**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

ADASUVE 4.5 mg inhalation powder, pre-dispensed

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose inhaler contains 5 mg loxapine and delivers 4.5 mg loxapine.

## 3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed (inhalation powder).

White device with a mouthpiece on one end and a pull-tab protruding from the other end.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ADASUVE is indicated for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder. Patients should receive regular treatment immediately after control of acute agitation symptoms.

### 4.2 Posology and method of administration

ADASUVE should be administered in a medical setting under the direct supervision of a healthcare professional. Patients should be observed during the first hour after each dose for signs and symptoms of bronchospasm.

**Short-acting beta-agonist bronchodilator treatment should be available for treatment of possible severe respiratory side-effects (bronchospasm).**

Posology

The recommended initial dose of ADASUVE is 9.1 mg. As this dose cannot be reach with this presentation (ADASUVE 4.5 mg), the presentation ADASUVE 9.1 mg should be used initially. A second dose can be given after 2 hours, if necessary. No more than two doses should be administered.

A lower dose of 4.5 mg may be given if the 9.1 mg dose was not previously tolerated by the patient or if the physician decides a lower dose is more appropriate.

*Elderly*

The safety and efficacy of ADASUVE in patients older than 65 years of age have not been established. No data are available.

*Renal and/or hepatic impairment*

ADASUVE has not been studied in patients with renal or hepatic impairment. No data are available.

*Paediatric population*

The safety and efficacy of ADASUVE in children (less than 18 years of age) have not been established. No data are available.

Method of administration

Inhalation use. The product is packaged in a sealed pouch.

When needed, the product is removed from the pouch. Once the pull-tab is removed, a green light turns on, indicating the product is ready for use (Note: the product must be used within 15 minutes of pulling the tab). To deliver the medicinal product, the patient inhales through the mouthpiece with a steady deep breath. Upon completion of the inhalation, the patient removes the mouthpiece from mouth and holds breath briefly. The medicinal product has been delivered when the green light turns off. The device exterior may become warm during use. This is normal.

For complete instructions on how to use ADASUVE see information for the healthcare professional section of the package leaflet.

## 4.3 Contraindications

Hypersensitivity to the active substance, or to amoxapine.

Patients with acute respiratory signs/symptoms (e.g., wheezing) or with active airways disease (such as patients with asthma or chronic obstructive pulmonary disease [COPD] (see section 4.4).

## 4.4 Special warnings and precautions for use

Correct use of ADASUVE inhaler is important for administration of the full dose of loxapine. Healthcare professionals should ensure the patient will use the inhaler properly.

ADASUVE may have limited effectiveness when patients are on concomitant medicinal products, predominantly other antipsychotics.

Bronchospasm

Bronchospasm has been reported following administration of ADASUVE, especially in patients with asthma or COPD and was typically reported within 25 minutes after dosing (see section 4.8). Consequently, ADASUVE is contraindicated in patients with asthma or COPD as well as patients with acute respiratory signs/symptoms (e.g., wheezing) (see section 4.3). ADASUVE has not been investigated in patients with other forms of lung disease. It is recommended to observe patients during the first hour for signs and symptoms of bronchospasm following administration of ADASUVE.
In patients who may develop bronchospasm, treatment with a short-acting beta-agonist bronchodilator, e.g., salbutamol should be considered (see sections 4.2 and 4.8).

ADASUVE should not be re-administered in patients who develop any respiratory signs/symptoms (see section 4.3).

Hypoventilation

Given the primary Central Nervous System (CNS) effects of loxapine, ADASUVE should be used with caution in patients with compromised respiration, such as hypovigilant patients or patients with CNS-depression due to alcohol or other centrally acting medicinal products, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. (see section 4.5).

Elderly patients with dementia-related psychosis

ADASUVE has not been studied in elderly patients, including those with dementia-related psychosis. Clinical studies with both atypical and conventional antipsychotic medicinal products have demonstrated that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. ADASUVE is not indicated for the treatment of patients with dementia-related psychosis.

Extrapyramidal symptoms

Extrapyramidal symptoms (including acute dystonia) are known class effects for antipsychotics. ADASUVE should be used with caution in patients with a known history of extrapyramidal symptoms.

Tardive dyskinesia

If signs and symptoms of tardive dyskinesia appear in a patient being treated with loxapine, discontinuation should be considered. These symptoms can temporally worsen or can even arise after discontinuation of treatment.

Neuroleptic malignant syndrome (NMS)

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, ADASUVE must be discontinued.

Hypotension

Mild hypotension was reported in short-term (24-hour), placebo-controlled trials in agitated patients administered ADASUVE. If vasopressor therapy is required, noradrenaline or phenylephrine is preferred. Adrenaline should not be used, since beta-adrenoceptor stimulation may worsen hypotension in the setting of loxapine-induced partial alpha-adrenoceptor blockade (see section 4.5).

Cardiovascular

No data are available on the use of ADASUVE in patients with underlying cardiovascular diseases. ADASUVE is not recommended in patient populations with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolaemia, and treatment with antihypertensive medicinal products).

QT interval

Clinically relevant QT prolongation does not appear to be associated with single and repeat doses of ADASUVE. Caution should be exercised when ADASUVE is administered in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products known to prolong the QT interval. The potential risk of QTc prolongation due to interaction with medicinal products known to prolong QTc interval is unknown.

Seizures / convulsions

Loxapine should be used with caution in patients with a history of convulsive disorders since it lowers the convulsive threshold. Seizures have been reported in patients receiving oral loxapine at

antipsychotic dose levels, and may occur in epileptic patients even with maintenance of routine anticonvulsant drug therapy (see section 4.5).

Anticholinergic activity

Because of anticholinergic action, ADASUVE should be used cautiously in patients with glaucoma or a tendency to urinary retention, particularly with concomitant administration of anticholinergic-type antiparkinson medicinal products.

Intoxication or physical disease (delirium)

The safety and efficacy of ADASUVE has not been evaluated in patients with agitation due to intoxication or physical disease (delirium). ADASUVE should be used with caution in patients who are intoxicated or delirious (see section 4.5).

Severe cutaneous adverse reactions (SCARs)

Drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, has been reported in relation to loxapine containing products. Patients should be advised of the signs and symptoms of DRESS and monitored closely for skin reactions. If the patient has developed DRESS with the use of loxapine, treatment with loxapine containing products should not be restarted.

## 4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of benzodiazepines or other hypnosedatives or respiratory depressants may be associated with excessive sedation and respiratory depression or respiratory failure. If benzodiazepine therapy is deemed necessary in addition to loxapine, patients should be monitored for excessive sedation and for orthostatic hypotension.

A study of inhaled loxapine and intramuscular lorazepam 1 mg in combination found no significant effects on respiratory rate, pulse oximetry, blood pressure, or heart rate compared with either drug administered alone. Higher doses of lorazepam have not been studied. The effects of the combination on sedation appeared to be additive.

Potential for ADASUVE to affect other medicinal products

Loxapine is not expected to cause clinically important pharmacokinetic interactions with medicinal products that are either metabolised by cytochrome P450 (CYP450) isozymes or glucuronidated by human uridine 5'-diphosphoglucuronosyl transferases (UGTs).

Caution is advised if loxapine is combined with other medicinal products known to lower the seizure threshold, e.g. phenothiazines or butyrophenones, clozapine, tricyclics or selective serotonine reuptake inhibitors (SSRIs), tramadol, mefloquine (see section 4.4).

*In vitro* studies indicated that loxapine was not a substrate for P-glycoprotein (P-gp), but does inhibit P-gp. At therapeutic concentrations, however, it is not expected to inhibit P-gp-mediated transport of other medicinal products in a clinically significant manner.

Given the primary CNS effects of loxapine, ADASUVE should be used with caution in combination with alcohol or other centrally acting medicinal products, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. The use of loxapine in patients with alcohol or medicinal product intoxication (either with prescribed or illicit medicinal products) has not been evaluated. Loxapine may cause severe respiratory depression if combined with other CNS-depressants (see section 4.4).

Potential for other medicinal products to affect ADASUVE

Loxapine is a substrate for flavin-containing mono-oxygenases (FMOs), and for several CYP450

isozymes (see section 5.2). Therefore, the risk of metabolic interactions caused by an effect on an individual isoform is limited. Caution should be used in patients receiving concomitant treatment with other medicinal products that are either inhibitors or inducers of these enzymes, particularly if the concomitant medicinal product is known to inhibit or induce several of the enzymes involved in loxapine metabolism. Such medicinal products may modify efficacy and safety of ADASUVE in an

irregular manner. Concomitant use of CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin, enoxacin, propranolol and refecoxib) should be avoided, if possible.

*Adrenaline*

Co-administration of loxapine and adrenaline may cause worsening of hypotension (see section 4.4).

## 4.6 Fertility, pregnancy and lactation

Pregnancy

New-born infants exposed repeatedly to antipsychotics during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, monitoring of new-borns should be considered. ADASUVE should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

The extent of the excretion of loxapine or its metabolites in human milk is not known. However, loxapine and its metabolites have been shown to be transported into the milk of lactating dogs. Patients should be advised not to breast feed for a period of 48 hours after receiving loxapine and discard the milk produced in the meantime.

Fertility

No loxapine specific human data on fertility are available. It is known that in humans, long-term treatment with antipsychotics may lead to loss of libido and amenorrhoea. In female rats, reproductive effects have been observed (see section 5.3).

## 4.7 Effects on ability to drive and use machines

ADASUVE has major influence on the ability to drive and use machines. Because of the potential for sedation/somnolence, fatigue, or dizziness, patients should not operate hazardous machines, including motor vehicles, until they are reasonably certain that loxapine has not affected them adversely (see section 4.8).

## 4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions from clinical study data is based on two Phase 3 and one Phase 2A short-term (24-hour) placebo-controlled clinical trials enrolling 524 adult patients with agitation associated with schizophrenia or bipolar disorder.

In those studies, bronchospasm was uncommonly found. However, in specific Phase 1 clinical safety trials in subjects with asthma or COPD, bronchospasm was commonly reported and often required treatment with a short-acting beta-agonist bronchodilator. Consequently, ADASUVE is contraindicated in patients with asthma,COPD or other active airway disease (see section 4.3).

The most commonly reported adverse reactions during treatment with ADASUVE were dysgeusia, sedation/somnolence and dizziness (dizziness was more common after placebo treatment than loxapine treatment).

Tabulated list of adverse reactions

The adverse reactions listed below are categorized using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

**Table 1: Adverse reactions**

| **MedDRA system organ classification** |
|---|
| **Nervous system disorders**<br>Very common: sedation/somnolence<br>Common: dizziness<br>Uncommon: dystonia, dyskinesia, oculogyration, tremor, akathisia/restlessness |
| **Vascular disorders**<br>Uncommon: hypotension |
| **Respiratory, thoracic and mediastinal disorders**<br>Common: throat irritation<br>Uncommon: bronchospasm (including shortness of breath) |
| **Gastrointestinal disorders**<br>Very common: dysgeusia<br>Common: dry mouth |
| **General disorders and administration site conditions**<br>Common: fatigue |

Description of selected adverse reactions

*Bronchospasm*

In short-term (24-hour), placebo-controlled trials in patients with agitation associated with schizophrenia or bipolar disorder without active airways disease, bronchospasm and possible symptoms of bronchospasm (which includes reports of wheezing, shortness of breath or cough) wereuncommon in patients treated with ADASUVE. However, in placebo-controlled clinical trials in subjects with mild-to-moderate persistent asthma or moderate-to-severe COPD, adverse reactions of bronchospasm were reported very commonly. Most of these events occurred within 25 minutes of dosing, were mild to moderate in severity, and could be relieved with an inhaled bronchodilator.

*Adverse reactions seen with chronic oral loxapine use*

With chronic oral administration of loxapine, the reported adverse reactions include sedation and drowsiness; extrapyramidal symptoms (e.g., tremor, akathisia, rigidity, and dystonia); cardiovascular effects (e.g., tachycardia, hypotension, hypertension, orthostatic hypotension, light-headedness, and syncope); and anticholinergic effects (e.g., dry eyes, blurred vision, and urinary retention).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

No cases of overdosage of ADASUVE were reported in clinical studies.

Symptoms

In the event of accidental overdosage, signs and symptoms will depend on the number of units taken and individual patient tolerance. As would be expected from the pharmacologic actions of loxapine, the clinical findings may range from mild depression of the CNS and cardiovascular systems to profound hypotension, respiratory depression, and unconsciousness (see section 4.4). The possibility of occurrence of extrapyramidal symptoms and/or convulsive seizures should be kept in mind. Renal failure following oral loxapine overdosage has also been reported.

Management

The treatment of overdosage is essentially symptomatic and supportive. Severe hypotension might be expected to respond to the administration of noradrenaline or phenylephrine. Adrenaline should not be used since its use in a patient with partial adrenergic blockage may further lower the blood pressure (see sections 4.4 and 4.5). Severe extrapyramidal reactions should be treated with anticholinergic antiparkinson medicinal products or diphenhydramine hydrochloride, and anticonvulsant therapy should be initiated as indicated. Additional measures include oxygen and intravenous fluids.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, antipsychotics; ATC code: N05AH01

The efficacy of loxapine is proposed to be mediated through high affinity antagonism of dopamine D2 receptors and serotonin 5-HT2A receptors. Loxapine binds with noradrenergic, histaminergic, and cholinergic receptors, and its interaction with these systems may influence the spectrum of its pharmacological effects.

Changes in the level of excitability of subcortical inhibitory areas have been observed in several animal species, associated with calming effects and suppression of aggressive behaviour.

Clinical efficacy

In the two Phase 3 studies patients were enrolled who had acute agitation of at least moderate level (14 or higher on Positive and Negative Syndrome Scale (PANSS) Excited Component (PEC) scale (poor impulse control, tension, hostility, uncooperativeness, and excitement). Inclusion in Study 004-301 required a diagnosis of schizophrenia. Inclusion in Study 004-302 required a diagnosis of bipolar disorder (current episode manic or mixed). Patients had significant and long-standing psychiatric disease (Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)), based on years since diagnosis and previous hospitalizations. Patients were randomised to placebo, ADASUVE 4.5 mg and ADASUVE 9.1 mg.

The mean age of randomized patients was 43.1 years in Study 004-301 and 40.8 years in Study 004-302: young adults (18-25 years old) were scarcely (7.3%) represented in either trial. Women in the schizophrenia trial were scarcely represented (26.5%), and about half of the patients were male (49.7%) in Study 004-302. About 35% of the patients with schizophrenia were taking concomitant antipsychotics at the time of dosing while approximately 13% of the patients with bipolar disorder were taking these drugs. A majority of the patients in both Phase 3 studies were smokers with about 82% of the patients with schizophrenia and 74% of the patients with bipolar disorder currently smoking.

After the first dose, a second dose was administered at least 2 hours later if the agitation had not subsided sufficiently. A third dose was administered if needed after at least 4 hours after dose 2. Rescue medication (intramuscular lorazepam) was given if medically required. Primary endpoint was absolute change in PEC score from baseline to 2 hours following Dose 1 for both doses of ADASUVE compared with placebo. Among the other endpoints were PEC and Clinical Global Impression –

Improvement (CGI-I) responders at 2 hours after dose 1, and total number of patients per group who received 1, 2, or 3 doses of study medication with and without rescue medication. Responders were considered patients with a ≥40% decrease from baseline in the total PEC score or patients with CGI-I score of 1 (very much improved) or 2 (much improved).

Decreased agitation was evident 10 minutes after Dose 1, the first assessment time, and at all subsequent assessments during the 24 hour evaluation period, for both 4.5 mg and 9.1 mg doses in both schizophrenia and bipolar disorder patients.

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

For the main results, see the table below.

**Main results of the pivotal efficacy studies: comparisons between ADASUVE 4.5 mg, 9.1 mg, and placebo**

| | **Study Patients** | **004-301 Schizophrenia** | | | **004-302 Bipolar Disorder** | | |
|---|---|---|---|---|---|---|---|
| | **Treatment N** | **PBO 115** | **4.5 mg 116** | **9.1 mg 112** | **PBO 105** | **4.5 mg 104** | **9.1 mg 105** |
| **PEC Change** | Baseline | 17.4 | 17.8 | 17.6 | 17.7 | 17.4 | 17.3 |
| | Change at 2 hr post dose | -5.5 | -8.1$^{+}$ | -8.6* | -4.9 | -8.1* | -9.0* |
| | SD | 4.9 | 5.2 | 4.4 | 4.8 | 4.9 | 4.7 |
| **PEC Responders** | 30 min post dose | 27.8% | 46.6% | 57.1% | 23.8% | 59.6% | 61.9% |
| | 2 hr post dose | 38.3% | 62.9% | 69.6% | 27.6% | 62.5% | 73.3% |
| **CGI-I Responder** | % CGI-I Responders | 35.7% | 57.4% | 67.0% | 27.6% | 66.3% | 74.3% |
| **# Doses Needed** | One | 46.1% | 54.4% | 60.9% | 26.7% | 41.3% | 61.5% |
| | Two | 29.6% | 30.7% | 26.4% | 41.0% | 44.2% | 26.0% |
| | Three | 8.7% | 8.8% | 7.3% | 11.4% | 5.8% | 3.8% |
| | Rescue | 15.6% | 6.1% | 5.4% | 21.0% | 8.6% | 8.6% |

*= $p<0.0001$ $^{+}$= $p<0.01$
PEC Responders = ≥ 40% change from PEC Baseline;
CGI-I Responders = Score of 1 (Very Much Improved) or 2 (Much Improved)
PBO = placebo SD=Standard Deviation

In a supportive Phase 2 single dose study enrolling a total of 129 patients with schizophrenia and schizoaffective disorder the decrease in PEC change after 2 hours was -5.0 for placebo, -6.7 for ADASUVE 4.5 mg, and -8.6 ($p<0.001$) for ADASUVE 9.1 mg. Rescue medication was administered in respectively 32.6%, 11.1 % and 14.6 % of patients.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ADASUVE in the subset of the paediatric population from birth to less than 12 years of age for the treatment of schizophrenia and in the subset from birth to less than 10 years of age for the treatment of bipolar disorder (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with ADASUVE in the subset of the paediatric population from 12 to less than 18 years of age for the treatment of schizophrenia and in the subset from 10 years to less than 18 years of age in bipolar disorder (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

Administration of ADASUVE resulted in rapid absorption of loxapine with a median time of maximum plasma concentration ($T_{max}$) by 2 minutes. Loxapine exposure in the first 2 hours after administration ($AUC_{0-2h}$, a measure of early exposure that is relevant to the onset of therapeutic effect) was 25.6 ng*h/mL for the 4.5 mg dose and 66.7 ng*h/mL for the 9.1 mg dose in healthy subjects.

The pharmacokinetic parameters of loxapine were determined in subjects on chronic, stable antipsychotic regimens following repeat administration of ADASUVE every 4 hours for a total of 3 doses (either 4.5 mg or 9.1 mg). Mean peak plasma concentrations were similar after the first and third dose of ADASUVE, indicating minimal accumulation during the 4-hour dosing interval.

Distribution

Loxapine is removed rapidly from the plasma and distributed in tissues. Animal studies following oral administration suggest an initial preferential distribution in the lungs, brain, spleen, heart and kidney. Loxapine is 96.6% bound to human plasma proteins.

Biotransformation

Loxapine is metabolised extensively in the liver, with multiple metabolites formed. The main metabolic pathways include hydroxylation to form 8-OH-loxapine and 7-OH-loxapine, N-oxidation to form loxapine N-oxide, and de-methylation to form amoxapine. For ADASUVE, the order of metabolites observed in humans (based on systemic exposure) was 8-OH-loxapine >> loxapine N oxide > 7-OH-loxapine > amoxapine, with plasma levels of 8-OH-loxapine similar to the parent compound. 8-OH-loxapine is not pharmacologically active at the D2 receptor while the minor metabolite, 7-OH-loxapine, has high binding affinity to D2 receptors.

Loxapine is a substrate for several CYP450 isozymes; *in vitro* studies demonstrated that 7-OH-loxapine is formed mainly by CYPs 3A4 and 2D6, 8-OH-loxapine is formed mainly by CYP1A2, amoxapine is formed mainly by CYP3A4, 2C19, and 2C8, and loxapine N-oxide is formed by FMOs.

The potential for loxapine and its metabolites (amoxapine, 7-OH-loxapine, 8-OH-loxapine, and loxapine-N-oxide) to inhibit CYP450 - mediated drug metabolism has been examined *in vitro* for CYPs 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. No significant inhibition was observed. *In vitro* studies indicate that loxapine and 8-OH-loxapine are not inducers of CYP1A2, 2B6 or 3A4 enzymes at clinically relevant concentrations. In addition, *in vitro* studies indicate that loxapine and 8-OH loxapine are not inhibitors of UGT1A1, 1A3, 1A4, 2B7 and 2B15.

Elimination

Loxapine excretion occurs mainly in the first 24 hours. Metabolites are excreted in the urine in the form of conjugates and in the faeces unconjugated. The terminal elimination half-life (T½) ranged from 6 to 8 hours.

Linearity/non-linearity

The mean plasma loxapine concentrations following administration of ADASUVE were linear over the clinical dose range. $AUC_{0\text{-}2h}$, $AUC_{inf}$, and $C_{max}$ increased in a dose-dependent manner.

Pharmacokinetics in special patient populations

*Smokers*

A population pharmacokinetic analysis that compared exposures in smokers versus non-smokers indicated that smoking, which induces CYP1A2, had a minimal effect on the exposure to ADASUVE. No dosage adjustment is recommended based on smoking status.

In female smokers exposure ($AUC_{inf}$) to ADASUVE and its active metabolite 7-OH-loxapine is lower than in female non-smokers (84% vs 109% 7-OH-loxapine/Loxapine Ratio), which is probably due to an increase in loxapine clearance in smokers.

*Demographics*

There were no important differences in the exposure or disposition of loxapine following administration of ADASUVE due to age, gender, race, weight, or body mass index (BMI).

### 5.3 Preclinical safety data

Non-clinical safety data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, and genotoxicity, except for changes to reproductive tissues related to the extended pharmacology of loxapine. Similar changes, e.g., gynecomastia, are known in humans, but only after long-term administration of medicines causing hyperprolactinaemia.

Female rats did not mate due to persistent diestrus after oral treatment with loxapine. Embryo/fetal developmental and perinatal studies have shown indications of developmental delay (reduced weights, delayed ossification, hydronephrosis, hydrourether, and/or distended renal pelvis with reduced or absent papillae) as well as increased numbers of perinatal and neonatal deaths in offspring of rats treated from mid-pregnancy with oral doses below the maximum recommended human dose for ADASUVE on a $mg/m^2$ basis (see section 4.6).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

None

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store in the original pouch until ready for use in order to protect from light and moisture.

This medicinal product does not require any special temperature storage conditions.

### 6.5 Nature and contents of container

The white inhaler (housing) is molded from a medical-grade polycarbonate.
Each inhaler is provided in a sealed, multilaminate aluminum foil pouch.
ADASUVE 4.5 mg is supplied in a carton of 1 or 5 units.

Not all pack-sized may be marketed.

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Ferrer Internacional, S.A.
Gran Vía Carlos III, 94
08028- Barcelona
España

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/823/001 (5 single-dose inhalers)
EU/1/13/823/003 (1 single-dose inhaler)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 February 2013
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

## 1. NAME OF THE MEDICINAL PRODUCT

ADASUVE 9.1 mg inhalation powder, pre-dispensed

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose inhaler contains 10 mg loxapine and delivers 9.1 mg loxapine.

## 3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed (inhalation powder).

White device with a mouthpiece on one end and a pull-tab protruding from the other end.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ADASUVE is indicated for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder. Patients should receive regular treatment immediately after control of acute agitation symptoms.

### 4.2 Posology and method of administration

ADASUVE should be administered in a medical setting under the direct supervision of a healthcare professional. Patients should be observed during the first hour after each dose for signs and symptoms of bronchospasm.

**Short-acting beta-agonist bronchodilator treatment should be available for treatment of possible severe respiratory side-effects (bronchospasm).**

Posology

The recommended initial dose of ADASUVE is 9.1 mg. A second dose can be given after 2 hours, if necessary. No more than two doses should be administered.

A lower dose of 4.5 mg may be given if the 9.1 mg dose was not previously tolerated by the patient or if the physician decides a lower dose is more appropriate.

*Elderly*

The safety and efficacy of ADASUVE in patients older than 65 years of age have not been established. No data are available.

*Renal and/or hepatic impairment*

ADASUVE has not been studied in patients with renal or hepatic impairment. No data are available.

*Paediatric population*

The safety and efficacy of ADASUVE in children (less than 18 years of age) have not been established. No data are available.

Method of administration

Inhalation use. The product is packaged in a sealed pouch.

When needed, the product is removed from the pouch. Once the pull-tab is removed, a green light turns on, indicating the product is ready for use (Note: the product must be used within 15 minutes of pulling the tab). To deliver the medicinal product, the patient inhales through the mouthpiece with a steady deep breath. Upon completion of the inhalation, the patient removes the mouthpiece from mouth and holds breath briefly. The medicinal product has been delivered when the green light turns off. The device exterior may become warm during use. This is normal.

For complete instructions on how to use ADASUVE see information for the healthcare professional section of the package leaflet.

## 4.3 Contraindications

Hypersensitivity to the active substance, or to amoxapine.

Patients with acute respiratory signs/symptoms (e.g., wheezing) or with active airways disease (such as patients with asthma or chronic obstructive pulmonary disease [COPD] (see section 4.4).

## 4.4 Special warnings and precautions for use

Correct use of ADASUVE inhaler is important for administration of the full dose of loxapine. Healthcare professionals should ensure the patient will use the inhaler properly.

ADASUVE may have limited effectiveness when patients are on concomitant medicinal products, predominantly other antipsychotics.

Bronchospasm

Bronchospasm has been reported following administration of ADASUVE, especially in patients with asthma or COPD and was typically reported within 25 minutes after dosing (see section 4.8). Consequently, ADASUVE is contraindicated in patients with asthma or COPD as well as patients with acute respiratory signs/symptoms (e.g., wheezing) (see section 4.3). ADASUVE has not been investigated in patients with other forms of lung disease. It is recommended to observe patients during the first hour for signs and symptoms of bronchospasm following administration of ADASUVE.
In patients who may develop bronchospasm, treatment with a short-acting beta-agonist bronchodilator, e.g., salbutamol should be considered (see sections 4.2 and 4.8).
ADASUVE should not be re-administered in patients who develop any respiratory signs/symptoms (see section 4.3).

Hypoventilation

Given the primary Central Nervous System (CNS) effects of loxapine, ADASUVE should be used with caution in patients with compromised respiration, such as hypovigilant patients or patients with CNS-depression due to alcohol or other centrally acting medicinal products, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. (see section 4.5).

Elderly patients with dementia-related psychosis

ADASUVE has not been studied in elderly patients, including those with dementia-related psychosis. Clinical studies with both atypical and conventional antipsychotic medicinal products have demonstrated that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. ADASUVE is not indicated for the treatment of patients with dementia-related psychosis.

Extrapyramidal symptoms

Extrapyramidal symptoms (including acute dystonia) are known class effects for antipsychotics. ADASUVE should be used with caution in patients with a known history of extrapyramidal symptoms.

Tardive dyskinesia

If signs and symptoms of tardive dyskinesia appear in a patient being treated with loxapine, discontinuation should be considered. These symptoms can temporally worsen or can even arise after discontinuation of treatment.

Neuroleptic malignant syndrome (NMS)

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, ADASUVE must be discontinued.

Hypotension

Mild hypotension was reported in short-term (24-hour), placebo-controlled trials in agitated patients administered ADASUVE. If vasopressor therapy is required, noradrenaline or phenylephrine is preferred. Adrenaline should not be used, since beta-adrenoceptor stimulation may worsen hypotension in the setting of loxapine-induced partial alpha-adrenoceptor blockade (see section 4.5).

Cardiovascular

No data are available on the use of ADASUVE in patients with underlying cardiovascular diseases. ADASUVE is not recommended in patient populations with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolaemia, and treatment with antihypertensive medicinal products).

QT interval

Clinically relevant QT prolongation does not appear to be associated with single and repeat doses of ADASUVE. Caution should be exercised when ADASUVE is administered in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products known to prolong the QT interval. The potential risk of QTc prolongation due to interaction with medicinal products known to prolong QTc interval is unknown.

Seizures / convulsions

Loxapine should be used with caution in patients with a history of convulsive disorders since it lowers the convulsive threshold. Seizures have been reported in patients receiving oral loxapine at

antipsychotic dose levels, and may occur in epileptic patients even with maintenance of routine anticonvulsant drug therapy (see section 4.5).

Anticholinergic activity

Because of anticholinergic action, ADASUVE should be used cautiously in patients with glaucoma or a tendency to urinary retention, particularly with concomitant administration of anticholinergic-type antiparkinson medicinal products.

Intoxication or physical disease (delirium)

The safety and efficacy of ADASUVE has not been evaluated in patients with agitation due to intoxication or physical disease (delirium). ADASUVE should be used with caution in patients who are intoxicated or delirious (see section 4.5).

Severe cutaneous adverse reactions (SCARs)

Drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, has been reported in relation to loxapine containing products. Patients should be advised of the signs and symptoms of DRESS and monitored closely for skin reactions. If the patient has developed DRESS with the use of loxapine, treatment with loxapine containing products should not be restarted.

## 4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of benzodiazepines or other hypnosedatives or respiratory depressants may be associated with excessive sedation and respiratory depression or respiratory failure. If benzodiazepine therapy is deemed necessary in addition to loxapine, patients should be monitored for excessive sedation and for orthostatic hypotension.

A study of inhaled loxapine and intramuscular lorazepam 1 mg in combination found no significant effects on respiratory rate, pulse oximetry, blood pressure, or heart rate compared with either drug administered alone. Higher doses of lorazepam have not been studied. The effects of the combination on sedation appeared to be additive.

Potential for ADASUVE to affect other medicinal products

Loxapine is not expected to cause clinically important pharmacokinetic interactions with medicinal products that are either metabolised by cytochrome P450 (CYP450) isozymes or glucuronidated by human uridine 5'-diphosphoglucuronosyl transferases (UGTs) .

Caution is advised if loxapine is combined with other medicinal products known to lower the seizure threshold, e.g. phenothiazines or butyrophenones, clozapine, tricyclics or selective serotonine reuptake inhibitors (SSRIs), tramadol, mefloquine (see section 4.4).

*In vitro* studies indicated that loxapine was not a substrate for P-glycoprotein (P-gp), but does inhibit P-gp. At therapeutic concentrations, however, it is not expected to inhibit P-gp-mediated transport of other medicinal products in a clinically significant manner.

Given the primary CNS effects of loxapine, ADASUVE should be used with caution in combination with alcohol or other centrally acting medicinal products, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. The use of loxapine in patients with alcohol or medicinal product intoxication (either with prescribed or illicit medicinal products) has not been evaluated. Loxapine may cause severe respiratory depression if combined with other CNS-depressants (see section 4.4).

Potential for other medicinal products to affect ADASUVE

Loxapine is a substrate for flavin-containing mono-oxygenases (FMOs), and for several CYP450 isozymes (see section 5.2). Therefore, the risk of metabolic interactions caused by an effect on an individual isoform is limited. Caution should be used in patients receiving concomitant treatment with other medicinal products that are either inhibitors or inducers of these enzymes, particularly if the concomitant medicinal product is known to inhibit or induce several of the enzymes involved in loxapine metabolism. Such medicinal products may modify efficacy and safety of ADASUVE in an

irregular manner. Concomitant use of CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin, enoxacin, propranolol and refecoxib) should be avoided, if possible.

*Adrenaline*

Co-administration of loxapine and adrenaline may cause worsening of hypotension (see section 4.4).

## 4.6 Fertility, pregnancy and lactation

Pregnancy

New-born infants exposed repeatedly to antipsychotics during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, monitoring of new-borns should be considered. ADASUVE should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

The extent of the excretion of loxapine or its metabolites in human milk is not known. However, loxapine and its metabolites have been shown to be transported into the milk of lactating dogs. Patients should be advised not to breast feed for a period of 48 hours after receiving loxapine and discard the milk produced in the meantime.

Fertility

No loxapine specific human data on fertility are available. It is known that in humans, long-term treatment with antipsychotics may lead to loss of libido and amenorrhoea. In female rats, reproductive effects have been observed (see section 5.3).

## 4.7 Effects on ability to drive and use machines

ADASUVE has major influence on the ability to drive and use machines. Because of the potential for sedation/somnolence, fatigue, or dizziness, patients should not operate hazardous machines, including motor vehicles, until they are reasonably certain that loxapine has not affected them adversely (see section 4.8).

## 4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions from clinical study data is based on two Phase 3 and one Phase 2A short-term (24-hour) placebo-controlled clinical trials enrolling 524 adult patients with agitation associated with schizophrenia or bipolar disorder.

In those studies, bronchospasm was uncommonly found. However, in specific Phase 1 clinical safety trials in subjects with asthma or COPD, bronchospasn was commonly reported and often required treatment with a short-acting beta-agonist bronchodilator. Consecuently, ADASUVE is contraindicated in patients with asthma, COPD or other active airway disease (see section 4.3).

The most commonly reported adverse reactions during treatment with ADASUVE were dysgeusia, sedation/somnolence and dizziness (dizziness was more common after placebo treatment than loxapine treatment).

Tabulated list of adverse reactions

The adverse reactions listed below are categorized using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

**Table 1: Adverse reactions**

| **MedDRA system organ classification** |
|---|
| **Nervous system disorders**<br>Very common: sedation/somnolence<br>Common: dizziness<br>Uncommon: dystonia, dyskinesia, oculogyration, tremor, akathisia/restlessness |
| **Vascular disorders**<br>Uncommon: hypotension |
| **Respiratory, thoracic and mediastinal disorders**<br>Common: throat irritation<br>Uncommon: bronchospasm (including shortness of breath) |
| **Gastrointestinal disorders**<br>Very common: dysgeusia<br>Common: dry mouth |
| **General disorders and administration site conditions**<br>Common: fatigue |

Description of selected adverse reactions

*Bronchospasm*

In short-term (24-hour), placebo-controlled trials in patients with agitation associated with schizophrenia or bipolar disorder without active airways disease, bronchospasm and possible symptoms of bronchospasm (which includes reports of wheezing, shortness of breath or cough) were uncommon in patients treated with ADASUVE. However, in placebo-controlled clinical trials in subjects with mild-to-moderate persistent asthma or moderate-to-severe COPD, adverse reactions of bronchospasm were reported very commonly. Most of these events occurred within 25 minutes of dosing, were mild to moderate in severity, and could be relieved with an inhaled bronchodilator.

*Adverse reactions seen with chronic oral loxapine use*

With chronic oral administration of loxapine, the reported adverse reactions include sedation and drowsiness; extrapyramidal symptoms (e.g., tremor, akathisia, rigidity, and dystonia); cardiovascular effects (e.g., tachycardia, hypotension, hypertension, orthostatic hypotension, light-headedness, and syncope); and anticholinergic effects (e.g., dry eyes, blurred vision, and urinary retention).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V .

## 4.9 Overdose

No cases of overdosage of ADASUVE were reported in clinical studies.

Symptoms

In the event of accidental overdosage, signs and symptoms will depend on the number of units taken and individual patient tolerance. As would be expected from the pharmacologic actions of loxapine, the clinical findings may range from mild depression of the CNS and cardiovascular systems to profound hypotension, respiratory depression, and unconsciousness (see section 4.4). The possibility of occurrence of extrapyramidal symptoms and/or convulsive seizures should be kept in mind. Renal failure following oral loxapine overdosage has also been reported.

Management

The treatment of overdosage is essentially symptomatic and supportive. Severe hypotension might be expected to respond to the administration of noradrenaline or phenylephrine. Adrenaline should not be used since its use in a patient with partial adrenergic blockage may further lower the blood pressure (see sections 4.4 and 4.5). Severe extrapyramidal reactions should be treated with anticholinergic antiparkinson medicinal products or diphenhydramine hydrochloride, and anticonvulsant therapy should be initiated as indicated. Additional measures include oxygen and intravenous fluids.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, antipsychotics; ATC code: N05AH01

The efficacy of loxapine is proposed to be mediated through high affinity antagonism of dopamine D2 receptors and serotonin 5-HT2A receptors. Loxapine binds with noradrenergic, histaminergic, and cholinergic receptors, and its interaction with these systems may influence the spectrum of its pharmacological effects.

Changes in the level of excitability of subcortical inhibitory areas have been observed in several animal species, associated with calming effects and suppression of aggressive behaviour.

Clinical efficacy

In the two Phase 3 studies patients were enrolled who had acute agitation of at least moderate level (14 or higher on Positive and Negative Syndrome Scale (PANSS) Excited Component (PEC) scale (poor impulse control, tension, hostility, uncooperativeness, and excitement). Inclusion in Study 004-301 required a diagnosis of schizophrenia. Inclusion in Study 004-302 required a diagnosis of bipolar disorder (current episode manic or mixed). Patients had significant and long-standing psychiatric disease (Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)), based on years since diagnosis and previous hospitalizations. Patients were randomised to placebo, ADASUVE 4.5 mg and ADASUVE 9.1 mg.

The mean age of randomized patients was 43.1 years in Study 004-301 and 40.8 years in Study 004-302: young adults (18-25 years old) were scarcely (7.3%) represented in either trial. Women in the schizophrenia trial were scarcely represented (26.5%), and about half of the patients were male (49.7%) in Study 004-302. About 35% of the patients with schizophrenia were taking concomitant antipsychotics at the time of dosing while approximately 13% of the patients with bipolar disorder were taking these drugs. A majority of the patients in both Phase 3 studies were smokers with about 82% of the patients with schizophrenia and 74% of the patients with bipolar disorder currently smoking.

After the first dose, a second dose was administered at least 2 hours later if the agitation had not subsided sufficiently. A third dose was administered if needed after at least 4 hours after dose 2. Rescue medication (intramuscular lorazepam) was given if medically required. Primary endpoint was absolute change in PEC score from baseline to 2 hours following Dose 1 for both doses of ADASUVE compared with placebo. Among the other endpoints were PEC and Clinical Global Impression –

Improvement (CGI-I) responders at 2 hours after dose 1, and total number of patients per group who received 1, 2, or 3 doses of study medication with and without rescue medication. Responders were considered patients with a ≥40% decrease from baseline in the total PEC score or patients with CGI-I score of 1 (very much improved) or 2 (much improved).

Decreased agitation was evident 10 minutes after Dose 1, the first assessment time, and at all subsequent assessments during the 24 hour evaluation period, for both 4.5 mg and 9.1 mg doses in both schizophrenia and bipolar disorder patients.

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

For the main results, see the table below.**Main results of the pivotal efficacy studies: comparisons between ADASUVE 4.5 mg, 9.1 mg, and placebo**

| | **Study Patients** | **004-301 Schizophrenia** | | | **004-302 Bipolar Disorder** | | |
|---|---|---|---|---|---|---|---|
| | **Treatment N** | **PBO 115** | **4.5 mg 116** | **9.1 mg 112** | **PBO 105** | **4.5 mg 104** | **9.1 mg 105** |
| **PEC Change** | Baseline | 17.4 | 17.8 | 17.6 | 17.7 | 17.4 | 17.3 |
| | Change at 2 hr post dose | -5.5 | -8.1$^{+}$ | -8.6* | -4.9 | -8.1* | -9.0* |
| | SD | 4.9 | 5.2 | 4.4 | 4.8 | 4.9 | 4.7 |
| **PEC Responders** | 30 min post dose | 27.8% | 46.6% | 57.1% | 23.8% | 59.6% | 61.9% |
| | 2 hr post dose | 38.3% | 62.9% | 69.6% | 27.6% | 62.5% | 73.3% |
| **CGI-I Responder** | % CGI-I Responders | 35.7% | 57.4% | 67.0% | 27.6% | 66.3% | 74.3% |
| **# Doses Needed** | One | 46.1% | 54.4% | 60.9% | 26.7% | 41.3% | 61.5% |
| | Two | 29.6% | 30.7% | 26.4% | 41.0% | 44.2% | 26.0% |
| | Three | 8.7% | 8.8% | 7.3% | 11.4% | 5.8% | 3.8% |
| | Rescue | 15.6% | 6.1% | 5.4% | 21.0% | 8.6% | 8.6% |

*= $p<0.0001$ $^{+}$= $p<0.01$
PEC Responders = ≥ 40% change from PEC Baseline;
CGI-I Responders = Score of 1 (Very Much Improved) or 2 (Much Improved)
PBO = placebo SD=Standard Deviation

In a supportive Phase 2 single dose study enrolling a total of 129 patients with schizophrenia and schizoaffective disorder the decrease in PEC change after 2 hours was -5.0 for placebo, -6.7 for ADASUVE 4.5 mg, and -8.6 ($p<0.001$) for ADASUVE 9.1 mg. Rescue medication was administered in respectively 32.6%, 11.1 % and 14.6 % of patients.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ADASUVE in the subset of the paediatric population from birth to less than 12 years of age for the treatment of schizophrenia and in the subset from birth to less than 10 years of age for the treatment of bipolar disorder (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with ADASUVE in the subset of the paediatric population from 12 to less than 18 years of age for the treatment of schizophrenia and in the subset from 10 years to less than 18 years of age in bipolar disorder (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

Administration of ADASUVE resulted in rapid absorption of loxapine with a median time of maximum plasma concentration ($T_{max}$) by 2 minutes. Loxapine exposure in the first 2 hours after administration ($AUC_{0-2h}$, a measure of early exposure that is relevant to the onset of therapeutic effect) was 25.6 ng*h/mL for the 4.5 mg dose and 66.7 ng*h/mL for the 9.1 mg dose in healthy subjects.

The pharmacokinetic parameters of loxapine were determined in subjects on chronic, stable antipsychotic regimens following repeat administration of ADASUVE every 4 hours for a total of 3 doses (either 4.5 mg or 9.1 mg). Mean peak plasma concentrations were similar after the first and third dose of ADASUVE, indicating minimal accumulation during the 4-hour dosing interval.

Distribution

Loxapine is removed rapidly from the plasma and distributed in tissues. Animal studies following oral administration suggest an initial preferential distribution in the lungs, brain, spleen, heart and kidney. Loxapine is 96.6% bound to human plasma proteins.

Biotransformation

Loxapine is metabolised extensively in the liver, with multiple metabolites formed. The main metabolic pathways include hydroxylation to form 8-OH-loxapine and 7-OH-loxapine, N-oxidation to form loxapine N-oxide, and de-methylation to form amoxapine. For ADASUVE, the order of metabolites observed in humans (based on systemic exposure) was 8-OH-loxapine >> loxapine N oxide > 7-OH-loxapine > amoxapine, with plasma levels of 8-OH-loxapine similar to the parent compound. 8-OH-loxapine is not pharmacologically active at the D2 receptor while the minor metabolite, 7-OH-loxapine, has high binding affinity to D2 receptors.

Loxapine is a substrate for several CYP450 isozymes; *in vitro* studies demonstrated that 7-OH-loxapine is formed mainly by CYPs 3A4 and 2D6, 8-OH-loxapine is formed mainly by CYP1A2, amoxapine is formed mainly by CYP3A4, 2C19, and 2C8, and loxapine N-oxide is formed by FMOs.

The potential for loxapine and its metabolites (amoxapine, 7-OH-loxapine, 8-OH-loxapine, and loxapine-N-oxide) to inhibit CYP450 - mediated drug metabolism has been examined *in vitro* for CYPs 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. No significant inhibition was observed. *In vitro* studies indicate that loxapine and 8-OH-loxapine are not inducers of CYP1A2, 2B6 or 3A4 enzymes at clinically relevant concentrations. In addition, *in vitro* studies indicate that loxapine and 8-OH loxapine are not inhibitors of UGT1A1, 1A3, 1A4, 2B7 and 2B15.

Elimination

Loxapine excretion occurs mainly in the first 24 hours. Metabolites are excreted in the urine in the form of conjugates and in the faeces unconjugated. The terminal elimination half-life (T½) ranged from 6 to 8 hours.

Linearity/non-linearity

The mean plasma loxapine concentrations following administration of ADASUVE were linear over the clinical dose range. $AUC_{0\text{-}2h}$, $AUC_{inf}$, and $C_{max}$ increased in a dose-dependent manner.

Pharmacokinetics in special patient populations

*Smokers*

A population pharmacokinetic analysis that compared exposures in smokers versus non-smokers indicated that smoking, which induces CYP1A2, had a minimal effect on the exposure to ADASUVE. No dosage adjustment is recommended based on smoking status.

In female smokers exposure ($AUC_{inf}$) to ADASUVE and its active metabolite 7-OH-loxapine is lower than in female non-smokers (84% vs 109% 7-OH-loxapine/Loxapine Ratio), which is probably due to an increase in loxapine clearance in smokers.

*Demographics*

There were no important differences in the exposure or disposition of loxapine following administration of ADASUVE due to age, gender, race, weight, or body mass index (BMI).

### 5.3 Preclinical safety data

Non-clinical safety data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, and genotoxicity, except for changes to reproductive tissues related to the extended pharmacology of loxapine. Similar changes, e.g., gynecomastia, are known in humans, but only after long-term administration of medicines causing hyperprolactinaemia.

Female rats did not mate due to persistent diestrus after oral treatment with loxapine. Embryo/fetal developmental and perinatal studies have shown indications of developmental delay (reduced weights, delayed ossification, hydronephrosis, hydrourether, and/or distended renal pelvis with reduced or absent papillae) as well as increased numbers of perinatal and neonatal deaths in offspring of rats treated from mid-pregnancy with oral doses below the maximum recommended human dose for ADASUVE on a $mg/m^2$ basis (see section 4.6).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

None

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

4 years

### 6.4 Special precautions for storage

Store in the original pouch until ready for use in order to protect from light and moisture.

This medicinal product does not require any special temperature storage conditions.

### 6.5 Nature and contents of container

The white inhaler (housing) is molded from a medical-grade polycarbonate.

Each inhaler is provided in a sealed, multilaminate aluminum foil pouch. ADASUVE 9.1 mg is supplied in a carton of 1 or 5 units.

Not all pack-sized may be marketed.

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Ferrer Internacional, S.A.
Gran Vía Carlos III, 94
08028- Barcelona
España

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/823/002 (5 single-dose inhalers)
EU/1/13/823/004 (1 single-dose inhaler)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 February 2013
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

FERRER INTERNACIONAL, S.A.
Joan Buscalla, 1-9, 08173 Sant Cugat del Vallès, Barcelona, Spain

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the
agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Addtional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority.

The MAH shall ensure that, following discussion and agreement with the National Competent Authorities in each Member State where ADASUVE is marketed, at launch and after launch, all healthcare professionals who are expected to use ADASUVE are provided with an information pack containing the following items:

- Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling
- Educational material for the healthcare professionals

Key elements to be included in the educational materials:

- Information on ADASUVE, including the approved indication according to the SmPC:

"ADASUVE is indicated for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder. Patients should receive regular treatment immediately after control of acute agitation symptoms".

- Detailed description of the administration procedures of ADASUVE:

ADASUVE should be administered in a medical-setting under the supervision of a healthcare professional.

The recommended initial dose of ADASUVE is 9.1 mg. A second dose can be given after 2 hours, if necessary. No more than two doses should be administered.

- Patient's preparation for the procedure and subsequent monitoring:

Patient should be observed during the first hour after each dose for signs and symptoms of bronchospasm.

- Management of early signs and symptoms of bronchospasm:

Short-acting beta-agonist bronchodilator treatment should be used for treatment of possible severe respiratory side-effects.

- Prior to administering ADASUVE:

Do not use ADASUVE in patients with active airways disease, such as patients with asthma or COPD.

Do not use ADASUVE in patients with acute respiratory signs or symptoms.

Caution should be exercised when ADASUVE is administered in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medical products known to prolong the QT interval.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

ADASUVE 4.5 mg inhalation powder, pre-dispensed
loxapine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each inhaler delivers 4.5 mg loxapine.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, pre-dispensed

1 single dose inhaler

5 single-dose inhalers

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Inhalation use

For single use only

This product is packaged in a sealed pouch and should remain in the pouch until ready to use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original pouch until ready for use in order to protect from light and moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ferrer Internacional, S.A.
Gran Vía Carlos III, 94
08028- Barcelona
España

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/823/001 (5 single-dose inhalers)
EU/1/13/823/003 (1 single-dose inhaler)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**POUCH**

## 1. NAME OF THE MEDICINAL PRODUCT

ADASUVE 4.5 mg inhalation powder
loxapine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each inhaler delivers 4.5 mg loxapine.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder

One single-dose inhaler

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Directions for use inside

Read the package leaflet before use

Inhalation use

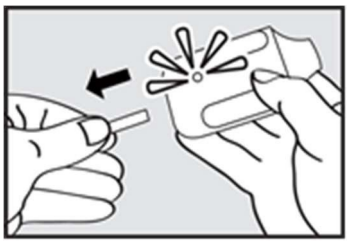
Directions for use

Read the following 5 steps before administering ADASUVE to a patient:

**1. Open pouch. Do not open pouch until ready to use.**

Tear open the foil pouch and remove the inhaler from the package.

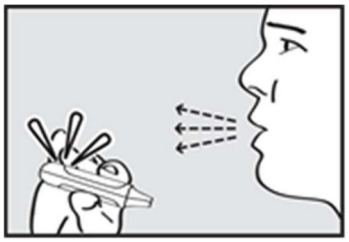
**2. Pull tab.** Firmly pull the plastic tab from the rear of the inhaler. The green light turns on indicating that the inhaler is ready for use.



**Use within 15 minutes after removing the tab (or until the green light turns off) to prevent automatic deactivation of the inhaler.**

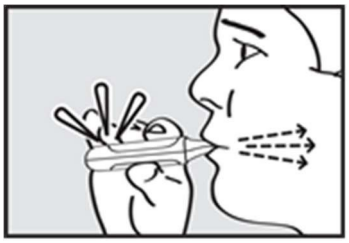
Instruct the patient to:

**3. Exhale.** Hold the inhaler away from the mouth and breathe out fully to empty lungs.

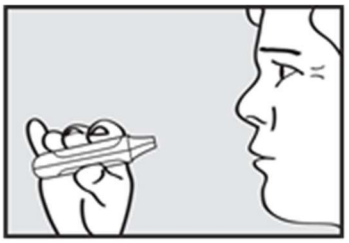


**4. Inhale.** Inhale through the mouthpiece with a steady, deep breath.

**IMPORTANT: Check that the green light turns off after the patient inhales.**



**5. Hold Breath.** Remove the mouthpiece from the mouth and hold breath briefly.



**Note: If the green light stays on after the patient inhales, instruct the patient to repeat steps 3 to 5.**

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use in patients with asthma or COPD or acute respiratory symptoms

A short-acting beta-agonist bronchodilator should be available for treatment of possible bronchospasm.

Patients should be observed during the first hour after each dose for signs and symptoms of bronchospasm.

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original pouch until ready for use in order to protect from light and moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ferrer Internacional, S.A.
Gran Vía Carlos III, 94
08028- Barcelona
España

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/823/001 (5 single-dose inhalers)
EU/1/13/823/003 (1 single-dose inhaler)

## 13. BATCH NUMBER

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**DEVICE HOUSING**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

ADASUVE 4.5 mg inhalation powder
loxapine

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

4.5 mg

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

ADASUVE 9.1 mg inhalation powder, pre-dispensed
loxapine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each inhaler delivers 9.1 mg loxapine.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, pre-dispensed

1 single dose inhaler

5 single-dose inhalers

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Inhalation use

For single use only

This product is packaged in a sealed pouch and should remain in the pouch until ready to use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original pouch until ready for use in order to protect from light and moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ferrer Internacional, S.A.
Gran Vía Carlos III, 94
08028- Barcelona
España

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/823/002 (5 single-dose inhalers)
EU/1/13/823/004 (1 single-dose inhaler)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}

SN: {number}
NN: {number}

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**POUCH**

## 1. NAME OF THE MEDICINAL PRODUCT

ADASUVE 9.1 mg inhalation powder
loxapine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each inhaler delivers 9.1 mg loxapine.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder

One single-dose inhaler

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Directions for use inside

Read the package leaflet before use

Inhalation use

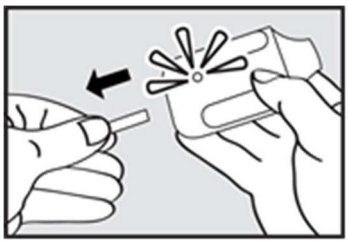
Directions for use

Read the following 5 steps before administering ADASUVE to a patient:

**1. Open pouch. Do not open pouch until ready to use.**

Tear open the foil pouch and remove the inhaler from the package.

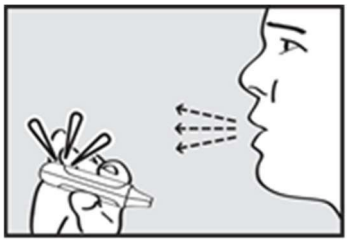
**2. Pull tab.** Firmly pull the plastic tab from the rear of the inhaler. The green light turns on indicating that the inhaler is ready for use.



**Use within 15 minutes after removing the tab (or until the green light turns off) to prevent automatic deactivation of the inhaler.**

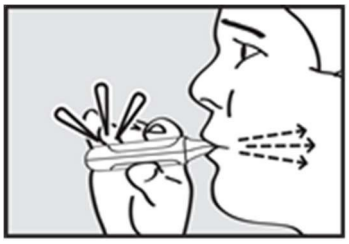
Instruct the patient to:

**3. Exhale.** Hold the inhaler away from the mouth and breathe out fully to empty lungs.

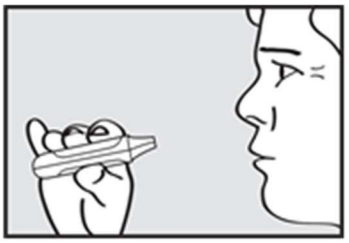


**4. Inhale.** Inhale through the mouthpiece with a steady, deep breath.

**IMPORTANT: Check that the green light turns off after the patient inhales.**



**5. Hold Breath.** Remove the mouthpiece from the mouth and hold breath briefly.



**Note: If the green light stays on after the patient inhales, instruct the patient to repeat steps 3 to 5.**

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use in patients with asthma or COPD or acute respiratory symptoms

A short-acting beta-agonist bronchodilator should be available for treatment of possible bronchospasm.

Patients should be observed during the first hour after each dose for signs and symptoms of bronchospasm.

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original pouch until ready for use in order to protect from light and moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ferrer Internacional, S.A.
Gran Vía Carlos III, 94
08028- Barcelona
España

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/823/002 (5 single-dose inhalers)
EU/1/13/823/004 (1 single-dose inhaler)

## 13. BATCH NUMBER

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**DEVICE HOUSING**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ADASUVE 9.1 mg inhalation powder
loxapine

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

9.1 mg

## 6. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**ADASUVE 4.5 mg inhalation powder, pre-dispensed**
loxapine

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What ADASUVE is and what it is used for

ADASUVE contains the active substance loxapine, which belongs to a group of medicines called antipsychotics. ADASUVE works by blocking certain chemicals in the brain (neurotransmitters) such as dopamine and serotonin thus causing calming effects and relieving aggressive behaviour.

ADASUVE is used to treat acute symptoms of mild-to-moderate agitation that may occur in adult patients who have schizophrenia or bipolar disorder. These are diseases characterised by symptoms such as:

- (Schizophrenia) Hearing, seeing, or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.
- (Bipolar disorder) Feeling “high”, having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas, and sometimes severe irritability.

## 2. What you need to know before you use ADASUVE

**Do not use ADASUVE**
- if you are allergic to loxapine or amoxapine;
- if you have symptoms of wheezing or shortness of breath;
- if you have lung problems like asthma or chronic obstructive pulmonary disease (which your doctor may have called “COPD”).

**Warnings and precautions**
Your doctor or nurse will talk to you before you use ADASUVE and determine whether it is appropriate for you.

- ADASUVE may cause narrowing of the airways (bronchospasm) and may cause you to wheeze, cough, feel chest tightness or have shortness of breath. Typically, this may occur within 25 minutes of use.
- Neuroleptic Malignant Syndrome (NMS) is a set of symptoms that can occur if you are taking antipsychotic medicines, including ADASUVE. These symptoms can be high fever, rigid muscles,

irregular or fast heart rate or pulse. NMS can cause death. Do not use ADASUVE again if NMS occurs.
- Antipsychotic medicines like ADASUVE can cause movements that you may not be able to control including making faces, sticking out your tongue, smacking or puckering your lips, blinking rapidly, or moving your legs, arms or fingers rapidly. Treatment with ADASUVE may have to be stopped if this occurs.
- ADASUVE should be used with caution in patients who are intoxicated or delirious.
- Serious skin reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with loxapine treatment. Seek medical attention immediately if you notice any of the following symptoms after the use of ADASUVE: Widespread rash, high body temperature and enlarged lymph nodes.

Before treatment with ADASUVE, tell your doctor or nurse if you:
- have or had breathing problems like asthma or other chronic lung diseases such as bronchitis or emphysema
- have or had heart problems or stroke
- have or had low or high blood pressure
- have or had seizures (convulsions)
- have or had glaucoma (increased pressure in the eye)
- have or had urinary retention (incomplete emptying of the bladder)
- already used ADASUVE and you developed symptoms of wheezing or shortness of breath
- ever had muscle or eye movements you can't control, lack of coordination, sustained muscle contraction, or feeling restless or unable to sit still
- are an older person with dementia (loss of memory and other mental abilities).
- have ever developed a severe widespread skin rash, high body temperature and enlarged lymph nodes after taking loxapine.

**Children and adolescents**
ADASUVE is not for use in children and adolescents under 18 years.

**Other medicines and ADASUVE**
Tell your doctor if you are using or have recently used or might use any other medicines, including:
- adrenaline
- medicines to treat a breathing problem
- medicines that may put you at a risk for seizures (for example, clozapine, tricyclics or SSRIs, tramadol, mefloquine)
- medicines to treat Parkinson's disease
- lorazepam or other centrally acting medicines (to treat anxiety, depression, pain, or to help you sleep) or any other medicines that cause sleepiness
- recreational (illegal) drugs
- medicines like fluvoxamine, propranolol, and enoxacin and other medicines that inhibit a certain liver enzyme called "CYP450 1A2."
- medicines to treat schizophrenia, depression, or pain since you may be more at risk for seizures

Using ADASUVE and adrenaline together may cause your blood pressure to drop.

**ADASUVE with alcohol**
Because ADASUVE affects the nervous system, alcohol should be avoided when using ADASUVE.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. You should not breast-feed for a period of 48 hours after receiving ADASUVE and should discard the milk produced in the meantime.

The following symptoms may occur in newborn babies of mothers that have repeatedly used antipsychotic medicines in the last three months of their pregnancy: shaking, muscle stiffness and/or

weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

**Driving and using machines**
Do not drive or use any tools or machines after using ADASUVE until you know how ADASUVE affects you since dizziness, sedation, and sleepiness have been reported as a potential side effect of ADASUVE.

## 3. How to use ADASUVE

Always use this medicine exactly as your doctor or nurse has told you. Check with your doctor or nurse if you are not sure.

The recommended initial dose is 9.1 mg. After 2 hours, your doctor may prescribe a second dose after carefully considering your condition and your dose may be reduced to 4.5 mg if your doctor believes that this is a more appropriate dose to treat your condition.

You will use ADASUVE under the supervision of a doctor or nurse.

ADASUVE is for inhalation use. After the doctor or nurse has prepared ADASUVE for you to use, you will be asked to take the device in your hand, exhale and then put the mouthpiece in your mouth, inhale the medicine through the device and then hold your breath briefly.

**If you use more ADASUVE than you should**

If you are concerned that you are given more ADASUVE than you feel necessary, tell your doctor or nurse of your concern. Patients who have been given more ADASUVE than they should may experience any of the following symptoms: extreme tiredness or sleepiness, trouble breathing, low blood pressure, throat irritation or a bad taste in the mouth, muscle or eye movements you can't control.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any of the following side effects, talk to your doctor immediately and stop taking the medicine:
- any breathing symptoms such as wheezing, cough, shortness of breath, or chest tightness, as these could mean that the medicine is irritating your airways (uncommon occurrence unless you have asthma or COPD);
- light-headedness or fainting, as these could mean that the medicine is lowering your blood pressure (uncommon occurrence);
- worsening agitation or confusion, especially combined with fever or muscle stiffness (rare occurrence). These can be associated with a severe condition called neuroleptic malignant syndrome (NMS)

**Also talk to your doctor if you have any of the following side effects that could also happen with other forms of this medicine:**

**Very common** (may affect more than 1 in 10 people): bad taste in the mouth or sleepiness.

**Common** (may affect up to 1 in 10 people): dizziness, throat irritation, dry mouth or tiredness.

**Uncommon** (may affect up to 1 in 100 people): muscle or eye movements you can't control, lack of coordination, sustained muscle contraction, or feeling restless or unable to sit still.

Additional side effects which have been related to long term use of loxapine by mouth and which may be relevant for ADASUVE include faintness upon standing, increased heart rate, increased blood pressure, blurred vision, dry eyes, and decreased urination.

**Reporting of side effects**
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store ADASUVE

Keep this medicine out of the sight and reach of children.

Do not use ADASUVE after the expiry date which is stated on the product label. The expiry date refers to the last day of that month.

Store in the original pouch until ready for use in order to protect from light and moisture.

Do not use ADASUVE if you notice an open or torn pouch or any signs of physical damage to the medicine.

Do not throw away any medicines via household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What ADASUVE contains**
The active substance is loxapine. Each single-dose inhaler contains 5 mg loxapine and delivers 4.5 mg of loxapine.

**What ADASUVE looks like and contents of the pack**
ADASUVE 4.5 mg inhalation powder, pre-dispensed consists of a single-dose, disposable white plastic inhaler that contains loxapine. Each inhaler is packaged in a sealed foil pouch. ADASUVE 4.5 mg is supplied in a carton of 1 or 5 single dose inhalers.

**Marketing Authorisation Holder**
Ferrer Internacional, S.A.
Gran Vía Carlos III, 94
08028- Barcelona
España

**Manufacturer**
Ferrer Internacional, S.A.
Joan Buscalla, 1-9, 08173 Sant Cugat del Vallès
Barcelona, Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

| | |
|---|---|
| **België/Belgique/Belgien** | **Lietuva** |
| Ferrer Internacional, S.A. | AOP Orphan Pharmaceuticals GmbH |
| Tél/Tel: +34 93 600 37 00 | Tel +370 672 12222 |

**България**
AOP Orphan Pharmaceuticals GmbH
Тел.: +35 988 6666096

**Česká republika**
AOP Orphan Pharmaceuticals GmbH
Tel: +420 251 512 947

**Danmark**
Ferrer Internacional, S.A.
Tlf: +34 93 600 37 00

**Deutschland**
Ferrer Deutschland GmbH
Tel: +49 (0) 2407 502311 0

**Eesti**
AOP Orphan Pharmaceuticals GmbH
Tel: +370 672 12222

**Ελλάδα**
Ferrer Galenica S.A.
Τηλ: +30 210 52 81 700

**España**
Ferrer Farma, S.A.
Tel.: +34 93 600 37 00

**France**
Ferrer Internacional, S.A.
Tél: +34 93 600 37 00

**Hrvatska**
AOP Orphan Pharmaceuticals GmbH
Tel: +43 1 5037244-0

**Ireland**
Ferrer Internacional, S.A.
Tel.: +34 93 600 37 00

**Ísland**
Ferrer Internacional, S.A.
Sími: +34 93 600 37 00

**Italia**
Angelini S.p.A. Tel: +39 06 780531

**Luxembourg/Luxemburg**
Ferrer Internacional, S.A.
Tél/Tel: +34 93 600 37 00

**Magyarország**
AOP Orphan Pharmaceuticals GmbH
Tel.: +36 1 3192633

**Malta**
Ferrer Internacional, S.A.
Tel.: +34 93 600 37 00

**Nederland**
Ferrer Internacional, S.A.
Tel.: +34 93 600 37 00

**Norge**
Ferrer Internacional, S.A.
Tlf: +34 93 600 37 00

**Österreich**
AOP Orphan Pharmaceuticals GmbH
Tel: +43 1 5037244-0

**Polska**
AOP Orphan Poland Sp. z o. o.
Tel: +48 22 5428180

**Portugal**
Ferrer Portugal, S.A.
Tel: +351 214449600

**România**
Galenica S.A.
Tel: +30 210 52 81 700

**Slovenija**
AOP Orphan Pharmaceuticals GmbH
Tel: +43 1 5037244-0

**Slovenská republika**
AOP Orphan Pharmaceuticals GmbH
Tel: +421 902 566333

**Suomi/Finland**
F

**Κύπρος**
Thespis Pharmaceutical Ltd Τηλ:
++357 22 67 77 10

**Latvija**
AOP Orphan Pharmaceuticals GmbH
Tel +370 672 12222

errer Internacional, S.A.
Puh/Tel: +34 93 600 37 00

**Sverige**
Ferrer Internacional, S.A.
Tel: +34 93 600 37 00

**This leaflet was last revised in**

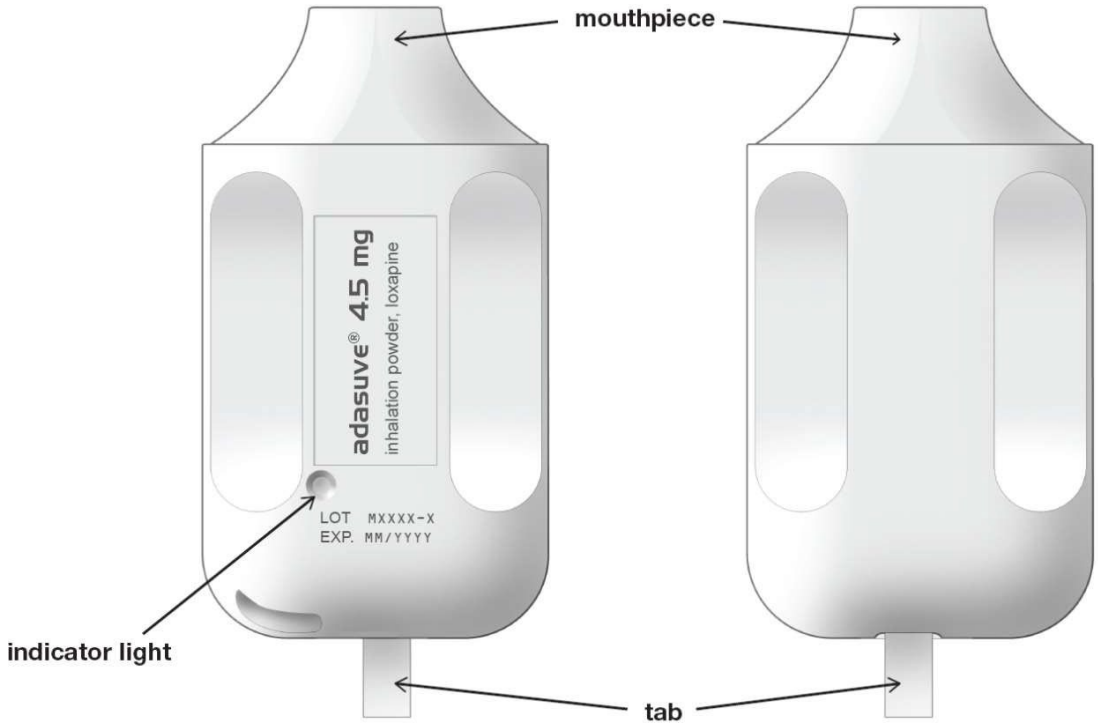
**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Read all instructions before use. See the SmPC for more information.

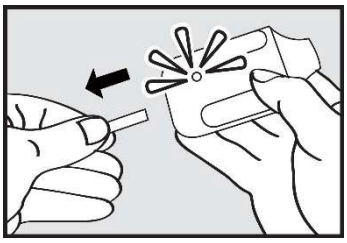
**Becoming familiar with ADASUVE:** The pictures below show the important features of ADASUVE.




- ADASUVE is provided in a sealed pouch.
- When ADASUVE is removed from the pouch, the indicator light is off.
- The indicator light turns on (green) when the tab is pulled out. The inhaler is then ready for use.
- The indicator light automatically turns off again when the medicine is inhaled.

Read the following 5 steps before administering ADASUVE to a patient.

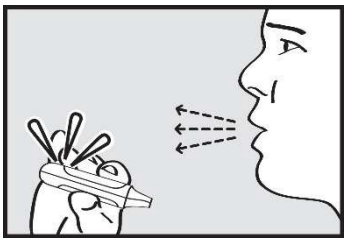
**1. Open pouch**
**Do not open the pouch until ready to use.** Tear open the foil pouch and remove the inhaler from the package.



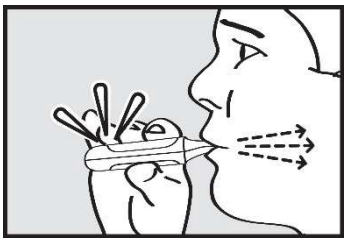
**2. Pull tab**
Firmly pull the plastic tab from the rear of the inhaler. The green light turns on indicating that the inhaler is ready for use.

**Use within *15* minutes after removing the tab (or until the green light turns off) to prevent automatic deactivation of the inhaler.**

**Instruct the patient to:**

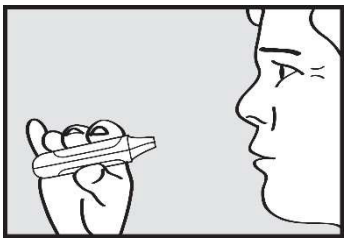


**3. Exhale**
Hold the inhaler away from the mouth and breathe out fully to empty lungs.



**4. Inhale**
Inhale through the mouthpiece with a steady deep breath.

**IMPORTANT: Check that the green light turns off after the patient inhales.**



**5. Hold breath**
Remove the mouthpiece from the mouth and hold breath briefly.

NOTE: If the green light stays on after the patient inhales, instruct the patient to repeat steps 3-5.

**Package leaflet: Information for the user**

**ADASUVE 9.1 mg inhalation powder, pre-dispensed**
loxapine

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What ADASUVE is and what it is used for

ADASUVE contains the active substance loxapine, which belongs to a group of medicines called antipsychotics. ADASUVE works by blocking certain chemicals in the brain (neurotransmitters) such as dopamine and serotonin thus causing calming effects and relieving aggressive behaviour.

ADASUVE is used to treat acute symptoms of mild-to-moderate agitation that may occur in adult patients who have schizophrenia or bipolar disorder. These are diseases characterised by symptoms such as:

- (Schizophrenia) Hearing, seeing, or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.
- (Bipolar disorder) Feeling “high”, having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas, and sometimes severe irritability.

## 2. What you need to know before you use ADASUVE

**Do not use ADASUVE**
- if you are allergic to loxapine or amoxapine;
- if you have symptoms of wheezing or shortness of breath;
- if you have lung problems like asthma or chronic obstructive pulmonary disease (which your doctor may have called “COPD”).

**Warnings and precautions**
Your doctor or nurse will talk to you before you use ADASUVE and determine whether it is appropriate for you.

- ADASUVE may cause narrowing of the airways (bronchospasm) and may cause you to wheeze, cough, feel chest tightness or have shortness of breath. Typically, this may occur within 25 minutes of use.
- Neuroleptic Malignant Syndrome (NMS) is a set of symptoms that can occur if you are taking antipsychotic medicines, including ADASUVE. These symptoms can be high fever, rigid muscles,

irregular or fast heart rate or pulse. NMS can cause death. Do not use ADASUVE again if NMS occurs.
- Antipsychotic medicines like ADASUVE can cause movements that you may not be able to control including making faces, sticking out your tongue, smacking or puckering your lips, blinking rapidly, or moving your legs, arms or fingers rapidly. Treatment with ADASUVE may have to be stopped if this occurs.
- ADASUVE should be used with caution in patients who are intoxicated or delirious.
- Serious skin reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with loxapine treatment. Seek medical attention immediately if you notice any of the following symptoms after the use of ADASUVE: Widespread rash, high body temperature and enlarged lymph nodes.

Before treatment with ADASUVE, tell your doctor or nurse if you:
- have or had breathing problems like asthma or other chronic lung diseases such as bronchitis or emphysema
- have or had heart problems or stroke
- have or had low or high blood pressure
- have or had seizures (convulsions)
- have or had glaucoma (increased pressure in the eye)
- have or had urinary retention (incomplete emptying of the bladder)
- already used ADASUVE and you developed symptoms of wheezing or shortness of breath
- ever had muscle or eye movements you can't control, lack of coordination, sustained muscle contraction, or feeling restless or unable to sit still
- are an older person with dementia (loss of memory and other mental abilities).
- have ever developed a severe widespread skin rash, high body temperature and enlarged lymph nodes after taking loxapine.

**Children and adolescents**
ADASUVE is not for use in children and adolescents under 18 years.

**Other medicines and ADASUVE**
Tell your doctor if you are using or have recently used or might use any other medicines, including:
- adrenaline
- medicines to treat a breathing problem
- medicines that may put you at a risk for seizures (for example, clozapine, tricyclics or SSRIs, tramadol, mefloquine)
- medicines to treat Parkinson's disease
- lorazepam or other centrally acting medicines (to treat anxiety, depression, pain, or to help you sleep) or any other medicines that cause sleepiness
- recreational (illegal) drugs
- medicines like fluvoxamine, propranolol, and enoxacin and other medicines that inhibit a certain liver enzyme called "CYP450 1A2."
- medicines to treat schizophrenia, depression, or pain since you may be more at risk for seizures

Using ADASUVE and adrenaline together may cause your blood pressure to drop.

**ADASUVE with alcohol**
Because ADASUVE affects the nervous system, alcohol should be avoided when using ADASUVE.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. You should not breast-feed for a period of 48 hours after receiving ADASUVE and should discard the milk produced in the meantime.

The following symptoms may occur in newborn babies of mothers that have repeatedly used antipsychotic medicines in the last three months of their pregnancy: shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops

any of these symptoms you may need to contact your doctor.

**Driving and using machines**
Do not drive or use any tools or machines after using ADASUVE until you know how ADASUVE affects you since dizziness, sedation, and sleepiness have been reported as a potential side effect of ADASUVE.

## 3. How to use ADASUVE

Always use this medicine exactly as your doctor or nurse has told you. Check with your doctor or nurse if you are not sure.

The recommended initial dose is 9.1 mg. After 2 hours, your doctor may prescribe a second dose after carefully considering your condition and your dose may be reduced to 4.5 mg if your doctor believes that this is a more appropriate dose to treat your condition.

You will use ADASUVE under the supervision of a doctor or nurse.

ADASUVE is for inhalation use. After the doctor or nurse has prepared ADASUVE for you to use, you will be asked to take the device in your hand, exhale and then put the mouthpiece in your mouth, inhale the medicine through the device and then hold your breath briefly.

**If you use more ADASUVE than you should**

If you are concerned that you are given more ADASUVE than you feel necessary, tell your doctor or nurse of your concern. Patients who have been given more ADASUVE than they should may experience any of the following symptoms: extreme tiredness or sleepiness, trouble breathing, low blood pressure, throat irritation or a bad taste in the mouth, muscle or eye movements you can't control.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any of the following side effects, talk to your doctor immediately and stop taking the medicine:
- any breathing symptoms such as wheezing, cough, shortness of breath, or chest tightness, as these could mean that the medicine is irritating your airways (uncommon occurrence unless you have asthma or COPD);
- light-headedness or fainting, as these could mean that the medicine is lowering your blood pressure (uncommon occurrence);
- worsening agitation or confusion, especially combined with fever or muscle stiffness (rare occurrence). These can be associated with a severe condition called neuroleptic malignant syndrome (NMS)

**Also talk to your doctor if you have any of the following side effects that could also happen with other forms of this medicine:**

**Very common** (may affect more than 1 in 10 people): bad taste in the mouth or sleepiness.

**Common** (may affect up to 1 in 10 people): dizziness, throat irritation, dry mouth or tiredness.

**Uncommon** (may affect up to 1 in 100 people): muscle or eye movements you can't control, lack of coordination, sustained muscle contraction, or feeling restless or unable to sit still.

Additional side effects which have been related to long term use of loxapine by mouth and which may be relevant for ADASUVE include faintness upon standing, increased heart rate, increased blood pressure, blurred vision, dry eyes, and decreased urination.

**Reporting of side effects**
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store ADASUVE

Keep this medicine out of the sight and reach of children.

Do not use ADASUVE after the expiry date which is stated on the product label. The expiry date refers to the last day of that month.

Store in the original pouch until ready for use in order to protect from light and moisture.

Do not use ADASUVE if you notice an open or torn pouch or any signs of physical damage to the medicine.

Do not throw away any medicines via household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What ADASUVE contains**
The active substance is loxapine. Each single-dose inhaler contains 10 mg loxapine and delivers 9.1 mg of loxapine.

**What ADASUVE looks like and contents of the pack**
ADASUVE 9.1 mg inhalation powder, pre-dispensed consists of a single-dose, disposable white plastic inhaler that contains loxapine. Each inhaler is packaged in a sealed foil pouch. ADASUVE 9.1 mg is supplied in a carton of 1 or 5 single dose inhalers.

**Marketing Authorisation Holder**
Ferrer Internacional, S.A.
Gran Vía Carlos III, 94
08028- Barcelona
España

**Manufacturer**
Ferrer Internacional, S.A.
Joan Buscalla, 1-9, 08173 Sant Cugat del Vallès
Barcelona, Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
Ferrer Internacional, S.A.
Tél/Tel: +34 93 600 37 00

**Lietuva**
AOP Orphan Pharmaceuticals GmbH
Tel +370 672 12222

**България**
AOP Orphan Pharmaceuticals GmbH
Тел.: +35 988 6666096

**Luxembourg/Luxemburg**
Ferrer Internacional, S.A.
Tél/Tel: +34 93 600 37 00

**Česká republika**
AOP Orphan Pharmaceuticals GmbH
Tel: +420 251 512 947

**Magyarország**
AOP Orphan Pharmaceuticals GmbH
Tel.: +36 1 3192633

**Danmark**
Ferrer Internacional, S.A.
Tlf: +34 93 600 37 00

**Malta**
Ferrer Internacional, S.A.
Tel.: +34 93 600 37 00

**Deutschland**
Ferrer Deutschland GmbH
Tel: +49 (0) 2407 502311 0

**Nederland**
Ferrer Internacional, S.A.
Tel.: +34 93 600 37 00

**Eesti**
AOP Orphan Pharmaceuticals GmbH
Tel: +370 672 12222

**Norge**
Ferrer Internacional, S.A.
Tlf: +34 93 600 37 00

**Ελλάδα**
Ferrer Galenica S.A.
Τηλ: +30 210 52 81 700

**Österreich**
AOP Orphan Pharmaceuticals GmbH
Tel: +43 1 5037244-0

**España**
Ferrer Farma, S.A.
Tel.: +34 93 600 37 00

**Polska**
AOP Orphan Pharmaceuticals Poland
Sp. z o. o.
Tel: +48 22 5428180

**France**
Ferrer Internacional, S.A.
Tél: +34 93 600 37 00

**Portugal**
Ferrer Portugal, S.A.
Tel: +351 214449600

**Hrvatska**
AOP Orphan Pharmaceuticals GmbH
Tel: +43 1 5037244-0

**România**
Galenica S.A.
Tel: +30 210 52 81 700

**Ireland**
Ferrer Internacional, S.A.
Tel.: +34 93 600 37 00

**Slovenija**
AOP Orphan Pharmaceuticals GmbH
Tel: +43 1 5037244-0

**Ísland**
Ferrer Internacional, S.A.
Sími: +34 93 600 37 00

**Slovenská republika**
AOP Orphan Pharmaceuticals GmbH
Tel: +421 902 566333

**Italia**
Angelini S.p.A.
Tel: +39 06 780531

**Κύπρος**
Thespis Pharmaceutical Ltd
Τηλ: ++357 22 67 77 10

**Suomi/Finland**
Ferrer Internacional, S.A.
Puh/Tel: +34 93 600 37 00

**Sverige**
Ferrer Internacional, S.A.
Tel: +34 93 600 37 00

**Latvija**
AOP Orphan Pharmaceuticals GmbH
Tel +370 672 12222

**This leaflet was last revised in**

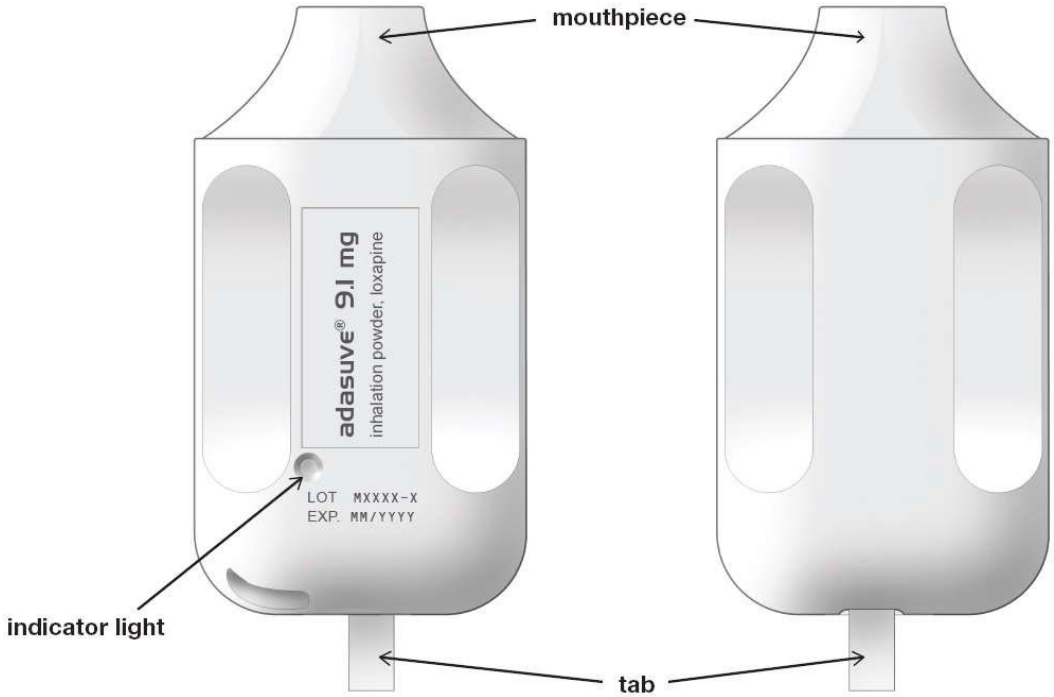
**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Read all instructions before use. See the SmPC for more information.

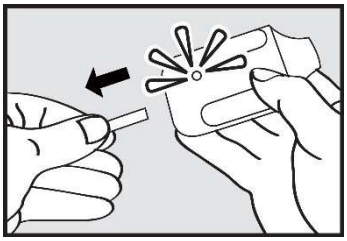
**Becoming familiar with ADASUVE:** The pictures below show the important features of ADASUVE.




- ADASUVE is provided in a sealed pouch.
- When ADASUVE is removed from the pouch, the indicator light is off.
- The indicator light turns on (green) when the tab is pulled out. The inhaler is then ready for use.
- The indicator light automatically turns off again when the medicine is inhaled.

Read the following 5 steps before administering ADASUVE to a patient.

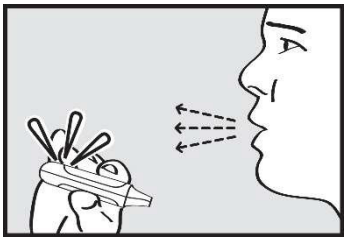
**1. Open pouch**
**Do not open the pouch until ready to use.** Tear open the foil pouch and remove the inhaler from the package.



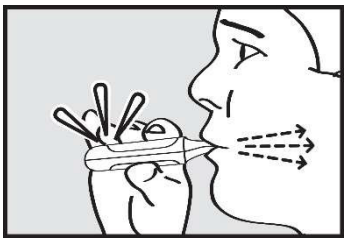
**2. Pull tab**
Firmly pull the plastic tab from the rear of the inhaler. The green light turns on indicating that the inhaler is ready for use.

**Use within *15* minutes after removing the tab (or until the green light turns off) to prevent automatic deactivation of the inhaler.**

**Instruct the patient to:**

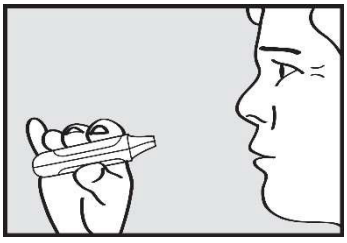


**3. Exhale**
Hold the inhaler away from the mouth and breathe out fully to empty lungs.



**4. Inhale**
Inhale through the mouthpiece with a steady deep breath.

**IMPORTANT: Check that the green light turns off after the patient inhales.**



**5. Hold breath**
Remove the mouthpiece from the mouth and hold breath briefly.

NOTE: If the green light stays on after the patient inhales, instruct the patient to repeat steps 3-5.

# Annex IV

## Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

## Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for loxapine (pre-dispensed inhalation powder), the scientific conclusions of PRAC are as follows:

In view of available data on drug rash with eosinophilia and systemic symptoms (DRESS) from the literature including a case report with very strong evidence (confirmed DRESS diagnosis with RegiSCAR 6 and a positive skin test for loxapine), the PRAC considers a causal relationship between loxapine (pre-dispensed inhalation powder) and DRESS at least a reasonable possibility. The PRAC concluded that the product information of products containing loxapine (pre-dispensed inhalation powder) should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

## Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for loxapine (pre-dispensed inhalation powder) the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing loxapine (pre-dispensed inhalation powder) is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.