

ADASUVE[®] **(LOXAPINE) INHALATION POWDER**

EDUCATION PROGRAM for HEALTHCARE PROFESSIONALS

July 2016



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



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 Program requires that ADASUVE is only administered in enrolled healthcare facilities:
 - With immediate access on site to supplies and personnel trained to manage acute bronchospasm and ready access to emergency response services
- 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 supplies and personnel trained to manage acute bronchospasm and ready access to emergency response services. This healthcare facility must have a short-acting bronchodilator (e.g., albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm.
 - Medical/psychiatric (physicians, nurses, etc.) staff on site at all times (24 hours a day/7 days a week) trained to manage acute bronchospasm.
- 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 (e.g., 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 (e.g., 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 (e.g., 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 mild-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%)
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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 mild-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

	Maximum % FEV ₁ ↓	Healthy Volunteer		Asthma		COPD	
		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.

Reference ID: 3991876

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®

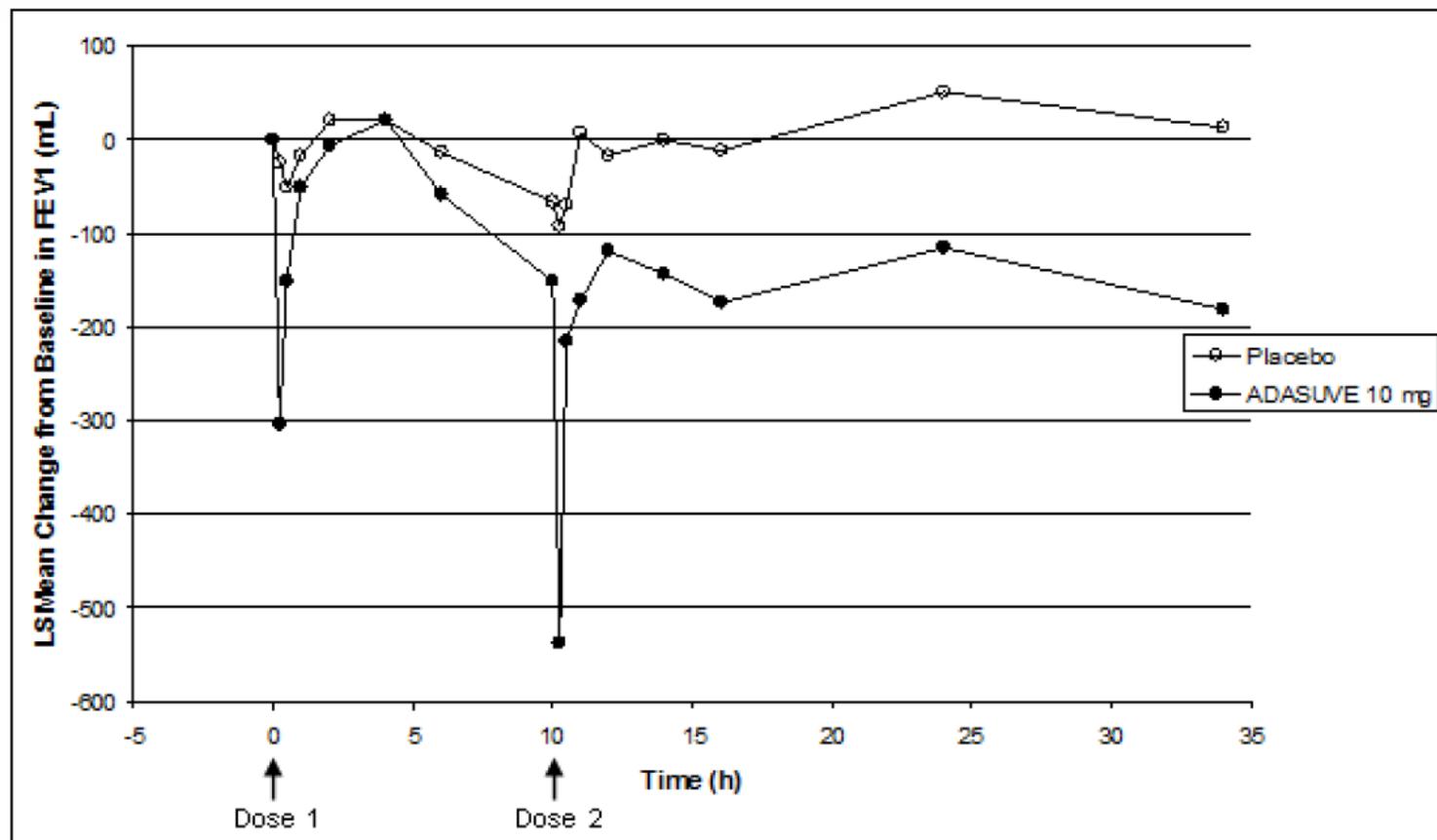
- A higher percentage of patients required albuterol treatment after Dose 2 compared to Dose 1 (Slide 9)
- A higher percentage of patients treated with ADASUVE had a decrease in FEV₁ after Dose 2 compared to Dose 1 (Slide 11)
- FEV₁s did not return to baseline up to 24 hours after administration of the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

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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 patient with schizophrenia, without a history of pulmonary disease, had significant bronchospasm requiring rescue treatment with a bronchodilator and oxygen



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 (e.g., 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 (e.g., albuterol)
- If medically necessary, provide additional therapy for bronchospasm per asthma guidelines



Reporting Adverse Events Associated with ADASUVE®

Healthcare professionals should understand the importance of reporting events of bronchospasm that require emergency response services, in addition to any fatalities that occur following ADASUVE treatment.

Suspected adverse events may be reported by the following methods:

- Teva Pharmaceuticals at 800-284-0062
- FDA at 1-800-FDA-1088
- FDA at www.fda.gov/medwatch/report.htm



Patient Counseling

Discuss the risks associated with ADASUVE® treatment with patients and their caregivers, including the safe use of ADASUVE.

Helping Patients and Caregivers Understand Risks

- Explain that 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
- Administer only a single dose within any 24-hour period
- ADASUVE must be administered only by a healthcare professional, in an enrolled healthcare facility

Required Examination Prior to Dosing:

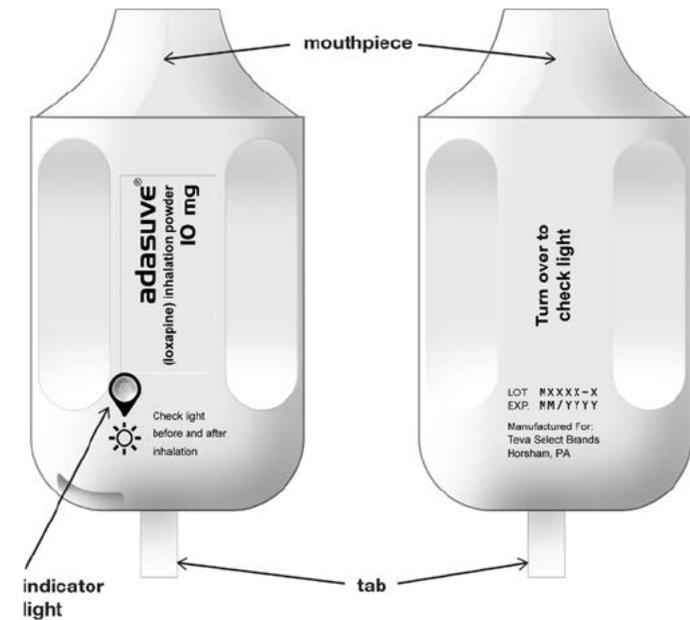
- Prior to administering ADASUVE, screen all patients for:
 - Current use of medications to treat asthma or COPD
 - History of asthma, COPD or other pulmonary disease
 - Examine patients (including chest auscultation) for respiratory abnormalities (e.g., wheezing)



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)



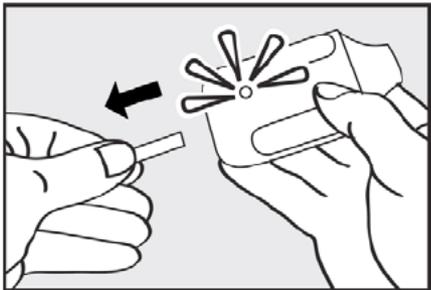
ADASUVE[®]: Important Administration Instructions

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.

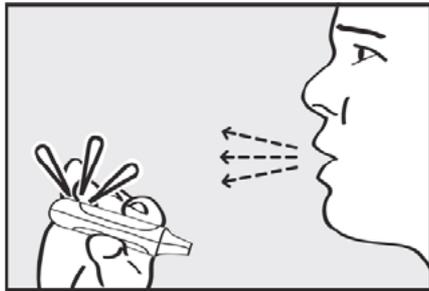


ADASUVE®: Important Administration Instructions

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- 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.

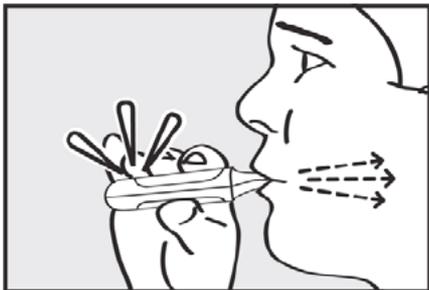
Inform the patient that the inhaler may produce a flash of light and a clicking sound, and it may become warm during use. These are normal.



- 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.

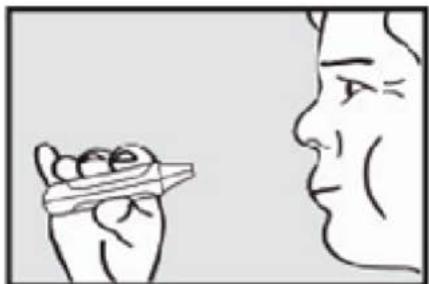
ADASUVE®: Important Administration Instructions

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- 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**
- Each healthcare facility must be able to provide:
 - Immediate access on site to supplies and personnel trained to manage acute bronchospasm and ready access to emergency response services. This healthcare facility must have a short-acting bronchodilator (e.g., albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm.
 - Medical/psychiatric (physicians, nurses, etc.) staff on site at all times (24 hours a day/7 days a week) trained to manage acute bronchospasm.
 - 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



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 risks and safe use of ADASUVE
- Information on healthcare facility enrollment requirements of the ADASUVE REMS Program



Other Resources Available at

www.adasuverems.com

- *Healthcare Facility Enrollment Information and Form*
- 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 emergency response services, 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, by accessing emergency response services



ADASUVE® Education Program Summary

- continued -

How to enroll in the ADASUVE REMS Program

- Each healthcare facility must be able to provide:
 - Immediate access on site to supplies and personnel trained to manage acute bronchospasm and ready access to emergency response services. This healthcare facility must have a short-acting bronchodilator (e.g., albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm.
 - Medical/psychiatric (physicians, nurses, etc.) staff on site at times (24 hours a day/7 days a week) trained to manage acute bronchospasm.
- 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

