Approved Professional Information for Ketamine Fresenius

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

KETAMINE 10 mg/1 ml FRESENIUS solution for injection or infusion

KETAMINE 50 mg/1 ml FRESENIUS solution for injection or infusion

KETAMINE 100 mg/1 ml FRESENIUS solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml solution contains ketamine hydrochloride equivalent to 10 mg, 50 mg or 100 mg ketamine respectively.

Preservative: benzethonium chloride 0,01 % *m/v*.

Sugar free.

Excipient with known effect:

KETAMINE 10 mg/1 ml FRESENIUS has been made isotonic with sodium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.

A clear, colourless solution in amber vials.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Induction of anaesthesia, or, in combination with oxygen and nitrous oxide, for the maintenance of general anaesthesia.

KETAMINE FRESENIUS may be used in children for the management of minor surgical and diagnostic procedures or for repeated procedures that require intense analgesia, such as changing burn dressings.

4.2 Posology and method of administration

Not for intrathecal use.

Doses should be individualised.

Administration should be preceded by atropine or another suitable antimuscarinic medicine.

KETAMINE FRESENIUS dosages:

Route	Dose mg/kg	Onset of anaesthesia	Duration Time
IV	1 – 2	30 seconds	5 to 10 minutes
IM	5 – 10	3 to 4 minutes	12 to 25 minutes

A. **KETAMINE FRESENIUS** may be administered by intravenous or intramuscular injection. Intravenous injection should be over a period of 60 seconds.

B. Alternative method:

An intravenous infusion solution (1 mg/ml) is prepared by mixing 500 mg of ketamine in 500 ml of 5 % glucose or 0,9 % sodium chloride solution. Induction is accomplished by infusing the solution until induction is complete. In general, the induction dose will be approximately 1 mg/kg. For maintenance, intravenous infusion rates need to be individualised to prevent nystagmus and response to surgical stimuli, 1 to 5 mg/kg/hour being the usual dose.

Upon termination of surgery, the **KETAMINE FRESENIUS** infusion is discontinued.

4.3 Contraindications

- Hypersensitivity to ketamine hydrochloride or to any of the inactive ingredients in **KETAMINE FRESENIUS**, as listed in section 6.1.
- **KETAMINE FRESENIUS** is contraindicated in patients in whom elevation of blood pressure would be a serious hazard including those with hypertension or a history of cerebrovascular accident.
- **KETAMINE FRESENIUS** should not be used in patients with eclampsia or pre-eclampsia, severe coronary or myocardial disease, or cerebral trauma.
- **KETAMINE FRESENIUS** should not be given to patients with increased intra-ocular pressure. Alternative anaesthetics should be considered in patients with penetrating wounds of the eye.
- Safety in pregnancy and lactation has not been established (see section 4.6).
- Not for intrathecal use (see section 4.2).

4.4 Special warnings and precautions for use

KETAMINE FRESENIUS should only be used in hospitals by, or under the supervision of, experienced medical practitioners except under emergency conditions.

The necessary equipment for airway support, intubation and resuscitation should always be readily available.

Respiratory depression may occur with overdosage of **KETAMINE FRESENIUS**, in which case supportive ventilation should be employed.

The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnoea and enhanced pressor response.

KETAMINE FRESENIUS does not reliably suppress pharyngeal and laryngeal reflexes and mechanical stimulation of the pharynx should be avoided unless a muscle relaxant, with proper attention to respiration, is used.

Patients should be intubated if there is a risk of aspiration as laryngeal reflexes are not necessarily maintained.

In surgical procedures involving visceral pain pathways, **KETAMINE FRESENIUS** should be supplemented with a medicine which obtunds visceral pain.

When **KETAMINE FRESENIUS** is used on an outpatient basis, the patient should not be released until recovery from anaesthesia is complete and then should be accompanied by a responsible adult.

Patients should not participate in decision making and should not take alcohol for 24 hours after receiving **KETAMINE FRESENIUS**.

KETAMINE FRESENIUS should be used with caution in patients with the following conditions: Patients with mild hypertension and impaired cardiac function should be appropriately monitored.

Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

KETAMINE FRESENIUS is metabolised in the liver and hepatic clearance is required for termination of clinical effects. A prolonged duration of action may occur in patients with cirrhosis or other types of liver impairment. Dose reductions should be considered in these patients. Abnormal liver function tests associated with **KETAMINE FRESENIUS** use have been reported, particularly with extended use (> 3 days) or drug abuse.

Dosage may need to be decreased in the event of renal impairment.

Since an increase in cerebrospinal fluid (CSF) pressure has been reported during **KETAMINE FRESENIUS** anaesthesia, **KETAMINE FRESENIUS** should be used with special caution in patients with preanaesthetic elevated cerebrospinal fluid pressure.

Use with caution in patients with globe injuries because the pressure may increase significantly after a single dose of **KETAMINE FRESENIUS**.

Use with caution in patients with neurotic traits or psychiatric illness (e.g., schizophrenia and acute psychosis).

Use with caution in patients with acute intermittent porphyria.

Use with caution in patients with a history of seizures.

Use with caution in patients with hyperthyroidism or patients receiving thyroid replacement as it may increase the risk of hypertension and tachycardia (see section 4.5).

Use with caution in patients with pulmonary or upper respiratory infection (**KETAMINE FRESENIUS** sensitises the gag reflex, potentially causing laryngospasm).

Use with caution in patients with intracranial mass lesions, a presence of head injury, or hydrocephalus.

KETAMINE FRESENIUS should be used with caution in patients with a history of convulsive disorders, prone to hallucinations or psychiatric disease.

Emergence reaction

The psychological manifestations vary in severity between pleasant dream-like states, vivid imagery, hallucinations, nightmares and emergence delirium (often consisting of dissociative or floating sensations). In some cases, these states have been accompanied by confusion, excitement, and irrational behaviour which a few patients recall as an unpleasant experience (see section 4.8).

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.

A short-acting benzodiazepine, such as diazepam 2,5 to 5 mg intravenously (0,05 to 0,1 mg/kg) decreases the incidence of hallucinations during ketamine anaesthesia and decreases the incidence of emergence reactions.

Cardiovascular

Because of the substantial increase in myocardial oxygen consumption, **KETAMINE FRESENIUS** should be used with caution in patients with hypovolaemia, dehydration or cardiac disease, especially coronary artery disease (e.g., congestive heart failure, myocardial ischaemia and myocardial infarction). In addition, **KETAMINE FRESENIUS** should be used with caution in patients with mild-to-moderate hypertension and tachydysrhythmias.

Elevation of blood pressure begins shortly after the injection of **KETAMINE FRESENIUS**, reaches a maximum within a few minutes and usually returns to preanaesthetic values within

15 minutes after injection. The median peak rise of blood pressure in clinical studies has ranged from 20 to 25 % of preanaesthetic values. Depending on the condition of the patients, this elevation of blood pressure may be considered a beneficial effect, or in others, an adverse reaction.

Long-term use

Cases of cystitis including haemorrhagic cystitis have been reported in patients being given **KETAMINE FRESENIUS** on a long-term basis. This adverse reaction develops in patients receiving long-term **KETAMINE FRESENIUS** treatment after a time ranging from 1 month to several years. **KETAMINE FRESENIUS is not indicated nor recommended for long-term use.**

Hepatotoxicity has also been reported in patients with extended use (> 3 days).

Drug abuse and dependence

KETAMINE FRESENIUS has been reported as being a drug of abuse. Reports suggest that **KETAMINE FRESENIUS** produces a variety of symptoms including, but not limited to, flashbacks, hallucinations, dysphoria, anxiety, insomnia, or disorientation (see section 4.8). 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 FRESENIUS** should be closely supervised, and it should be prescribed and administered with caution.

KETAMINE 10 mg/1 ml FRESENIUS contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction

Incompatibility exists with soluble barbiturates, and these should not be combined in the same syringe. It is also not recommended that **KETAMINE FRESENIUS** be combined with ergometrine. Concomitant use with ergometrine may lead to an increase in blood pressure.

KETAMINE FRESENIUS is chemically incompatible with diazepam because of precipitate formation. Therefore, it should not be mixed in the same syringe or infusion fluid. Diazepam is also known to increase the half-life of ketamine and prolongs its pharmacodynamic effects. Dose adjustments may therefore be needed.

Inhalational anaesthetics, such as ether and halothane, and other cerebral depressants may prolong the effect of **KETAMINE FRESENIUS** and delay recovery. Prolonged recovery has also occurred when barbiturates and/or opioids have been given with **KETAMINE FRESENIUS**.

Concurrent use of **KETAMINE FRESENIUS** (especially in high doses or when rapidly administered) with halogenated anaesthetics can increase the risk of developing bradycardia, hypotension or decreased cardiac output (see section 4.8).

KETAMINE FRESENIUS may potentiate the neuromuscular blocking effects of atracurium and tubocurarine, including respiratory depression with apnoea (see section 4.8).

The use of **KETAMINE FRESENIUS** with other central nervous system (CNS) depressants (e.g., ethanol, phenothiazines, sedating H_1-blockers or skeletal muscle relaxants) can potentiate CNS depression and/or increase risk of developing respiratory depression (see section 4.8). Reduced doses of **KETAMINE FRESENIUS** may be required with concurrent administration of other anxiolytics, sedatives and hypnotics (see section 4.2).

KETAMINE FRESENIUS has been reported to antagonise the hypnotic effect of thiopental.

Patients taking thyroid hormones have an increased risk of developing hypertension and tachycardia when given **KETAMINE FRESENIUS** (see section 4.4).

Concurrent use of **KETAMINE FRESENIUS** and antihypertensive medicines increases the risk of developing hypotension.

Sympathomimetics (directly or indirectly acting) and vasopressin may enhance the sympathomimetic effects of **KETAMINE FRESENIUS**.

When **KETAMINE FRESENIUS** and theophylline are given concurrently, a clinically significant reduction in the seizure threshold is observed. Unpredictable extensor-type seizures have been reported with concurrent administration of these medicines.

Medicines that inhibit CYP3A4 enzyme activity generally decrease hepatic clearance, resulting in increased plasma concentration of CYP3A4 substrate medicines, such as ketamine. Coadministration of **KETAMINE FRESENIUS** with medicines that inhibit CYP3A4 enzyme may require a decrease in ketamine dosage to achieve the desired clinical outcome.

Medicines that induce CYP3A4 enzyme activity generally increase hepatic clearance, resulting in decreased plasma concentration of CYP3A4 substrate medicines, such as ketamine. Coadministration of **KETAMINE FRESENIUS** with medicines that induce CYP3A4 enzyme may require an increase in ketamine dosage to achieve the desired clinical outcome.

4.6 Fertility, pregnancy and lactation

The safety in pregnancy and lactation has not been established (see section 4.3).

KETAMINE FRESENIUS crosses the placenta.

Neonates exposed to ketamine during delivery have experienced respiratory depression and low Apgar scores requiring new-born resuscitation.

Marked increases in maternal blood pressure and uterine tone have been observed at intravenous doses greater than 2 mg/kg.

Fertility

Studies in animals have shown reproductive toxicity.

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 receiving **KETAMINE FRESENIUS**.

4.8 Undesirable effects

Immune system disorders:

Less frequent: Anaphylactic reaction.

Metabolism and nutrition disorders:

Less frequent: Anorexia.

Psychiatric disorders:

Frequent: Hallucinations, abnormal dreams, nightmares, confusion, agitation, abnormal behaviour.

Less frequent: Anxiety, delirium, flashback, dysphoria, insomnia, disorientation.

Nervous system disorders:

Frequent: Hypertonia, tonic clonic movements.

The following side effect has been reported and the frequency is unknown:

Raised cerebrospinal fluid pressure.

Eye disorders:

Frequent: Diplopia, nystagmus.

The following side effects have been reported and the frequencies are unknown:

Lacrimation raised intra-ocular pressure.

Cardiac disorders:

Frequent: Blood pressure increased; heart rate increased.

Less frequent: Dysrhythmias, bradycardia.

Vascular disorders:

Less frequent: Hypotension.

Respiratory, thoracic and mediastinal disorders:

Frequent: Respiratory rate increased.

Less frequent: Respiratory depression, apnoea, laryngospasm, obstructive airway disorder.

Gastrointestinal disorders:

Frequent: Nausea, vomiting.

Less frequent: Salivary hypersecretion.

Hepatobiliary disorders:

The following side effects has been reported and the frequency is unknown:

Liver function test abnormalities, medicine-induced liver injury*

*Reported with extended use (> 3 days) or drug abuse.

Skin and subcutaneous tissue disorders:

Frequent: Erythema, rash morbilliform.

The following side effects have been reported and the frequencies are unknown:

Transient skin rashes.

Renal and urinary disorders:

Less frequent: Cystitis, haemorrhagic cystitis.

General disorders and administration site conditions:

Less frequent: Injection site pain, injection site rash.

Post-marketing data:

Less frequent: increased risk of abdominal pain, including pancreatitis has been reported.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of **KETAMINE FRESENIUS** is important. It allows continued monitoring of the benefit/risk balance of **KETAMINE FRESENIUS**. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Health care providers are asked to report any suspected Adverse Drug Reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com, and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Respiratory depression can result from an overdosage. Supportive ventilation should always be available when general anaesthesia is administered. Supportive ventilation should be employed using mechanical support to maintain adequate blood oxygen saturation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.1 Anaesthetics

Pharmacotherapeutic group: Other general anaesthetics.

ATC code: N01AX03.

Ketamine is a rapidly acting general anaesthetic for intravenous or intramuscular use.

Ketamine produces dissociative anaesthesia, which is characterised by a state of sedation, immobility, amnesia and marked analgesia as well as a strong feeling of dissociation.

It acts on the cortex and the limbic system.

Muscular relaxation is poor and muscle tone may be increased. Respiration is maintained, although transient depression may occur. Pharyngeal and laryngeal reflexes are partially retained, but the cough reflex is depressed. Airway resistance is decreased.

Arterial blood pressure increases by as much as 25 % and cardiac output and rate increase. Cerebral metabolism and blood flow increase, leading to a potential increase in intracranial pressure.

Intense analgesia and amnesia are established rapidly.

5.2 Pharmacokinetic properties

Ketamine is rapidly distributed into perfused tissues including brain and placenta.

In humans at an intravenous bolus dose of 2,5 mg/kg, the distribution phase of ketamine lasts about 45 minutes, with a half-life of 10 to 15 minutes, which is associated with the duration of the anaesthetic effect (about 20 minutes). Plasma ketamine concentrations are about 1,8 to 2,0 µg/ml at 5 minutes after an intravenous bolus injection of 2 mg/kg dose, and about 1,7 to 2,2 µg/ml at 15 minutes after an intramuscular injection of 6 mg/kg dose in adults and children.

In parturients receiving an intramuscular dose of 250 mg (approximately 4,2 mg/kg), placental transfer rate of ketamine from maternal artery to umbilical vein was 47 % at the time of delivery (1,72 versus 0,75 µg/ml). Average delivery time for these parturients was 12 minutes from the time of ketamine injection to vaginal delivery of a new-born.

Biotransformation takes place in the liver. Termination of anaesthetic is partly by redistribution from the brain to other tissues and partly by metabolism.

Elimination half-life is about 2 – 3 hours and excretion occurs renally, mostly as conjugated metabolites.

5.3 Preclinical safety data

No information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

Benzethonium chloride

Sodium hydroxide (for pH-adjustment)

Hydrochloric acid (for pH-adjustment)

Sodium chloride (only present in **KETAMINE 10 mg/1 ml FRESENIUS**).

6.2 Incompatibilities

KETAMINE FRESENIUS is chemically incompatible with barbiturates and diazepam because of precipitate formation (see section 4.5). Therefore, these medicines should not be mixed in the same syringe or infusion fluid.

6.3 Shelf life

KETAMINE 10 mg/1 ml and **100 mg/1 ml FRESENIUS:** 60 months.

KETAMINE 50 mg/1 ml FRESENIUS: 48 months.

After dilution the solutions should be used immediately.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

KETAMINE 10 mg/1 ml FRESENIUS: 20 ml amber Type I glass vials, sealed with a chlorobutyl rubber stopper and crimped with an aluminium seal, containing 20 ml of solution as 10 mg ketamine per ml.

KETAMINE 50 mg/1 ml FRESENIUS: 10 ml amber Type I glass vials sealed with a chlorobutyl rubber stopper and crimped with an aluminium seal, containing 10 ml of solution as 50 mg ketamine per ml.

KETAMINE 100 mg/1 ml FRESENIUS: 10 ml amber Type I glass vials sealed with a

chlorobutyl rubber stopper and crimped with an aluminium seal, containing 10 ml of solution as 100 mg ketamine per ml.

Pack sizes: packs of fives, tens or singles per outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused contents at the end of each operating session.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd

6 Gibaud Road

Korsten, 6020

Gqeberha

South Africa

8. REGISTRATION NUMBERS

KETAMINE 10 mg/1 ml FRESENIUS: Y/2.1/373

KETAMINE 50 mg/1 ml FRESENIUS: Y/2.1/273

KETAMINE 100 mg/1 ml FRESENIUS: Y/2.1/274

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 May 1992

10. DATE OF REVISION OF THE TEXT

25 April 2023