

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.