Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ketamine 50 mg/ml multidose, solution for injection or infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains: Ketamine 50.0 mg (as hydrochloride)
Each 10 ml and 20 ml vial contains 500 mg and 1000 mg ketamine, respectively.

The solution contains benzethonium chloride at 0.1 mg/ml.
For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

The medicinal product is a clear and colourless, aqueous solution for injection or infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. As the sole anaesthetic agent for short diagnostic and surgical procedures which do not require skeletal muscle relaxation.
2. Induction of general anaesthesia prior to administration of other anaesthetics.
3. To supplement other anaesthetic agents.

Specific areas of application or types of procedures:

1. When the intramuscular route of administration is more convenient.
2. Debridement, painful dressings, and skin grafting in burned patients, as well as other superficial surgical procedures.
3. For certain neurological, radiodiagnostic and therapeutic procedures in children to abolish movement.
4. When airway control is difficult.

4.2 Posology and method of adminstration

For intravenous infusion, intravenous injection or intramuscular injection in adults, elderly (> 65 years) and children. For surgery in elderly patients ketamine has been shown to be suitable either alone or supplemented with other anaesthetic agents.

NOTE: All doses are given in terms of ketamine base.

As with other general anaesthetic agents, the individual response to ketamine is somewhat varied depending on the dose, route of administration, age of patient, and concomitant use of other agents, so that dosage recommendations cannot be absolutely fixed. The dose should be titrated against the patient's requirements. The intravenous dose should be administered over a period of 60-120 seconds. More rapid administration may result in transient respiratory depression or apnoea and enhanced pressor response.

An intravenous dose of 1-2 mg/kg usually produces surgical anaesthesia within 30 sec - 1 min after injection and the

anaesthetic effect usually lasts 5 to 10 min. An intramuscular dose of 10 mg/kg usually produces surgical anaesthesia within 3 to 4 min following injection and the anaesthetic effect usually lasts 12 to 25 min. Return to consciousness is gradual.

Premedication
Ketamine increases salivation. Atropine, hyoscine, or glycopyrrone should be given pre-operatively.

Midazolam, diazepam, lorazepam, or flunitrazepam used as a premedicant or as an adjunct to ketamine, have been effective in suppressing the initial hyperkinetic circulation and in reducing the incidence of emergence reactions.

A. Ketamine as the sole anaesthetic agent

Intravenous Infusion
The use of ketamine by continuous infusion enables the dose to be titrated more closely, thereby reducing the amount of drug administered compared with intermittent administration. This results in a shorter recovery time and better stability of vital signs.

A solution containing 1mg/ml of ketamine in dextrose 5%, Ringer's lactate or sodium chloride 0.9% is suitable for administration by infusion.

If fluid restriction is required, ketamine can be added to 250 ml infusion fluid to provide a ketamine concentration of 2 mg/ml.

Induction: An infusion corresponding to 0.5 - 2 mg/kg as total induction dose.
Maintenance: Anaesthesia may be maintained using an infusion of 10 - 40 µg/kg/min (approximately 1 - 3 mg/min). The rate of infusion will depend on the patient's reaction and response to anaesthesia. The dosage required may be reduced when a long acting neuromuscular blocking agent is used.

Intermittent Injection
Induction:
Intravenous Route: The initial dose of ketamine administered intravenously may range from 1 mg/kg to 4.5 mg/kg. The average amount required to produce 5 to 10 min of surgical anaesthesia has been 2.0 mg/kg.
Intramuscular Route: The initial dose of ketamine administered intramuscularly may range from 6.5 to 13 mg/kg, usually l0 mg/kg. A dose of 10 mg/kg will usually produce 12 to 25 min of surgical anaesthesia.
Maintenance: Anaesthesia is maintained by the administration of additional doses of ketamine by either the intravenous or intramuscular route. Each additional dose is from 1/2 to the full induction dose recommended above for the route selected for maintenance, regardless of the route used for induction.
The larger the total amount of ketamine administered, the longer will be the time to complete recovery.
Purposeless and tonic-clonic movements of extremities may occur during the course of anaesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anaesthetic.

B. Ketamine as induction agent prior to the use of other general anaesthetics
Induction is accomplished by a full intravenous or intramuscular dose of ketamine as defined above. If ketamine has been administered intravenously and the principal anaesthetic is slow-acting, a second dose of ketamine may be required 5 to 8 min following the initial dose. If ketamine has been administered intramuscularly and the principal anaesthetic is rapid-acting, administration of the principal anaesthetic may be delayed up to 15 min following the injection of ketamine.

C. Ketamine as supplement to anaesthetic agents
Ketamine is clinically compatible with the commonly used general and local anaesthetic agents when an adequate respiratory exchange is maintained. The dose of ketamine for use in conjunction with other anaesthetic agents is usually in the same range as the dosage stated above; however, the use of another anaesthetic agent may allow a reduction in the dose of ketamine.

D. Management of patients in recovery
Following the procedure the patient should be observed but left undisturbed. This does not preclude the monitoring of

vital signs.
If, during the recovery, the patient shows any indication of emergence delirium, consideration may be given to the use of diazepam (5 to 10 mg iv in an adult). A hypnotic dose of a thiobarbiturate (50 to 100 mg iv) may be used to terminate severe emergence reactions. If any one of these agents is employed, the patient may experience a longer recovery period.

4.3 Contraindications

Ketamine is contraindicated in patients with
- known hypersensitivity,
- in severe hypertension,
- in patients with a history of cerebral vascular accident or cerebral trauma,
- in severe myocardial disease and in severe heart failure,
- in eclampsia or preeclampsia.

4.4 Special warnings and precautions for use

Relative contraindications are unstable angina or recent myocardial infarction, increased intracranial pressure except under adequate ventilation, in glaucoma or perforating injury of the eye.
Ketamine should be used only with caution in surgical procedures involving pharynx, larynx or trachea as it increases salivary and tracheo-bronchial secretions and does not reliably suppress pharyngeal or laryngeal reflexes.

1. To be used only in hospitals by or under the supervision of experienced medically qualified anaesthetists except under emergency conditions.
2. As with any general anaesthetic agent, resuscitative equipment should be available and ready for use.
3. Use of this agent should always be preceded by appropriate doses of atropine, hyoscine or another drying agent.
4. Ketamine is chemically incompatible with barbiturates and diazepam. Therefore, these should not be mixed in the same syringe or infusion fluid.
5. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with ketamine.
6. Emergence delirium phenomena may occur during the recovery period. The incidence of these reactions may be reduced if verbal and tactile stimulation of the patient is minimised during the recovery period. This does not preclude the monitoring of vital signs.
7. Because pharyngeal and laryngeal reflexes usually remain active, mechanical stimulation of the pharynx should be avoided unless muscle relaxants, with proper attention to respiration, are used.
8. The high plasma concentration following intravenous administration has been shown to depress respiration and the pharyngo-laryngeal reflexes for a brief period. Slow injection of the dilute solution is required to minimize these effects. Aspiration of contrast medium has been reported during ketamine anaesthesia under experimental conditions and, although in clinical practice aspiration is seldom a problem, the possibility should be borne in mind.
9. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.
10. Since an increase in cerebrospinal fluid pressure has been reported under ketamine, ketamine should be used with special caution in patients with pre-anaesthetic elevated cerebrospinal fluid pressure.
11. Respiratory depression may occur with overdosage of ketamine, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to the administration of analeptics.
12. In surgical procedures involving visceral pain pathways, ketamine should be supplemented with an agent which obtunds visceral pain.
13. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.
14. In patients with a psychiatric history ketamine anaesthesia requires special medical supervising.
15. The possibility of psychological reactions during recovery can be greatly reduced by a benzodiazepine or droperidol before or during anaesthesia.
16. When Ketamine is used on outpatient basis, the patient should not be released until recovery from anaesthesia is complete and then should be accompanied by a responsible adult.
17. Ketamine has been reported as being a drug of abuse. If used on a daily basis for a few weeks, dependence and tolerance may develop, particularly in individuals with a history of drug abuse and dependence. Therefore the use of Ketamine should be closely supervised and it should be prescribed and administered with caution.

4.5 Interaction with other medicinal products and other forms of interaction

1. The use of barbiturates or narcotic agents concurrently with ketamine may prolong the recovery period, as may also benzodiazepines.
2. Other general anaesthetics block the centrally mediated cardiovascular stimulant properties of ketamine. Significant cardiovascular depression has occurred with concurrent use of halothane or enflurane anaesthesia.
3. Halothane used concomitantly slows distribution and redistribution of ketamine and inhibits its hepatic metabolism.
4. Concurrent use of N_2O will reduce the required dose of ketamine.
5. Concurrent use of diazepam or other benzodiazepines will increase plasma levels and reduce the clearance rate of ketamine.
6. The concomitant use with gallamine will lead to tachycardia, and with pancuronium to hypertension. Neither relaxant should be used with Ketamine.
7. Ketamine should be used cautiously in patients receiving thyroid hormone because of an increased risk of hypertension and tachycardia.
8. Theophylline given concomitantly with ketamine may lower seizure threshold.

4.6 Pregnancy and lactation

Ketamine readily crosses the placental barrier and may cause respiratory depression in the newborn at doses > 2 mg/kg iv. With the exception of administration during surgery for abdominal delivery or vaginal delivery, no controlled clinical studies in pregnancy have been conducted. It is not known whether ketamine is excreted in breast milk. The safe use in pregnancy and in lactation has not been established.

4.7 Effects on ability to drive and use machines

Patients should be cautioned that driving a car, operating hazardous machinery or engaging in hazardous activities should not be undertaken for 24 hours or more after anaesthesia.

4.8 Undesirable effects

Vital Signs: Ketamine may produce respiratory depression, apnea, and/or transient increases in blood pressure and pulse rate.

Cardiovascular: Transient elevation of blood pressure and pulse rate is frequently observed. However, hypotension and bradycardia to cardiac arrest have also been reported. Arrhythmias have also occurred. The median peak rise of blood pressure in clinical studies has ranged from 20 to 25 per cent of preanaesthetic values. Depending on the condition of the patient, the elevation of blood pressure may be considered an adverse reaction or a beneficial effect.

Respiratory: Respiratory depression, apnea, and respiratory arrest may occur. Ketamine may produce bronchodilation and increased salivary and tracheo-bronchial secretions. Laryngospasm and other forms of airway obstruction have occurred.

Ocular: Diplopia and nystagmus may occur following ketamine HCl administration. A slight elevation in intraocular pressure may also occur.

Psychological: During recovery from anaesthesia the patient may experience emergence delirium, characterised by vivid dreams (pleasant or unpleasant), with or without psychomotor activity, manifested by confusion and irrational behaviour. The fact that these reactions are observed less often in the young (< 15 years) makes ketamine especially useful in paediatric anaesthesia. These reactions are also less frequent in the elderly (> 65 years) patient. No residual psychological effects are known to have resulted from the use of ketamine.

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements. These movements do not imply a light plane of anaesthesia and are not indicative of a need for additional doses of the anaesthetic.

Gastrointestinal: Anorexia, nausea, and vomiting have been observed; however, these are uncommon and are not usually severe.

Hypersensitivity reaction: There have been a number of reported cases of anaphylaxis.

Other: Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported. Increased salivation leading to respiratory difficulties may occur.

4.9 Overdose

Respiratory depression can result from an overdosage of ketamine HCl. Supportive ventilation should be employed. Ketamine has a wide margin of safety.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ketamine is a rapidly acting general anaesthetic for intravenous or intramuscular use with a distinct pharmacological action. Ketamine HCl produces dissociative anaesthesia characterised by catalepsy, amnesia, and marked analgesia which may persist into the recovery period. Ketamine is a non-competitive antagonist at NMDA receptors. In sub-anaesthetic doses ketamine interacts with the biogenic amine and endogenous opiate system. Ketamine does usually not affect pharyngeal and laryngeal reflexes, and muscle tone remains normal or increases somewhat. Blood pressure increases by ca 25% and heart rate is increased. Respiration is virtually unaffected when administered as recommended but may be depressed if administration is too rapid or in cases of overdose. Ketamine has bronchodilating efficacy.

5.2 Pharmacokinetic properties

Ketamine is rapidly distributed into perfused tissues including brain and placenta. Animal studies have shown ketamine to be highly concentrated in body fat, liver and lung. Biotransformation takes place in liver. Termination of anaesthetic is partly by redistribution from brain to other tissues and partly by metabolism. Elimination half-life is approximately 2-3 hours, and excretion renal, mostly as conjugated metabolites.

5.3 Preclinical safety data

Pre-clinical safety data does not add anything of further significance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzethonium chloride
Water for injections
Nitrogen

6.2 Incompatibilities

Ketamine is chemically incompatible with barbiturates and diazepam. Therefore, these should not be mixed in the same syringe or infusion fluid.

6.3 Shelf Life

Shelf-life before first opening

3 years.

Shelf-life after first opening

28 days at 20-25°C.

Shelf-life after dilution

Chemical and physical in-use stability has been demonstrated for 72 hours at 20-25°C.

From the microbiological point of view, the product should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Not applicable.

6.5 Nature and contents of container

Colourless glass vials (type 1 glass) containing 10 or 20 ml solution.

Package quantities:

Pack of	1 vial	à	10 ml
	10 vials	à	10 ml
	50 vials	à	10 ml
Pack of	1 vial	à	20 ml
	10 vials	à	20 ml
	50 vials	à	20 ml

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The injection should not be used if particles are present.

For dilution the following standard solutions for infusion may be used:
-0.9% Sodium chloride
-5% Glucose
-Ringer's lactate

7 MARKETING AUTHORISATION HOLDER

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Langes Feld 13
31789 Hameln
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