Part VI: Summary of the risk management plan

Summary of risk management plan for ADASUVE (Loxapine)

This is a summary of the risk management plan (RMP) for ADASUVE. The RMP details important risks of ADASUVE, how these risks can be minimised, and how more information will be obtained about ADASUVE's risks and uncertainties (missing information).

ADASUVE's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ADASUVE should be used.

This summary of the RMP for ADASUVE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ADASUVE's RMP.

I. The medicine and what it is used for

ADASUVE is authorised for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder (see SmPC for the full indication). It contains loxapine as the active substance and it is given by inhalation.

Further information about the evaluation of ADASUVE's benefits can be found in ADASUVE's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/adasuve link to product's EPAR summary landing page on the EMA webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of ADASUVE, together with measures to minimise such risks and the proposed studies for learning more about ADASUVE's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of ADASUVE, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of ADASUVE is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of ADASUVE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ADASUVE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Bronchospasm
Important potential risks	• Interaction between loxapine and medicinal products known to prolong QTc interval, including other antipsychotic agents
Missing information	• Off-label use during extended periods of time • Safety in repeated use (multiple doses and/or multiple cycles) • Safety in patients with underlying cardiovascular disease

II.B Summary of important risks

Important identified risk: Bronchospasm	
Evidence for linking the risk to the medicine	The evidence of the risk of bronchospasm arose from the specific studies 004-105 (asthma) and 004-108 (COPD), in addition to the randomized, blinded trials. These identified the population at risk for bronchospasm, the nature of the bronchospasm events, and the response to bronchodilator treatment. Post-marketing experience.
Risk factors and risk groups	The SmPC contraindicates use of ADASUVE in patients with acute respiratory signs/symptoms (eg, wheezing) or with active airways disease (such as patients with asthma or COPD).
Risk minimisation measures	Routine risk minimisation measures:

Important identified risk: Bronchospasm	
	SmPC section 4.8. *PL section 4.* *SmPC section 4.2 indicates the hospital-setting administration of ADASUVE.* *SmPC section 4.2 where short-acting beta-agonist bronchodilator treatment should be available.* *SmPC section 4.3 where administration is contraindicated in patients with acute respiratory signs/symptoms or with active airways disease.* *SmPC section 4.4 on observation of patients after ADASUVE administration.* *PL section 2 details the symptoms of airways narrowing.* *PL section 2 where advice is given on informing the physician in case of respiratory events.* *Legal status: restricted medical prescription.* Additional risk minimisation measures: *Education material for Healthcare Professionals.*

Important potential risk: Interaction between loxapine and medicinal products known to prolong QTc interval, including other antipsychotic agents	
Evidence for linking the risk to the medicine	The events of QT prolongation and Torsade de pointes have been associated with non-sedating antihistamines, antibiotics, antipsychotics, antidepressants and a gastrointestinal pro-kinetic agent and drugs within these classes constitute the vast majority of non-cardiovascular compounds associated with these potentially serious side-effects (**¡Error! No se encuentra el origen de la referencia.**, 2003).
Risk factors and risk groups	Patients concomitantly receiving medicinal product which may prolong QTc interval, including other antipsychotic agents.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where caution administering ADASUVE in patients in concomitant use with other medicinal products known to prolong the QT interval is recommended.* *PL section 2 advises to inform in case of heart problems.* *Legal status: restricted medical prescription.* Additional risk minimisation measures: *Education material for Healthcare Professionals.*

Missing information: Off-label use during extended periods of time	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8.* *PL section 4.* *SmPC section 4.2 where posology information is provided.* *PL section 3 where posology information is provided.* *Legal status: restricted medical prescription.* Additional risk minimisation measures: *Education material for Healthcare Professionals.*

Missing information: Safety in repeated use (multiple doses and/or multiple cycles)	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2 where posology information is provided.* *PL section 3 where posology information is provided.* *Legal status: restricted medical prescription.* Additional risk minimisation measures: *Education material for Healthcare Professionals.*

Missing information: Safety in patients with underlying cardiovascular disease	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where recommendation on not to use ADASUVE in patients with known cardiovascular diseases is provided* *Legal status: restricted medical prescription.* Additional risk minimisation measures: *Education material for Healthcare Professionals.*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ADASUVE.

II.C.2 Other studies in post-authorisation development plan

There are no on-going or planned studies.