.
- Informing healthcare professionals in these settings about the safe use of ADASUVE, including appropriate patient selection, monitoring, and management.

II. REMS ELEMENTS

A. Communication Plan

Teva Pharmaceuticals will implement a communication plan to healthcare providers to support the implementation of the REMS. This communication plan will include the following:

Dear Healthcare Professional Letter

Teva will ensure that Dear Healthcare Professional Letters will be distributed at least 2 weeks prior to product launch. The letter will include information on the risks associated with the use of ADASUVE and will explain the requirements of the REMS. The target audience for the letter will include psychiatrists and emergency medicine healthcare practitioners. These include healthcare practitioners who could be involved in the

prescribing, dispensing or administration of ADASUVE or the monitoring of patients who are administered ADASUVE, or who may have patients that receive ADASUVE.

Distribution will include, but not be limited to the member lists of the following professional organizations:

- American Psychiatric Association
- American Association for Emergency Psychiatry
- American Academy of Emergency Medicine
- Society for Academic Emergency Medicine
- American College of Emergency Physicians
- Emergency Nurses Association
- American Psychiatric Nurses Association
- College of Psychiatric and Neurologic Pharmacists
- US Psychiatric and Mental Health Congress
- American College of Nurse Practitioners

The letter will be available on the ADASUVE REMS website for 1 year from the date of the mailing.

The Dear Healthcare Professional Letter is part of the ADASUVE REMS and is appended.

B. Elements To Assure Safe Use

1. ADASUVE will only be dispensed in healthcare settings that are specially certified.

- a) Teva will ensure that ADASUVE will only be dispensed in certain healthcare settings that are specially certified. To become certified to dispense ADASUVE, each healthcare facility must enroll in the ADASUVE REMS Program.
- b) Each healthcare facility must designate an authorized representative to complete enrollment on behalf of the healthcare facility.
- c) Each healthcare facility must have immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation.

- d) Each healthcare facility must be equipped to provide immediate access on-site to a metered-dose inhaled and nebulized form of a short-acting beta-agonist bronchodilator (e.g., albuterol).
- e) Each healthcare facility must:
- Screen patients, prior to treatment with ADASUVE, for a current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD) or other lung disease associated with bronchospasm, acute respiratory signs/symptoms (e.g. wheezing), and current use of medications to treat airways disease such as asthma or COPD; and examine patients (including chest auscultation) for respiratory abnormalities.
 - Monitor patients at least every 15 minutes for a minimum of one hour following treatment with ADASUVE for symptoms and signs of bronchospasm (i.e., vital signs and chest auscultation).
 - Limit administration of ADASUVE to a single dose per patient within a 24-hour period.
- f) Each healthcare facility must train relevant staff (e.g., staff involved in prescribing, dispensing or administering ADASUVE and monitoring patients after ADASUVE administration) on the safe use of ADASUVE, as described in the ADASUVE REMS Education Program. This training and ongoing training must be documented and is subject to audit.
- g) Each healthcare facility must not dispense ADASUVE for outpatient use.
- h) Each healthcare facility must renew its enrollment in the ADASUVE REMS Program within 3 years from the date of initial enrollment, and every three years thereafter.
- i) Each healthcare facility must obtain ADASUVE from wholesalers/distributors that are enrolled in the ADASUVE REMS Program only.
- j) Each healthcare facility must not sell, loan, or transfer any ADASUVE inventory to any other pharmacy, institution, distributor, or prescriber.
- k) Each healthcare facility must establish procedures, protocols and/or order sets to help ensure compliance with the safe use conditions required in the ADASUVE REMS, and as described II.A.1.e through j., above. Healthcare facility procedures, protocols and/or order sets must be documented and are subject to audit.
- l) The authorized representative must complete and sign the *Healthcare Facility Enrollment Form* to enroll the healthcare facility. In signing the *Healthcare Facility Enrollment Form*, the authorized representative is required to acknowledge that:

- i) The representative has reviewed the ADASUVE REMS Education Program and understands that treatment with ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest.
- ii) The representative understands that ADASUVE is contraindicated in patients with a current diagnosis or history of asthma, COPD or other lung disease associated with bronchospasm, and patients with acute respiratory signs/symptoms (e.g., wheezing) or who are taking medications to treat airways disease, such as asthma or COPD.
- iii) The healthcare facility will meet the requirements in b. through j. above.
- iv) The representative understands the importance of reporting events of bronchospasm that require intubation or other advanced airway management, in addition to any fatalities that occur following ADASUVE treatment. To report suspected adverse events contact Teva Pharmaceuticals at 888-483-8279 (888-4TEVA-RX), or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch/report.htm.
- m) Teva will ensure that enrollment can successfully be completed online, by mail, or by faxing the completed forms, and that the ADASUVE REMS Education Program will be available as an in-service or online.
- n) Teva will ensure that as part of the enrollment process, the following materials, that are part of the ADASUVE REMS, are available to healthcare facilities. These materials are appended:
 - 1. Healthcare Facility Enrollment Information and Form
 - 2. Healthcare Provider Brochure
 - 3. Steps for Safe Use of ADASUVE
 - 4. Order Set / Protocol Template
 - 5. ADASUVE Education Program
 - 6. ADASUVE REMS website (www.adasuverems.com)
- o) Teva will ensure that all materials listed in or appended to the ADASUVE REMS will be available through the ADASUVE REMS Program website www.ADASUVEREMS.com or by calling the call center at 855-755-0492.

C. Implementation System

- 1. Teva will ensure that wholesalers/distributors who distribute ADASUVE are enrolled in the ADASUVE REMS Program. The wholesaler/distributor enrollment process is comprised of the

following steps that must be completed by the distributor's authorized representative, prior to receiving ADASUVE for distribution:

- a) Review the distributor ADASUVE REMS Program materials
- b) Complete and sign the *Wholesaler/Distributor Enrollment Form* and send it to Teva (by fax or mail). In signing the *Wholesaler/Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that ADASUVE is available only through the ADASUVE REMS Program and acknowledge that they must comply with the following ADASUVE REMS Program requirements:
 - i) The Wholesaler/Distributor will ensure that ADASUVE is only distributed to healthcare facilities in which enrollment in the ADASUVE REMS Program has been validated.
 - ii) The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that ADASUVE is distributed in accordance with the ADASUVE REMS Program requirements.
 - iii) Wholesalers/Distributors will be required to renew their enrollment in the ADASUVE REMS Program every three (3) years.
- c) Teva will ensure that all forms are complete prior to enrolling a distributor in the ADASUVE REMS Program.
- d) Teva will notify distributors when they are enrolled in the ADASUVE REMS Program and, therefore, able to distribute ADASUVE.
- e) The following materials are part of the REMS and are appended:
 - 1) Wholesaler/Distributor Enrollment Form
- 2. Teva will maintain a validated and secured database that includes a list of all certified healthcare facilities, which will be available to wholesalers/distributors to ensure distribution of the product only to certified facilities. Teva will monitor and review enrollment and product distribution data to assess compliance with the requirement that ADASUVE will only be distributed to certified facilities.
- 3. Teva will notify certified healthcare facilities and wholesalers/distributors before their enrollment is due to expire of the need to re-enroll in the ADASUVE REMS Program.
- 4. If there are substantive changes to the ADASUVE REMS Program, Teva will update all affected materials and notify healthcare facilities and wholesalers/distributors of the changes, as applicable.

5. Based on monitoring and evaluation of the ADASUVE REMS Elements to Assure Safe Use, Teva will take reasonable steps to improve implementation of these elements and to maintain compliance with the ADASUVE REMS Program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Teva will submit REMS Assessments to the FDA at 6 and 12 months from the date of the REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Teva will submit each assessment so that it will be received by the FDA on or before the due date.

IMPORTANT DRUG WARNING

- Risk of bronchospasm with ADASUVE® (loxapine) inhalation powder
- ADASUVE is available only in enrolled healthcare facilities, under an FDA-required REMS Program

Dear Healthcare Professional:

This letter contains important safety information for ADASUVE (loxapine) inhalation powder.

ADASUVE is a drug-device combination product that delivers the antipsychotic, loxapine, by oral inhalation. ADASUVE has been approved by the US Food and Drug Administration (FDA) for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of treatment outweigh the risk of bronchospasm in patients treated with ADASUVE.

ADASUVE is not available in an outpatient setting. If you are an outpatient provider, you are receiving this letter because ADASUVE may be, or may have been, administered to one of your patients in an enrolled healthcare facility. **Enrolled healthcare facilities, such as an acute care or inpatient setting, must have immediate on-site access to equipment and personnel trained to manage acute bronchospasm, including advanced airway management, eg, intubation and mechanical ventilation.** (See below for more facility enrollment requirements.)

It is important that anyone caring for patients treated with ADASUVE be aware of the risk of bronchospasm after administration.

Risk of Bronchospasm With ADASUVE®

- ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest
- Patients with asthma, chronic obstructive pulmonary disease (COPD), or other lung diseases associated with bronchospasm are at increased risk of bronchospasm
- ADASUVE is contraindicated in patients with the following:
 - Current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm
 - Acute respiratory symptoms or signs (eg, wheezing)
 - Current use of medications to treat airways disease, such as asthma or COPD
 - History of bronchospasm following ADASUVE treatment
- ADASUVE administration is limited to a single dose per patient within a 24-hour period

Other Safety Information

- ADASUVE is also contraindicated in patients with hypersensitivity to loxapine or amoxapine (eg, serious skin reaction)
- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ADASUVE is not approved for the treatment of patients with dementia-related psychosis

To Administer ADASUVE[®], Healthcare Facilities Must Enroll in the ADASUVE REMS Program

ADASUVE can only be administered in healthcare facilities that are enrolled in the ADASUVE REMS Program. To enroll in the ADASUVE REMS Program, a healthcare facility must have the following:

- Immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation
- Immediate access to a metered-dose inhaled and nebulized form of a short-acting beta-agonist bronchodilator (eg, albuterol)
- Established policies, procedures or order sets in place to comply with the necessary screening and monitoring requirements of the ADASUVE REMS Program

Staff who prescribe, dispense, or administer ADASUVE, or monitor patients after receiving ADASUVE, must be trained on the safe use of ADASUVE via the ADASUVE REMS Education Program. The REMS Education Program is available as an in-service, conducted at enrolled healthcare facilities, or can be completed online.

If you would like more information please call 855-755-0492 or visit the website at www.adasuverems.com.

Adverse Event Reporting

Healthcare professionals should report suspected adverse events associated with ADASUVE to Teva Pharmaceuticals at 888-483-8279 (888-4TEVA-RX). In addition, adverse event reports may also be reported to the FDA MedWatch Reporting System by the following methods:

- Online at www.fda.gov/medwatch/report.htm or
- Phone at 1-800-FDA-1088

Sincerely,

Enclosure: ADASUVE Full Prescribing Information

ADASUVE® (loxapine) Inhalation Powder

ADASUVE

Risk Evaluation and Mitigation Strategy (REMS) Program Healthcare Provider Brochure

This brochure includes information about:

- The risk of bronchospasm
- Recommendations for safe use of ADASUVE
- What to communicate to your patients
- Instructions for Healthcare Facility enrollment



Please share this Healthcare Provider Brochure with anyone in your healthcare facility who is involved in prescribing, dispensing, or administering ADASUVE or who monitors patients after treatment with ADASUVE.

Questions about ADASUVE?

Contact Teva Pharmaceuticals Medical Services Department at
888-483-8279 (888-4TEVA-RX).

Reference ID: 3419276 Please see Full Prescribing Information, including Boxed Warning.

About This Brochure

The Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of ADASUVE® outweigh the risk of bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Patients with asthma, chronic obstructive pulmonary disease (COPD), or other pulmonary diseases are at increased risk of bronchospasm after taking ADASUVE. This brochure contains information for providers on the benefits, risks, and safe use of ADASUVE, as well as information on healthcare facility enrollment requirements of the ADASUVE REMS Program; ADASUVE can only be distributed to and administered in healthcare facilities that are enrolled in the ADASUVE REMS Program.

Indications and Usage

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

“Psychomotor agitation” is defined in DSM-IV as “excessive motor activity associated with a feeling of inner tension.” Patients experiencing agitation often manifest behaviors that interfere with their care (eg, threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior), leading clinicians to the use of rapidly absorbed antipsychotic medications to achieve immediate control of the agitation.

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.

Limitations of Use:

As part of the ADASUVE REMS Program to mitigate the risk of bronchospasm, ADASUVE must be administered only in an enrolled healthcare facility.

Important Safety Information

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 symptoms or signs (eg, wheezing)
- Current use of medications to treat airways disease, such as asthma or COPD
- History of bronchospasm following ADASUVE treatment
- Known hypersensitivity to loxapine or amoxapine (eg, serious skin reaction)



Boxed Warning for ADASUVE®

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, screen patients regarding a current diagnosis, history, or symptoms of asthma, COPD, and other lung diseases and examine (including chest auscultation) patients for respiratory signs. Monitor for signs and symptoms of bronchospasm following treatment with ADASUVE.

Restricted Use to Mitigate Bronchospasm

Because of the risk of bronchospasm, ADASUVE is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ADASUVE REMS. Under the ADASUVE REMS Program, healthcare facilities and distributors must enroll in the program.

Increased Mortality In Elderly Patients With Dementia-related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ADASUVE is not approved for the treatment of patients with dementia-related psychosis.





These risks do not constitute a complete list of all the risks associated with ADASUVE. Please see the enclosed full prescribing information for more information regarding the risks associated with ADASUVE.

Steps for the Safe Use of ADASUVE®

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.

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

ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Patients with asthma, chronic obstructive pulmonary disease (COPD), or other lung disease associated with bronchospasm are at increased risk of bronchospasm.

Steps for Safe Use of ADASUVE	
 SCREEN	<ul style="list-style-type: none">□ Ask if patient is taking medication to treat asthma or COPD and/or check medical records□ Ask if patient has a current diagnosis or history of asthma, COPD, or other lung disease, and/or check medical records□ Examine patients (including chest auscultation) for respiratory abnormalities (eg, wheezing) <p>Do not use in patients with acute respiratory signs or symptoms; with a current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm; or with current use of medications to treat airways disease, such as asthma or COPD</p>
 COUNSEL	<ul style="list-style-type: none">□ Counsel patient/caregiver on potential for bronchospasm that may occur after dosing and the need for them to report symptoms immediately
 MONITOR	<ul style="list-style-type: none">□ Monitor patient every 15 minutes for at least 1 hour after treatment for signs and symptoms of bronchospasm including chest auscultation□ Ask patient every 15 minutes about any difficulty breathing
 MANAGE	<ul style="list-style-type: none">□ Treat bronchospasm with an inhaled short-acting beta-agonist bronchodilator (eg, albuterol)□ If medically necessary, provide additional therapy for bronchospasm per asthma guidelines, including intubation and mechanical ventilation as needed

Reporting Adverse Events

Healthcare professionals should understand the importance of reporting events of bronchospasm that require intubation or other advanced airway management, in addition to any fatalities that occur following ADASUVE treatment. To report suspected adverse events contact Teva Pharmaceuticals at 888-483-8279 (888-4TEVA-RX), FDA at 1-800-FDA-1088, or www.fda.gov/medwatch/report.htm.



Patient Counseling

Discuss the benefits and risks associated with ADASUVE® therapy with patients and their caregivers.

Helping Patients and Caregivers Understand the Risks

- Explain that in certain patients, ADASUVE may cause narrowing of the airways (bronchospasm) and may cause them to wheeze, cough, feel chest tightness, or have shortness of breath
- Ask patients to tell you if they are currently taking any medications to treat asthma, COPD, or a breathing problem or have a history of asthma, COPD, or other respiratory conditions
- Inform patients that other serious side effects may occur, such as neuroleptic malignant syndrome, tardive dyskinesia, orthostatic hypotension, or seizures
- Inform patients about other common side effects that may include dysgeusia (taste) and sleepiness

Helping Patients and Caregivers Report the Signs and Symptoms of Bronchospasm

- Ask patients to tell you immediately if they experience difficulty breathing or feel chest tightness or wheezing after they have received a treatment
- Tell patients you have a medicine available to treat any breathing problems that might occur

ADASUVE is provided with a Medication Guide. If practical, please review the Medication Guide with your patient or their caregiver before administering the product.

About ADASUVE®

Administration of ADASUVE

- ADASUVE is only administered by oral inhalation
- ADASUVE must be administered only by a healthcare professional, in an enrolled healthcare facility
- Administer only a single dose per patient within a 24-hour period

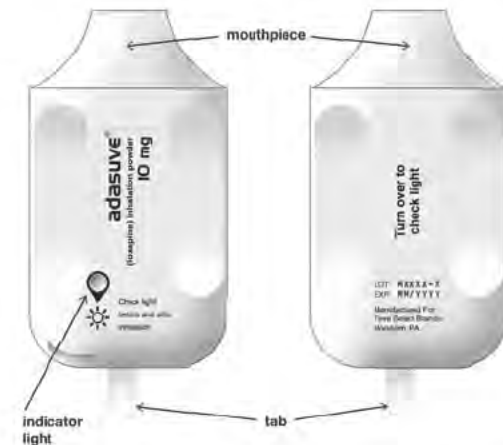
Required Examination Prior to Dosing

Prior to administering ADASUVE, screen all patients for current use of medications to treat asthma or COPD, a history of asthma, COPD, or other lung disease, and examine patients (including chest auscultation) for respiratory abnormalities (eg, wheezing).

Becoming Familiar With ADASUVE

- ADASUVE is provided in a sealed pouch
- The indicator light is off when ADASUVE is removed from the pouch
- The indicator light turns on (green) when the tab is pulled out. The inhaler is then ready for use
- The indicator light turns off after the patient inhales. This indicates that the dose has been delivered
- If the indicator light does NOT turn off, the dose has NOT been delivered. See Instructions for Use

The pictures below show the important features of the ADASUVE product (both sides shown).



Important Administration Instructions



1. Open the pouch.

When ready to use, tear open the foil pouch and remove the inhaler from the package.

When the ADASUVE® inhaler is removed from the pouch, the indicator light is off.



2. Pull tab.

Firmly pull the plastic tab from the rear of the inhaler. Check that the green light turns on. This indicates that the inhaler is ready for use. Use the inhaler within 15 minutes after removing the tab to prevent automatic deactivation of the inhaler. The green light will turn off, indicating that the inhaler is not usable. Discard the inhaler after one use.

3. Explain procedures to the patient.

Explain the administration procedures to the patient prior to use, and advise the patient that it is important to follow the instructions. Inform the patient that the inhaler may produce a flash of light and a clicking sound, and it may become warm during use. These are normal.



4. Instruct the patient to exhale.

Instruct the patient to hold the inhaler away from the mouth and breathe out fully to empty the lungs.



5. Instruct the patient to inhale.

Instruct the patient to put the mouthpiece of the inhaler between the lips, close the lips, and inhale through the mouthpiece with a steady deep breath. Check that the green light turns off indicating that the dose has been delivered.



6. Instruct the patient to hold breath.

Instruct the patient to remove the mouthpiece from the mouth and hold the breath for as long as possible, up to 10 seconds.

IMPORTANT

If the green light remains on after the patient inhales, the dose of ADASUVE has NOT been delivered. Instruct the patient to repeat Step 4, Step 5, and Step 6 up to 2 additional times. If the green light still does not turn off, discard the inhaler and use a new one.

Monitoring to Assess Safety

Monitor the patient for signs and symptoms of bronchospasm after ADASUVE administration. Perform a physical examination, including chest auscultation, at least every 15 minutes for at least 1 hour after ADASUVE administration.

Prescribing and Administering ADASUVE® at Your Healthcare Facility

- **ADASUVE will be dispensed only to patients in certain healthcare facilities that are enrolled in the ADASUVE REMS Program**
- **Wholesalers/distributors will ship ADASUVE only to enrolled healthcare facilities**

Healthcare Facility Qualifications for Enrollment

The healthcare facility requirements include having the following:

- Immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation
- Immediate access on-site to a metered-dose inhaled and nebulized form of a short-acting beta-agonist bronchodilator (eg, albuterol)
- Procedures, protocols, and/or order sets to ensure the following:
 - Patients are screened, prior to treatment with ADASUVE, for a history of pulmonary disease and for acute respiratory signs and symptoms by physical exam, including taking vital signs and chest auscultation, and inquiring if patient is taking medication to treat asthma or COPD
 - Patients are monitored at least every 15 minutes for a minimum of 1 hour following treatment with ADASUVE for signs and symptoms of bronchospasm, including taking vital signs and chest auscultation
 - Administration of ADASUVE is limited to 1 dose per patient within 24 hours
- Healthcare providers within the facility (prescribers, nurses, monitoring staff, or pharmacists) who are trained on safe use of ADASUVE using the ADASUVE REMS Education Program



Prescribing and Administering ADASUVE® at Your Healthcare Facility (cont'd)

Authorized Healthcare Facility Representative

For each healthcare facility, an *authorized healthcare facility representative* is required to review the **ADASUVE REMS Education Program**, and complete and sign the **Healthcare Facility Enrollment Form** acknowledging that the enrolled healthcare facility meets specific requirements. This representative may be a pharmacist or another healthcare professional with the appropriate level of responsibility within the healthcare facility, who is authorized to act on behalf of the facility.

To enroll your healthcare facility, please read and complete the Healthcare Facility Enrollment Form that is available at www.adasuverems.com.

For questions about the ADASUVE REMS Program, please call 855-755-0492.

ADASUVE® REMS Materials for Enrolled Healthcare Facilities

The following materials are part of the ADASUVE REMS Program and will assist enrolled healthcare facilities in complying with ADASUVE REMS requirements. They are available to review, order, or print at www.adasuverems.com or by calling 855-755-0492.

1. ADASUVE REMS Education Program

Must be reviewed by all healthcare providers within an enrolled healthcare facility who will be prescribing or administering ADASUVE, or observing patients after ADASUVE is administered.

2. Steps for Safe Use of ADASUVE Poster

Should be posted where ADASUVE is administered within enrolled healthcare facilities.

3. Order Set/Protocol Template

For use by enrolled healthcare facilities to assist with designing procedures, protocols, and/or order sets that meet the requirements of the ADASUVE REMS Program.

4. ADASUVE Healthcare Provider Brochure

Contains information for providers on the benefits, risks, and safe use of ADASUVE, as well as information on healthcare facility enrollment requirements of the ADASUVE REMS Program.

Other resources are available at www.adasuverems.com

- Dear Healthcare Professional Letter
- Healthcare Facility Enrollment Information and Form
- Full Prescribing Information
- ADASUVE Instructions for Use
- ADASUVE Medication Guide



Reporting Adverse Events

Healthcare professionals should report suspected adverse events associated with ADASUVE® treatment to Teva Pharmaceuticals at 888-483-8279 (888-4TEVA-RX). In addition, adverse events may be reported to the FDA MedWatch Reporting System by the following methods:

- Online at www.fda.gov/medwatch/report.htm
- Phone at **1-800-FDA-1088**
- Fax at **1-800-FDA-0718**, using the MedWatch Form 3500 (available at www.fda.gov/medwatch/getforms.htm)

The Full Prescribing Information and Medication Guide are also available from your local sales representative or by calling **800-545-8800**.



Please share this Healthcare Provider Brochure with anyone in your healthcare facility who is involved in prescribing, dispensing, or administering ADASUVE or who monitors patients after treatment with ADASUVE.

Please see Full Prescribing Information, including Boxed Warning.







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Steps for Safe Use of ADASUVE®

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

ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Patients with asthma, chronic obstructive pulmonary disease (COPD), or other lung disease associated with bronchospasm are at increased risk of bronchospasm.



Steps for Safe Use of ADASUVE	
 SCREEN	<ul style="list-style-type: none"><input type="checkbox"/> Ask if patient is taking medication to treat asthma or COPD and/or check medical records<input type="checkbox"/> Ask if patient has a current diagnosis or history of asthma, COPD, or other lung disease, and/or check medical records<input type="checkbox"/> Examine patients (including chest auscultation) for respiratory abnormalities (eg, wheezing)<input type="checkbox"/> Do not use in patients with acute respiratory signs or symptoms; with a current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm; or with current use of medications to treat airways disease, such as asthma or COPD
 COUNSEL	<ul style="list-style-type: none"><input type="checkbox"/> Counsel patient/caregiver on potential for bronchospasm that may occur after dosing and the need for them to report symptoms immediately
 MONITOR	<ul style="list-style-type: none"><input type="checkbox"/> Monitor patient every 15 minutes for at least 1 hour after treatment for signs and symptoms of bronchospasm including chest auscultation<input type="checkbox"/> Ask patient every 15 minutes about any difficulty breathing
 (if bronchospasm occurs) MANAGE	<ul style="list-style-type: none"><input type="checkbox"/> Treat bronchospasm with an inhaled short-acting beta-agonist bronchodilator (eg, albuterol)<input type="checkbox"/> If medically necessary, provide additional therapy for bronchospasm per asthma guidelines, including intubation and mechanical ventilation as needed

Phone 855-755-0492 Fax 855-755-0493 www.adasuverems.com



ADASUVE® REMS Program
**WHOLESALE/DISTRIBUTOR
ENROLLMENT FORM**



Enrollment must be complete to distribute ADASUVE. Please complete this form and do one of the following:

Fax	855-755-0493
Scan and e-mail to	Enrollment@AdasuveREMSProgram.com
Submit online at	www.adasuverems.com/enrollment

WHOLESALE/DISTRIBUTOR AGREEMENT

I understand that ADASUVE is available only through the ADASUVE REMS Program and acknowledge that I must comply with the following program requirements:

- I will ensure that ADASUVE is distributed only to healthcare facilities in which enrollment in the ADASUVE REMS Program has been validated
- I agree to cooperate with periodic audits or non-compliance investigations to ensure that ADASUVE is distributed in accordance with the program requirements
- I understand I will be required to renew the wholesaler/distributor's enrollment in the ADASUVE REMS Program every three (3) years
- I understand that this information may be shared with government agencies

Wholesaler/Distributor Authorized Representative (**Signature**)

Date

Wholesaler/Distributor Authorized Representative (**Print**)

Title

WHOLESALE/DISTRIBUTOR INFORMATION

Wholesaler/Distributor Name _____
Primary Ship to Address _____
City _____ State _____ ZIP _____
Office Phone _____ Fax _____

AUTHORIZED REPRESENTATIVE INFORMATION

First Name _____ Last Name _____
Position/Title _____
Phone _____ Fax _____
Email _____

HOW TO ENROLL IN THE ADASUVE[®] REMS PROGRAM (Risk Evaluation and Mitigation Strategy)



HEALTHCARE FACILITY ENROLLMENT INFORMATION

ADASUVE is only available from wholesalers and distributors that are enrolled in the ADASUVE REMS Program. A healthcare facility (HCF) that wants to administer ADASUVE must enroll in the ADASUVE REMS Program to order and receive ADASUVE.

3 STEPS TO HEALTHCARE FACILITY ENROLLMENT

For each healthcare facility, an **authorized healthcare facility representative** is required to complete and sign the *Healthcare Facility Enrollment Form* acknowledging that the enrolled HCF meets specific requirements. This representative may be a pharmacist, or another healthcare professional with the appropriate level of responsibility within the healthcare facility, who is authorized to act on behalf of the facility.

REVIEW

The authorized healthcare facility representative must review the following:

- *Healthcare Facility Enrollment Form* to become familiar with the enrollment requirements for healthcare facilities
- *ADASUVE REMS Education Program* to become familiar with the safe use conditions for ADASUVE

COMPLETE AND SIGN

The healthcare facility representative completes the *Healthcare Facility Enrollment Form* online at www.adasuverems.com/enrollment, or prints the form and then completes and signs it.

By signing the form, the representative is attesting that the healthcare facility will meet all the ADASUVE REMS Program requirements prior to ordering ADASUVE.

SUBMIT

If the form was completed online, follow the instructions to submit online.

OR

Submit completed, signed form via fax at:
855-755-0493

OR

Scan completed, signed form and submit via e-mail at:
Enrollment@
AdasuveREMSProgram.com

Note

Healthcare facilities must re-enroll every 3 years. You will be notified by fax or e-mail 60 days prior to your re-enrollment date.

ORDERING ADASUVE

- Once the completed enrollment form is received by the ADASUVE REMS Program, it will be entered into the ADASUVE REMS Program database, which is a secured database and is accessed only by the wholesaler/distributor and Teva Pharmaceuticals
- When you place an order for ADASUVE through your wholesaler/distributor, they will check the database to confirm that your healthcare facility is enrolled. Once enrollment is confirmed, the wholesaler/distributor is allowed to ship ADASUVE to your facility

ADASUVE® REMS Program
**HEALTHCARE FACILITY
ENROLLMENT FORM**



Enrollment must be complete to order and receive ADASUVE from your wholesaler/distributor.

☐ New Enrollment

☐ Re-Enrollment (Required every 3 years)

To be enrolled in the
ADASUVE REMS Program,
complete this form and and
do one of the following:

Fax

855-755-0493 (Fax both pages)

Scan and e-mail to

Enrollment@AdasuveREMSProgram.com

Submit online at

www.adasuverems.com/enrollment

HEALTHCARE FACILITY INFORMATION

Healthcare Facility Name _____

Facility DEA or NPI Number _____

Facility Type ☐ Medical Hospital ☐ Psychiatric Hospital ☐ Other _____

Facility Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

AUTHORIZED HEALTHCARE FACILITY REPRESENTATIVE INFORMATION

First Name _____ Last Name _____

Position/Title _____

Phone _____ Fax _____

E-mail _____

Preferred communication method ☐ E-mail ☐ Fax

HEALTHCARE FACILITY AGREEMENT

As an authorized representative for this facility, I acknowledge that:

- i. I am authorized to complete enrollment on behalf of this healthcare facility.
- ii. I have reviewed the ADASUVE REMS Education Program and understand that treatment with ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest.
- iii. I understand that ADASUVE is contraindicated in patients with a current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD) or other lung disease associated with bronchospasm, and patients with acute respiratory signs/symptoms (eg, wheezing) or who are taking medications to treat airways disease, such as asthma or COPD.

HEALTHCARE FACILITY AGREEMENT (cont'd)

- iv. This healthcare facility has immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation.
- v. This healthcare facility is equipped to provide immediate access on-site to a metered-dose inhaler and nebulized form of a short-acting beta-agonist bronchodilator (eg, albuterol).
- vi. This healthcare facility must establish procedures, protocols and/or order sets that are subject to audit, to help ensure compliance with the safe use conditions required in the ADASUVE REMS including the following:
- Screening patients, prior to treatment with ADASUVE, for a current diagnosis or history of asthma, COPD and other lung disease associated with bronchospasm, acute respiratory signs or symptoms (eg, wheezing), and current use of medications to treat airways disease such as asthma or COPD; and examine patients (including chest auscultation) for respiratory abnormalities
 - Monitoring patients at least every 15 minutes for a minimum of one hour following treatment with ADASUVE for signs or symptoms of bronchospasm (ie, vital signs and chest auscultation)
 - Limiting administration of ADASUVE to a single dose per patient within a 24 hour period
- vii. This healthcare facility must train relevant staff (eg, staff involved in prescribing, dispensing or administering ADASUVE and monitoring patients after ADASUVE administration) on the safe use of ADASUVE, as described in the ADASUVE REMS Education Program. This training and ongoing training must be documented and is subject to audit.
- viii. This healthcare facility must not dispense ADASUVE for outpatient use.
- ix. I understand this healthcare facility must renew its enrollment in the ADASUVE REMS Program within 3 years from the date of initial enrollment, and every three years thereafter.
- x. I understand this healthcare facility must obtain ADASUVE from wholesalers/distributors that are enrolled in the ADASUVE REMS Program only.
- xi. I understand that this healthcare facility must not sell, loan or transfer any ADASUVE inventory to any other pharmacy, institution, distributor, or prescriber.
- xii. The representative understands the importance of reporting events of bronchospasm that require intubation or other advanced airway management, in addition to any fatalities that occur following ADASUVE treatment. To report suspected adverse events contact Teva Pharmaceuticals at 888-483-8279 (888-4TEVA-RX), FDA at 1-800-FDA-1088 or www.fda.gov/medwatch/report.htm.

I confirm that the information above is correct. I understand that this information will be used to document healthcare facilities that are eligible to receive ADASUVE. I also understand that this information may be shared with government agencies.

Authorized Healthcare Facility Representative (**Signature**)

Date

Authorized Healthcare Facility Representative (**Print**)

Title

ORDER SET/PROTOCOL TEMPLATE

This template is to be used as a guideline for developing procedures, protocols and/or order sets around the use of ADASUVE® to ensure that REMS requirements are being met.

INDICATION

- ☐ Agitation associated with bipolar I disorder
- ☐ Agitation associated with schizophrenia

PATIENT SCREENING

PRIOR TO DOSING:

Assess for acute respiratory symptoms

- ☐ wheezing ☐ cough
- ☐ dyspnea ☐ other: _____

Assess for respiratory signs
(include chest auscultation)

- ☐ wheezing ☐ other: _____

Inquire and/or check medical records for:

- ☐ current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm
- ☐ current use of medications to treat airways disease, such as asthma or COPD
- ☐ history of bronchospasm following ADASUVE treatment
- ☐ known hypersensitivity (eg, serious skin reaction) to loxapine or amoxapine

If any of the above screening is positive, DO NOT USE ADASUVE. ADASUVE is contraindicated in these patients.

DOSE ADMINISTERED

TIME: _____

Limit ADASUVE use to a single dose per patient within a 24-hour period.

POST-TREATMENT OBSERVATION/MONITORING

Patient must be monitored every 15 minutes for at least 1 hour after treatment for signs/symptoms of bronchospasm.

MONITORING

TIME: _____

- ☐ Heart rate (rate per minute): _____
- ☐ Respiratory rate (rate per minute): _____
- ☐ Chest auscultation (clear/other) _____
- ☐ Check for respiratory signs/symptoms
 - ☐ wheezing ☐ cough
 - ☐ dyspnea ☐ chest tightness
 - ☐ other: _____

TIME: _____

- ☐ Heart rate (rate per minute): _____
- ☐ Respiratory rate (rate per minute): _____
- ☐ Chest auscultation (clear/other) _____
- ☐ Check for respiratory signs/symptoms
 - ☐ wheezing ☐ cough
 - ☐ dyspnea ☐ chest tightness
 - ☐ other: _____

TIME: _____

- ☐ Heart rate (rate per minute): _____
- ☐ Respiratory rate (rate per minute): _____
- ☐ Chest auscultation (clear/other) _____
- ☐ Check for respiratory signs/symptoms
 - ☐ wheezing ☐ cough
 - ☐ dyspnea ☐ chest tightness
 - ☐ other: _____

TIME: _____

- ☐ Heart rate (rate per minute): _____
- ☐ Respiratory rate (rate per minute): _____
- ☐ Chest auscultation (clear/other) _____
- ☐ Check for respiratory signs/symptoms
 - ☐ wheezing ☐ cough
 - ☐ dyspnea ☐ chest tightness
 - ☐ other: _____

Note: Treat bronchospasm with inhaled short-acting beta agonist bronchodilator (eg, albuterol) and other measures as clinically indicated.

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

-continued-

- 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 treatment 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

Asthma	Placebo (N = 26)	ADASUVE® (N = 26)
Number of subjects receiving albuterol rescue at any time	3/26 (12%)	14/26 (54%)
Number receiving rescue after Dose 1	1/26 (4%)	7/26 (27%)
Number receiving rescue after Dose 2	2/25 (8%)	7/17 (41%)
COPD	Placebo (N = 27)	ADASUVE® (N = 26)
Number of subjects receiving albuterol rescue at any time	4/27 (15%)	6/26 (23%)
Number receiving rescue after Dose 1	1/27 (4%)	2/26 (8%)
Number receiving rescue after Dose 2	3/26 (12%)	4/19 (21%)

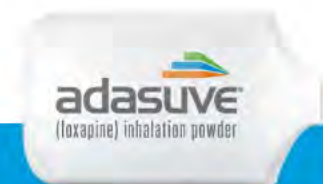


Pulmonary Safety Studies in Patients with Asthma and COPD

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 FEV₁ from Baseline in Healthy Volunteer, Asthma and COPD Trials

		Healthy Volunteer		Asthma		COPD	
	Maximum % FEV ↓	Placebo N (%)	ADASUVE N (%)	Placebo N (%)	ADASUVE N (%)	Placebo N (%)	ADASUVE N (%)
After any Dose		N=26	N=26	N=26	N=26	N=27	N=25
	≥10	7 (27%)	7 (27%)	3 (12%)	22 (85%)	18 (67%)	20 (80%)
	≥15	1 (4%)	5 (19%)	1 (4%)	16 (62%)	9 (33%)	14 (56%)
	≥20	0	1 (4%)	1 (4%)	11 (42%)	3 (11%)	10 (40%)
After Dose 1		N=26	N=26	N=26	N=26	N=27	N=25
	≥10	4 (15%)	5 (19%)	2 (8%)	16 (62%)	8 (30%)	16 (64%)
	≥15	1 (4%)	2 (8%)	1 (4%)	8 (31%)	4 (15%)	10 (40%)
	≥20	0	0	1 (4%)	6 (23%)	2 (7%)	9 (36%)
After Dose 2		N=26	N=25	N=25	N=17	N=26	N=19
	≥10	5 (19%)	6 (24%)	3 (12%)	12 (71%)	15 (58%)	12 (63%)
	≥15	0	5 (20%)	1 (4%)	9 (53%)	6 (23%)	10 (53%)
	≥20	0	1 (4%)	1 (4%)	5 (30%)	1 (4%)	5 (26%)

FEV₁ 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 FEV₁ did not receive a second dose of study drug.
 Dose 1 = time 0, Dose 2 = 10 hours after time 0



Pulmonary Safety Studies in Patients with Asthma and COPD

Increased Pulmonary Adverse Events after Dose 2 of ADASUVE®

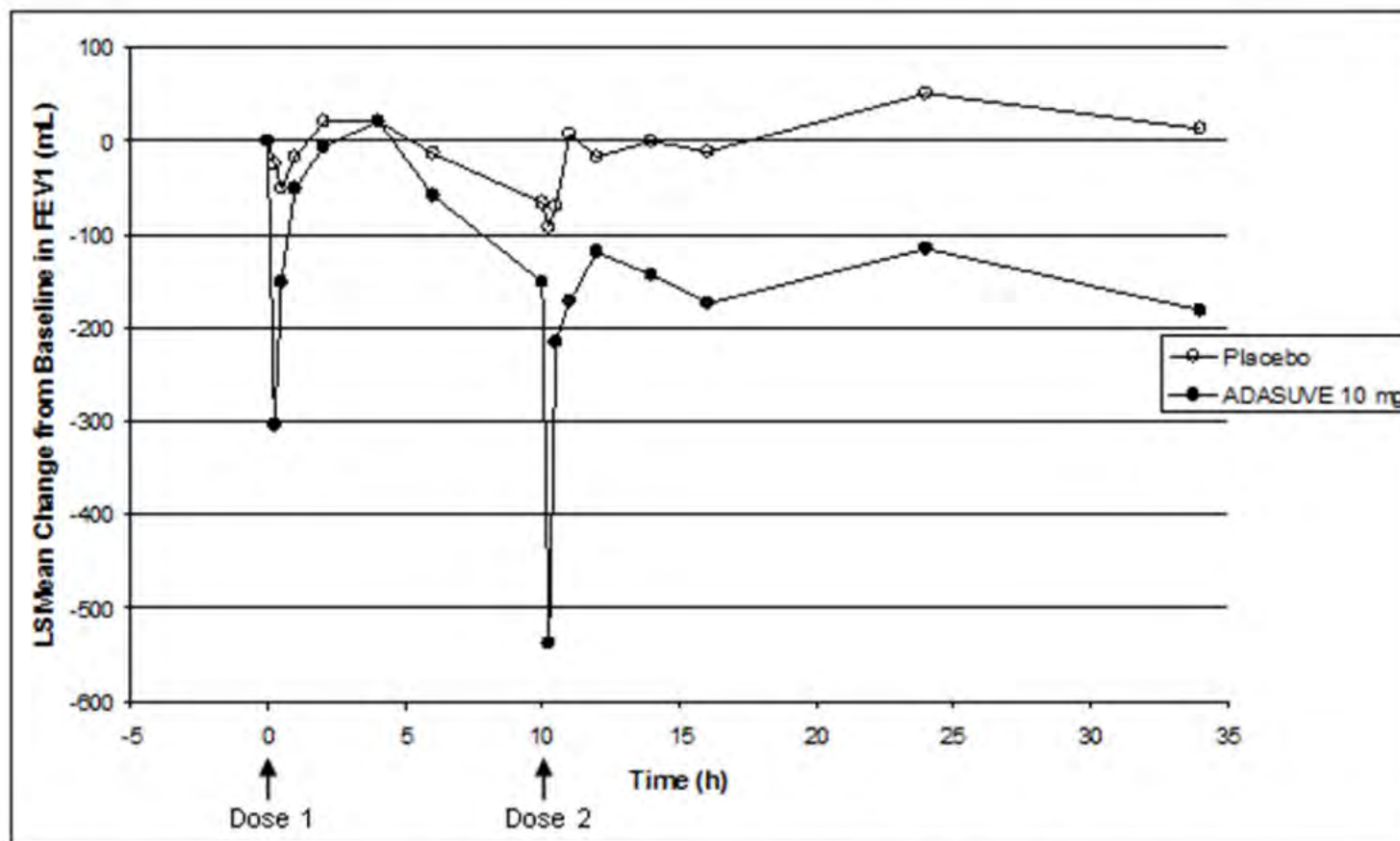
- A higher percentage of patients required albuterol treatment after Dose 2 compared to Dose 1 (Slide 9)
- A higher percentage of patients treated with ADASUVE had a decrease in FEV₁ after Dose 2 compared to Dose 1 (Slide 11)
- FEV₁s did not return to baseline up to 24 hours after administration of the 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.



Mean Change from Baseline in FEV₁ in Patients with Asthma



Subjects in the ADASUVE group who had a >20% decrease in FEV₁ 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^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^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

a And before Dose 2 in those who received it at the 10-hour time point

b Forced expiratory volume in 1 second, as measured by spirometry



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**

ADASUVE® 10 mg 0.8% (2/259)

Placebo 0% (0/263)

- 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^a in Premarketing Agitation Trials

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

Adverse Reaction	Placebo (n = 263)	10 mg ADASUVE (n = 259)
Dysgeusia	5%	14%
Sedation	10%	12%
Throat Irritation	0%	3%

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.



Steps for Safe Use of ADASUVE®



SCREEN



COUNSEL



OBSERVE



MANAGE

- Ask if patient is taking medication to treat asthma or COPD and / or check medical records
- Ask if patient has a current diagnosis or history of asthma, COPD or other lung disease and / or check medical records
- Examine patients (including chest auscultation) for respiratory abnormalities (eg, wheezing)
- **Do not use in patients with acute respiratory signs or symptoms, with a current diagnosis or history of asthma, COPD or other lung disease associated with bronchospasm; or with current use of medications to treat airways disease, such as asthma or COPD**
- Counsel patient/caregiver on potential for bronchospasm that may occur after dosing and the need to report symptoms immediately
- Monitor patients every 15 minutes for at least 1 hour after treatment for signs or symptoms of bronchospasm, including chest auscultation
- Ask patient every 15 minutes about any difficulty breathing
- Treat bronchospasm with an inhaled short-acting beta-agonist bronchodilator (eg, albuterol)
- If medically necessary, provide additional therapy for bronchospasm per asthma guidelines, including intubation and mechanical ventilation as needed



Reporting Adverse Events Associated with ADASUVE®

Healthcare professionals should understand the importance of reporting events of bronchospasm that require intubation or other advanced airway management, in addition to any fatalities that occur following ADASUVE treatment.

Suspected adverse events may be reported by the following methods:

- Teva Pharmaceuticals at 888-483-8279 (888-4TEVA-RX)
- FDA at 1-800-FDA-1088
- FDA at www.fda.gov/medwatch/report.htm



Patient Counseling

Discuss the benefits and risks associated with ADASUVE® treatment with patients and their caregivers.

Helping Patients and Caregivers Understand Risks

- Explain that certain patients may have bronchospasm after using ADASUVE
- Ask patients to tell you if they are **currently taking medications** to treat asthma, COPD, other breathing problems
- Inform patients of other common side effects that may occur with ADASUVE (taste and sleepiness)
- Inform patients of other serious side effects that can occur with antipsychotics, in general

Helping Patients Report Signs / Symptoms of Bronchospasm

- Ask patients to tell you **immediately** if they experience:
 - Difficulty breathing
 - Chest tightness
 - Wheezing
- Tell patients you have a medicine available to treat breathing problems that might occur



Administration of ADASUVE®

- ADASUVE is only administered by oral inhalation
- ADASUVE must be administered only by a healthcare professional, in an enrolled healthcare facility

Required Examination Prior to Dosing:

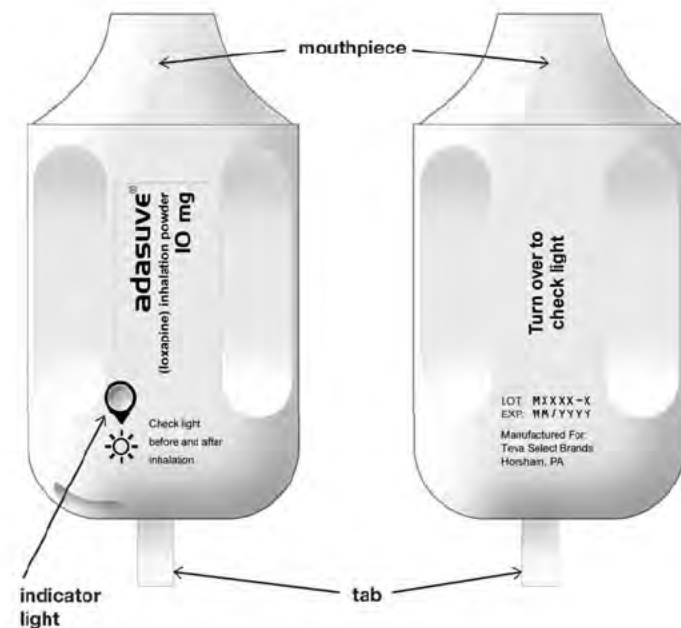
- Prior to administering ADASUVE, screen all patients for:
 - Current use of medications to treat asthma or COPD
 - History of asthma, COPD or other pulmonary disease
 - Examine patients (including chest auscultation) for respiratory abnormalities (eg, wheezing)



Becoming Familiar with ADASUVE®

- ADASUVE is provided in a sealed pouch
- The indicator light is off when ADASUVE is removed from the pouch
- The indicator light turns on (green) when the tab is pulled out. The product is then ready for use
- The indicator light turns off after the patient inhales. This indicates the dose has been delivered
- If the indicator light does NOT turn off, the dose has NOT been delivered

The pictures below show the important features of the ADASUVE product



(both sides shown)



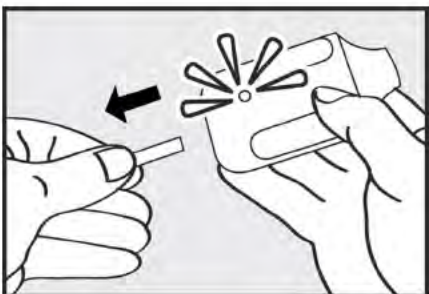
ADASUVE®: Important Administration Instructions

Before administering ADASUVE:



- 1. Open the pouch.** When ready to use, tear open the foil pouch and remove the inhaler from the package.

When the ADASUVE inhaler is removed from the pouch, the indicator light is off.



- 2. Pull tab.** Firmly pull the plastic tab from the rear of the inhaler. Check that the green light turns on. This indicates that the inhaler is ready for use.

Use the inhaler within 15 minutes after removing tab to prevent automatic deactivation of the product.

The green light will turn off, indicating that the inhaler is not usable. Discard the inhaler after one use.



ADASUVE®: Important Administration Instructions

-continued-

- 3. Explain procedures to the patient.** Explain the administration procedures to the patient prior to use, and advise the patient that it is important to follow the instructions.

Inform the patient that the inhaler may produce a flash of light and a clicking sound, and it may become warm during use. These are normal.

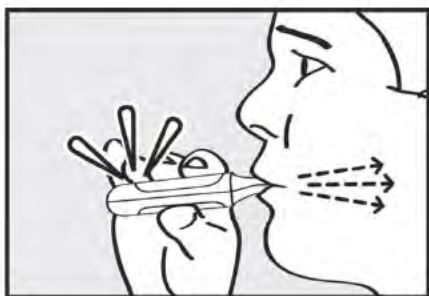


- 4. Instruct the patient to exhale.** Instruct the patient to hold the inhaler away from the mouth and breathe out fully to empty the lungs.



ADASUVE®: Important Administration Instructions

-continued-



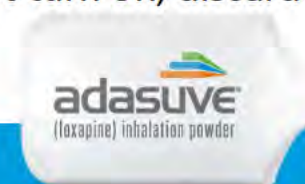
- 5. Instruct the patient to inhale.** Instruct the patient to put the mouthpiece of the inhaler between the lips, close the lips, and inhale through the mouthpiece with a steady deep breath.

Check that the green light turns off indicating that the dose has been delivered.



- 6. Instruct the patient to hold breath.** Instruct the patient to remove the mouthpiece from the mouth and hold the breath for as long as possible, up to 10 seconds.

Important: If the green light remains on after the patient inhales, the dose of ADASUVE has NOT been delivered. Instruct the patient to repeat Step 4, Step 5, and Step 6 up to 2 additional times. If the green light still does not turn off, discard the inhaler and use a new one.



ADASUVE®: Monitoring to Assess Safety

- Monitor the patient for signs or symptoms of bronchospasm after ADASUVE administration.
- Perform a physical examination, including chest auscultation, at least every 15 minutes for at least one hour after ADASUVE administration



How to Enroll in the ADASUVE® REMS Program

- **ADASUVE will be dispensed only to patients in certain healthcare facilities that are enrolled in the ADASUVE REMS Program**
- **Wholesalers / Distributors will ship ADASUVE only to enrolled healthcare facilities**
- Healthcare facility qualifications for enrolling include having:
 - Immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation
 - Immediate access on-site to a metered-dose inhaled and nebulized form of a short-acting beta-agonist bronchodilator (eg, albuterol)
 - Healthcare providers within the facility (prescribers, nurses, monitoring staff, or pharmacists) who are trained on safe use of ADASUVE using the ADASUVE Education Program
 - Procedures, protocol and / or order sets guiding safe use of ADASUVE



Procedures, Protocols, Order Sets for Safe Use of ADASUVE®

Procedures, protocols and / or order sets to ensure the following:

- Patients are screened, prior to treatment with ADASUVE:
 - for a history of pulmonary disease
 - for acute respiratory signs and symptoms by physical exam, including taking vital signs and chest auscultation
 - inquiring if patient is taking medication to treat asthma or COPD
- Patients are monitored at least every 15 minutes for a minimum of 1 hour following treatment with ADASUVE for signs and symptoms of bronchospasm
 - Taking vital signs
 - Chest auscultation
- Administration of ADASUVE is limited to one dose per patient within 24 hours

Order Set / Protocol templates are available to review, order, or print at www.adasuverems.com or by calling 1-855-755-0492



Designate an Authorized Healthcare Facility Representative

For each facility, an authorized healthcare facility representative is required to:

- Review the *ADASUVE® Education Program*
- Complete and sign the *Healthcare Facility Enrollment Information and Form*
 - Acknowledging that the enrolled healthcare facility meets specific requirements
- Healthcare Facility Representative:
 - May be a Pharmacist or another healthcare professional with appropriate level of responsibility within the facility
 - Authorized to act on behalf of the facility



Authorized Healthcare Facility Representative Actions

- Review the *Healthcare Facility Enrollment Information and Form* to become familiar with the enrollment requirements
- Review the *ADASUVE REMS Education Program* to become familiar with safe use conditions for ADASUVE
- Complete and sign the *Healthcare Facility Enrollment Form*
- Submit the completed form on-line, via fax, via email

The *Healthcare Facility Enrollment Information and Form* are available at www.adasuverems.com or by calling 855-755-0492



ADASUVE® REMS Materials for Enrolled Healthcare Facilities

The following materials are part of the ADASUVE REMS Program and will assist enrolled healthcare facilities in complying with ADASUVE REMS requirements. They are available to review, order or print at www.adasuverems.com or by calling 855-755-0492.

1. ADASUVE REMS Education Program

- Must be reviewed by all healthcare providers within an enrolled healthcare facility who will be prescribing or administering ADASUVE, or observing patients after ADASUVE is administered

2. Steps for Safe Use of ADASUVE poster

- Should be posted where ADASUVE is administered within enrolled healthcare facilities

3. Order Set / Protocol Template

- For use by enrolled healthcare facilities to assist with designing procedures, protocols and / or order sets that meet the requirements of the ADASUVE REMS Program

4. ADASUVE Healthcare Provider Brochure

- Contains information for providers on the benefits, risks, and safe use of ADASUVE
- Information on healthcare facility enrollment requirements of the ADASUVE REMS Program



Other Resources Available at www.adasuverems.com

- *Dear Healthcare Professional Letter*
- *Healthcare Facility Enrollment Information and Form*
- Full Prescribing Information
- ADASUVE® Instructions for Use
- ADASUVE® Medication Guide



ADASUVE® Education Program Summary

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

- ADASUVE REMS Program Information
 - The ADASUVE REMS Program is necessary to mitigate the risk of bronchospasm that has the potential to cause respiratory distress and respiratory arrest
- Important safety information
 - ADASUVE can cause bronchospasm
 - Patients with active airways disease (asthma, COPD) are at increased risk of bronchospasm after dosing with ADASUVE
 - It is important to report events of bronchospasm that require intubation or other advanced airway management, in addition to any fatalities, that occur following ADASUVE treatment
 - Administer only a single dose of ADASUVE per patient within any 24-hour period



ADASUVE® Education Program Summary

- continued -

- How to use ADASUVE safely
 - SCREEN patients to identify and select appropriate ADASUVE patients
 - OBSERVE and MONITOR patients every 15 minutes for at least 1 hour after ADASUVE treatment
 - MANAGE bronchospasm with an inhaled short-acting beta-agonist bronchodilator or if necessary, with advanced airway equipment
- How to enroll in the ADASUVE REMS Program
 - A healthcare facility must meet specific requirements including immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation
 - For each facility, an authorized healthcare facility representative is required to complete and sign the Healthcare Facility Enrollment Information and Form acknowledging that the enrolled healthcare facility meets specific requirements
 - Find more information at www.adasuverems.com



REMS Program
Enrollment

ADASUVE
Education Program

Healthcare
Provider Brochure

Steps for Safe Use
of ADASUVE

Dear Healthcare
Professional Letter

ADASUVE
Instructions for Use

ADASUVE[®] REMS Program

ADASUVE is a drug-device combination product that delivers an aerosol of the antipsychotic agent loxapine in a single oral inhalation. ADASUVE has been approved by the US Food and Drug Administration (FDA) for the acute treatment of agitation associated with schizophrenia and bipolar I disorder in adults.

The FDA has determined that a *Risk Evaluation and Mitigation Strategy (REMS)* is necessary for ADASUVE to ensure that the benefits of treatment outweigh the risks of bronchospasm.

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.

In order to mitigate the risk, the ADASUVE REMS Program requires that ADASUVE is only administered in enrolled healthcare facilities with immediate, on-site resources to manage bronchospasm and/or respiratory distress.

In addition, the REMS Program will inform healthcare professionals about:

- The risk of bronchospasm after ADASUVE administration
- Appropriate patient selection
- Monitoring patients after ADASUVE administration
- Management of bronchospasm, if it occurs

Click here to see the *REMS Program Enrollment Information for Healthcare Facilities and Wholesalers/Distributors*

Click the links below to see the *Materials for Healthcare Professionals:*

- [▶ Dear Healthcare Professional Letter](#)
- [▶ Healthcare Provider Brochure](#)
- [▶ Steps for Safe Use of ADASUVE](#)
- [▶ ADASUVE Education Program](#)
- [▶ ADASUVE Instructions for Use](#)
- [▶ ADASUVE Order Set/Protocol Template](#)

Important Safety Information About ADASUVE

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).





ADASUVE is contraindicated in patients with a current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD), or other lung disease associated with bronchospasm because they are at increased risk of bronchospasm.

ADASUVE is also contraindicated in patients with acute respiratory signs/symptoms (eg, wheezing) or who are currently taking medications to treat airways disease, such as asthma or COPD.

ADASUVE is contraindicated in patients with a history of bronchospasm following ADASUVE treatment.

Prior to administering ADASUVE, screen patients regarding a current diagnosis or history or symptoms of asthma, COPD, and other lung diseases, and examine (including chest auscultation) patients for respiratory signs. Monitor for signs and symptoms of bronchospasm following treatment with ADASUVE.

The Use of ADASUVE Should Be Accompanied by a 4-step Process of: Screening, Counseling, Monitoring, and Management

Steps for Safe Use of ADASUVE	
 SCREEN	Ask if patient is taking medication to treat asthma or COPD and/or check medical records
	Ask if patient has a current diagnosis or history of asthma, COPD, or other lung disease and/or check medical records
	Examine patients (including chest auscultation) for respiratory signs (eg, wheezing)
	Do not use in patients with acute respiratory signs or symptoms; with a current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm; or with current use of medications to treat airways disease, such as asthma or COPD
 COUNSEL	Counsel patient/caregiver on potential for bronchospasm that may occur after dosing and the need for them to report symptoms immediately
 MONITOR	Monitor patient every 15 minutes for at least 1 hour after treatment for signs and symptoms of bronchospasm including chest auscultation
	Ask patient every 15 minutes about any difficulty breathing
 If bronchospasm occurs MANAGE	Treat bronchospasm with an inhaled short-acting beta-agonist bronchodilator (eg, albuterol)
	If medically necessary, provide additional therapy for bronchospasm per asthma guidelines, including intubation and mechanical ventilation as needed

These risks do not constitute a complete list of all the risks associated with ADASUVE. Please see the [Full Prescribing Information](#), including Boxed Warning, for more information regarding the risks associated with ADASUVE.



ADASUVE[®] REMS Program Enrollment

HEALTHCARE FACILITY

- Enrolls in ADASUVE REMS Program
- Authorized healthcare facility representative attests to certain criteria required for receipt of ADASUVE order

[▶ CLICK HERE TO ENROLL](#)

WHOLESALER/ DISTRIBUTOR

- Enrolls in ADASUVE REMS Program
- Distributes ADASUVE only to enrolled healthcare facilities

[▶ CLICK HERE TO ENROLL](#)

[Click here to enroll as
a Healthcare Facility in
the ADASUVE REMS Program](#)

Click on a link below to view, print
or order the corresponding material
intended for healthcare professionals in
enrolled Healthcare Facilities:

[▶ Schedule ADASUVE Education
Program In-service](#)

[▶ View or print ADASUVE Education
Program online](#)

[▶ View, print, or order Steps for Safe
Use of ADASUVE](#)

[▶ View or print Healthcare
Facility Enrollment Information
Letter and Form](#)

[▶ View or print ADASUVE Order Set/
Protocol Template](#)

To order any of the above materials,
contact Teva at 855-755-0492.

[Click here to enroll as
a Wholesaler/Distributor in
the ADASUVE REMS Program](#)

ADASUVE Healthcare Facility Enrollment

ADASUVE will be dispensed only to patients in healthcare facilities that are enrolled in the ADASUVE REMS Program.

Authorized Healthcare Facility Representative

For each healthcare facility, an **authorized healthcare facility representative** is required to complete and sign the Healthcare Facility Enrollment Form acknowledging that the enrolled healthcare facility meets specific requirements. This representative may be a pharmacist, or another healthcare professional with the appropriate level of responsibility within the healthcare facility, who is authorized to act on behalf of the facility.

Healthcare Facility Qualifications for Enrollment

The healthcare facility requirements include having the following:

- Immediate access onsite to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation
- Immediate access onsite to a metered-dose inhaled and nebulized form of a short-acting beta-agonist bronchodilator (eg, albuterol)
- Procedures, protocols, and/or order sets to ensure the following:
 - Patients are screened, prior to treatment with ADASUVE, for a history of pulmonary disease and for acute respiratory signs and symptoms by physical exam, including taking vital signs and chest auscultation, and inquiring if patient is taking medication to treat asthma or COPD
 - Patients are monitored at least every 15 minutes for a minimum of 1 hour following treatment with ADASUVE for signs and symptoms of bronchospasm, including taking vital signs and chest auscultation
 - Administration of ADASUVE is limited to 1 dose per patient within 24 hours
- Healthcare providers within the facility (prescribers, nurses, monitoring staff, or pharmacists) who are trained on the safe use of ADASUVE using the ADASUVE Education Program

ADASUVE Wholesaler/Distributor Enrollment

ADASUVE is only available to enrolled wholesalers/distributors that agree to the following requirements:

- Will only distribute ADASUVE to healthcare facilities in which enrollment in the ADASUVE REMS Program has been validated
- Agree to cooperate with periodic audits or noncompliance investigations to ensure that ADASUVE is distributed in accordance with the program requirements
- Understand that wholesalers/distributors are required to renew enrollment in the ADASUVE REMS Program every three (3) years

These risks do not constitute a complete list of all the risks associated with ADASUVE. Please see the [Full Prescribing Information](#), including Boxed Warning, for more information regarding the risks associated with ADASUVE.



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Reference ID: 3419276



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/s/

MITCHELL V Mathis
12/09/2013