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

Summary of safety concerns
Important identified risks
- Dependence and tolerance
- Use in patients with liver impairment
Important potential risks
- Drug abuse
- Accidental overdose
- off-label use
Missing information
- Use in pregnancy and breast feeding

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

There are no on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan.

VI.1.3 Summary of Post authorisation efficacy development plan

There is no Post authorisation efficacy development plan.

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks - Dependence and tolerance	(proposed) text in SmPC: *Abuse and dependence* Ketamine has been reported as being a drug of abuse. Reports suggest that ketamine produces a variety of symptoms including, but not limited to, flashbacks, hallucinations, dysphoria, anxiety, insomnia or disorientation. Cases of cystitis, including haemorrhagic cystitis have also been reported. Dependence and tolerance may develop in individuals with a history of drug abuse and dependence. Therefore ketamine should be prescribed and administered with caution.	N/A

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
- Use in patients with liver impairment	• (Proposed) text in SmPC section 4.2: *Dosing in hepatic impairment:* Dose reduction should be considered for patients with cirrhosis or hepatic impairment for other reasons	N/A
	• (Proposed) text in SmPC section 4.4: Ketamine is metabolised in the liver and hepatic clearance is required for termination of the clinical effects. A prolonged duration of action may occur in patients with cirrhosis or other types of liver impairment. Dose reduction should be considered in these patients. Liver toxicity has been reported in patients after prolonged use (>3 days).	N/A
Important potential risks - Drug abuse	• (Proposed) text in SmPC section 4.4 *Abuse and dependence* Ketamine has been reported as being a drug of abuse. Reports suggest that ketamine produces a variety of symptoms including, but not limited to, flashbacks, hallucinations, dysphoria, anxiety, insomnia or disorientation. Cases of cystitis, including haemorrhagic cystitis have also been reported. Dependence and tolerance may develop in individuals with a history of drug abuse and dependence. Therefore ketamine should be prescribed and administered with caution.	N/A
	• (Proposed) text in SmPC section 4.2 Ketamine should only be administered by or under	N/A

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	supervision of medically qualified anaesthetists or emergency physicians. Equipment to ensure the vital functions should be available.	
- Accidental overdose	• (Proposed) text in SmPC section 4.9 Clinical signs of overdose are convulsions, cardiac arrest and respiratory depression. Respiratory depression should be treated with assisted or controlled ventilation until adequate spontaneous respiration is restored. Convulsion should be treated with intravenous diazepam. If this treatment does not give the desired result is intravenous administration of phenytoin or thiopental recommended. No specific antidote is available.	N/A
Missing information - Use in pregnancy and breast feeding	• (Proposed) text in SmPC section 4.6 <u>*Pregnancy*</u> No controlled clinical studies in pregancy have been conducted. The safe use in pregnancy has not been established, and such use is not recommended, with the exception of administration during surgery for abdominal or vaginal delivery. Ketamine readily crosses the placenta.Some neonates exposed to ketamine at maternal intravenous doses >1.5 mg/kg during delivery have experienced respiratory depression and low Apgar scores requiring newborn resuscitation. Marked increases in maternal blood pressure and uterine tone have been observerd at intravenous doses greater than 2 mg/kg. <u>*Breast-feeding*</u>	N/A

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Ketamine is excreted in the breast milk, but the risk for the infant seems unlikely with therapeutic doses. Since necessary data is lacking the use cannot be recommended.	

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Ketamal is a narcotic agent and is used:

- For the induction and maintenance (with additional injection doses, or by intravenous infusion) of anaesthesia in diagnostic and surgical procedures, as the only anaesthetic or in combination with other anaesthetic agents;
- Prior to the administration of, or as a complement to, local anaesthesia;

Note:

In children's surgery and in emergency medicine, only ketamine solely is used;

In the case of the other indications the combination with hypnotics is recommended.

VI.2.2 Summary of treatment benefits

Ketamine has numerous beneficial effects as an adjuvant anesthetic in patients with pre-existing diseases. In patients with refractory bronchospasm, ketamine decreases audible wheeze, bronchodilator requirements, and improves respiratory rate as well as oxygenation. In addition, ketamine does not promote respiratory depression. Furthermore, ketamine remains a useful and unique drug in cardiac anesthesia that can provide excellent blood flow stability during induction of general anesthesia in patients with poor heart pumping function. Ketamine offers a favorable hemodynamic profile compared to fentanyl, midazolam, or propofol in that it does not result in significant blood pressure, heart rate, or blood vessel resistance equilibria. It has been commonly causing increased heart rate that can be detrimental in patients with coronary artery disease or stenotic heart lesions. It has been shown to reduce the inflammatory response to heart/lung bypass (CPB), but the correlation with clinical benefits remains uncertain.

Therefore, the available evidence suggests that ketamine is safe and effective tool for sedation.

Note:

In children's surgery and in emergency medicine, only ketamine solely is used;

In the case of the other indications the combination with hypnotics is recommended.

VI.2.3 Unknowns relating to treatment benefits

Pregnancy

No controlled clinical studies in pregancy have been conducted. Therefore, use under pregnancy is considered missing information.The safe use in pregnancy has not been established, and such use is not recommended, with the exception of administration during surgery for abdominal or vaginal delivery. Ketamine readily crosses the placenta.Some neonates exposed to ketamine at maternal intravenous doses >1.5 mg/kg during delivery have experienced respiratory depression and low Apgar scores requiring newborn resuscitation. Marked increases in maternal blood pressure and uterine tone have been observerd at intravenous doses greater than 2 mg/kg.

Breast-feeding

Ketamine is excreted in the breast milk, but the risk for the infant seems unlikely with therapeutic doses. As there is limited data in the use of ketamine during breastfeeding so its use cannot be recommended.

*VI.2.4 Summary of safety concerns**Important potential risks*

Risk	**What is known**	**Preventability**
- Drug abuse	Ketamine has been reported as being a drug of abuse. Reports suggest that ketamine produces a variety of symptoms including, but not limited to, flashbacks, hallucinations, dysphoria, anxiety, insomnia or disorientation. Cases of cystitis, including haemorrhagic cystitis have also been reported. Dependence and tolerance may develop in individuals with a history of drug abuse and dependence	ketamine should be prescribed and administered with caution. Ketamine should only be administered by or under supervision of medically qualified anaesthetists
- Accidental overdose	Clinical signs of overdose are respiratory depression. Respiratory depression should be treated with assisted or controlled ventilation until adequate spontaneous respiration is restored. No specific antidote is available.	ketamine should be prescribed and administered with caution. Ketamine should only be administered by or under supervision of medically qualified anaesthetists.

Risk	What is known	Preventability
- off-label use	Recently new areas of therapeutic interest have come to light, about the off-label use of ketamine, and its unexpected therapeutic benefit in the emerging clinical areas as its use in chronic pain, and its anti-depressant effect.	ketamine should be prescribed and administered with caution.

Missing information

Risk	What is known	Preventability
- Use in pregnancy and breast feeding	There is limited data on the use of ketamine during pregnancy in humans. There is limited data in use of ketamine during caesarian section labour or via vaginal delivery. Ketamine is passed in the breast milk, but the risk for the infant seems unlikely with normal therapeutic doses.	It is not recommended to use keatamine during pregnancy. Ketamine can pass through the placenta to the foetus There is limited data in use of ketamine during breastfeeding so its use cannot be recommended

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 those. An abbreviated version of this in lay language is provided in the form of the patient information leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

All labelling is comprehensively set up. The legal status of the product is mentioned. And the pack sizes are clearly distinguishable.

The Summary of Product Characteristics and the Patient Information Leaflet for Ketamal are publicly available.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

There is no post authorisation development plan in place for Ketamal.

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Version 1.0	28-02-2017	Identified Risks: 2 Potential Risks: 2 Missing information: 1	First version of the RMP submitted within the registration procedure.