

Part VI. SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1. Elements for Summary Tables in the EPAR

VI.1.1. Summary Table of Safety Concerns

Table 33. Summary of Safety Concerns

Important identified risks	Anaphylactic reactions Blood pressure increased Emergence reactions Intraocular pressure increased Laryngospasm Hepatotoxicity Abuse and dependence
Important potential risks	Urinary tract-related adverse events, including cystitis
Missing information	Use in Pregnancy and lactation

VI.1.2. Table of Ongoing and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan

There are no on-going or planned additional pharmacovigilance studies.

VI.1.3. Summary of Post-Authorisation Efficacy Development Plan

No post-authorisation efficacy studies are planned.

VI.1.4. Summary Table of Risk Minimisation Measures

Table 34. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimization Measures
Important Identified Risks		
Anaphylactic reactions	Labeling: 4.3 Contraindications and 4.8 Undesirable effects.	None proposed.
Blood pressure increased	Labeling: 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None proposed.
Emergence reactions	Labeling: 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None proposed.
Intraocular pressure increased	Labeling: 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None proposed.
Laryngospasm	Labeling: 4.4 Special warnings and	None proposed.

Table 34. Summary of Risk Minimisation Measures

	precautions for use and 4.8 Undesirable effects.	
Hepatotoxicity	Labeling: 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None proposed.
Abuse and dependence	Labeling: 4.4 Special warnings and precautions for use.	None proposed.
Important Potential Risks		
Urinary tract-related adverse events, including cystitis	Labeling: 4.4 Special warnings and precautions for use.	None proposed.
Missing Information		
Use in Pregnancy and Lactation	Labeling: 4.6 Pregnancy and lactation.	None proposed.

VI.2. Elements for a Public Summary

VI.2.1. Overview of Disease Epidemiology

Esketamine is an anaesthetic medicine. Medicines in this family work to control pain during surgery or medical procedures. These medicines work by helping the body to relax, block pain and make you feel sleepy or unconscious for surgery.

VI.2.2. Summary of Treatment Benefits

Esketamine is a fast-acting medicine that provides pain relief and sedation. It can be used alone or combined with other medicines. It can be administered into the veins or into the muscles over a large range of doses. Most patients are able to maintain their breathing and reflexes while under sedation. The after effects of nausea and vomiting are seen far less often with this medicine than with others that are similar to it.

VI.2.3. Unknowns Relating to Treatment Benefits

Not applicable.

VI.2.4. Summary of Safety Concerns

Table 35. Important Identified Risks

Risk	What is Known	Preventability
Severe allergic reactions that can close the airway (Anaphylactic reactions)	Severe allergic reactions are usually dependent on the dose administered and related to the drugs. There are also times when someone just doesn't tolerate these medicines or is allergic.	Patients who have had allergic responses to this medicine or any of its components should not use esketamine.
Blood pressure increased	Increased blood pressure has been observed in patients treated with esketamine.	Patients with a history of high blood pressures or certain

Table 35. Important Identified Risks

Risk	What is Known	Preventability
		other heart conditions should not use esketamine.
Serious psychological reactions (Emergence reactions)	These reactions can vary from dream-like states to severe confusion and irrational behavior.	Patients with psychiatric disturbances should discuss the benefits and risks of using esketamine with their physician.
Pressure within the eye increased (Intraocular pressure increased)	Increases in pressure within the eye have been observed shortly after administration of ketamine.	Use precaution when using esketamine in connection with eye examinations or surgery in which intraocular pressure should not increase.
Uncontrolled contraction of the muscles in the throat (Laryngospasm)	In procedures of the breathing tract, uncontrolled muscle contractions in the throat (laryngospasms) are possible, especially in children. Other medicines and supplemental breathing may be necessary in procedures on the throat.	Physicians should use caution when administering esketamine during procedures of the lungs and respiratory tract. Additional medications may be required to treat this condition.
Damage to the liver (Hepatotoxicity)	Patients who have past damage to their liver or patients using esketamine for long periods of time may have new or additional liver damage as a result of esketamine.	Physicians should use caution when administering esketamine to patients with prior liver injury or for long periods of time.
Drug abuse and dependence	Ketamine has been reported being used as a drug of abuse. Reports suggest that ketamine produces a variety of symptoms including, among others, flashbacks, hallucinations, uneasy feelings, anxiety, insomnia, or disorientation. Cases of bladder damage, including bleeding bladder damage, and cases of liver damage have also been reported. Similar effects therefore cannot be ruled out following esketamine use. Esketamine dependence and tolerance may develop in individuals with a history of drug abuse or dependence. Therefore, esketamine should be prescribed and administered with caution.	Physicians should use caution when prescribing or administering esketamine to patients with a history of drug abuse or dependence.

Table 36. Important Potential Risks

Risk	What is Known
Urinary tract-related adverse events, including cystitis	Cases of cystitis, including hemorrhagic cystitis, have been reported in patients using ketamine on a long-term basis (one month to several years). Similar effects may also occur following esketamine abuse.

Table 37. Missing Information

Risk	What is Known
Use in Pregnancy and lactation	This medicine should not be used during pregnancy unless your doctor has advised you that there is no safer alternative. It could cause problems with the baby's breathing rate if used during delivery. This medicine can pass into breast-milk however it is unlikely to affect the baby when it is used at the recommended doses.

VI.2.5. Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for esketamine can be found in the esketamine's EPAR page.

VI.2.6. Planned Post-Authorisation Development Plan

No post-authorisation studies are planned.

VI.2.7. Studies that are a Condition of the Marketing Authorisation

Not applicable.

VI.2.8. Summary of Changes to the Risk Management Plan Over Time

Major changes to the Risk Management Plan over time are shown in Table 38.

Table 38. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.0	01 August 2013	Important identified risks: Anaphylactic reactions Blood pressure increased Emergence reactions Intraocular pressure increased Laryngospasm Important potential risks: Abuse and dependence Urinary tract-related adverse events, including cystitis	

Table 38. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
		Missing information: Use in Pregnancy and lactation	
2.0	25 November 2015	Hepatotoxicity was added as an important identified risk. Drug abuse and dependence was reclassified as an important identified risk.	