PROFESSIONAL INFORMATION

SCHEDULING STATUS S5

1. NAME OF THE MEDICINE

ZENZIKET 10 mg/ml (solution for injection or infusion)

ZENZIKET 50 mg/ml (solution for injection or infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of ZENZIKET 10 mg/ml contains ketamine hydrochloride equivalent to 10 mg ketamine base.

Each 1 ml of ZENZIKET 50 mg/ml contains ketamine hydrochloride equivalent to 50 mg ketamine base.

Excipient with known effect

ZENZIKET 10 mg/ml contains 2,6 mg sodium per ml or 26 mg per 10 ml ampoule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (IV/IM) or infusion.

A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

ZENZIKET 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.

Posology

Doses should be individualised. The individual response to ZENZIKET varies according to a number of factors, such as the dose, route of injection and the patient's weight. The dosage therefore cannot be rigidly set and must be adjusted to each patient. The dosages stated are in terms of ketamine base.

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

ZENZIKET dosages:

Route	**Dosage (mg/kg body weight)**	**Onset of anaesthesia**	**Duration (time)**
IV	1 – 2	30 seconds	5 – 10 minutes
IM	5 – 10	3 – 4 minutes	12 – 25 minutes

ZENZIKET may be administered by intravenous or intramuscular injection. The intravenous injection should be administered over a period of 60 seconds.

Alternatively, ZENZIKET may be diluted and administered as an intravenous infusion. An intravenous infusion solution (1 mg/ml) is prepared by mixing 500 mg of ZENZIKET in 500 ml of 5 % glucose or 0,9 % sodium chloride solution.

Induction is accomplished by infusing ZENZIKET 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 ZENZIKET infusion is discontinued.

Development of tolerance

When ZENZIKET is administered repeatedly over a short period of time, acute tolerance may occur, particularly in young children; an appropriate increase in the ketamine dose provides the desired anaesthetic effect in these patients.

Paediatric population

To date, the dosage of ketamine has not been adequately studied in children and adolescents. Due to limited information and experience, the dosage of ZENZIKET in children and adolescents (as in adults) is determined according to body weight.

ZENZIKET must not be used in children aged less than 3 months due to potential respiratory complications.

Method of administration

ZENZIKET is administered by intravenous or intramuscular injection.

Alternatively, ZENZIKET may be diluted and administered as an intravenous infusion.

4.3 Contraindications

- Hypersensitivity to ketamine hydrochloride or to any of the excipients listed in section 6.1.
- ZENZIKET 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.
- ZENZIKET should not be used in patients with eclampsia or pre-eclampsia, severe coronary or myocardial disease, or cerebral trauma.
- ZENZIKET 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

ZENZIKET should only be used in hospitals by, or under the supervision of, experienced medical practitioners, who are experienced in general anaesthetic techniques, unless under emergency conditions. The necessary equipment for airway support, intubation and resuscitation must always be readily available. Intravenous injections must be performed slowly, over a period of 60 seconds. Too rapid injections or excessively high doses may result in respiratory depression and apnoea (ventilatory support may be required), as well as more marked increases in blood pressure. Resuscitation equipment should be available when ZENZIKET is used, as its use requires careful respiratory monitoring.

Particular caution is required in the following cases:

- Mild hypertension and impaired cardiac function;
- Unstable angina or myocardial infarction within the last six months;
- Intracranial hypertension, unless the patient is receiving adequate respiratory support;
- Glaucoma and perforating eye injuries.

In patients with hypertension or cardiac decompensation, cardiac function must be monitored continuously during the procedure.

Caution must be exercised in cases of pre-existing intracranial hypertension, as ZENZIKET may increase cerebrospinal fluid pressure.

ZENZIKET 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. Hence, muscle relaxation and appropriate ventilatory support are particularly indicated during procedures on the pharynx, larynx and bronchial tree. Patients should be intubated if there is a risk of

aspiration as laryngeal reflexes are not necessarily maintained.

In cases of visceral surgery, ZENZIKET should be supplemented with a medicine which obtunds visceral pain.

In ophthalmic diagnostic and surgical procedures, adjuvant administration of a local anaesthetic has been shown to be useful, e.g., via the subconjunctival, equatorial or intramuscular route in strabismus surgery, or via the retrobulbar route during intraocular procedures.

In cases of chronic alcoholism or intoxication with alcohol, ZENZIKET must be used with caution. Concomitant administration of barbiturates or opiates may prolong the recovery phase.

When used as a sole anaesthetic agent, a state of transient disorientation may occur during the awakening phase. 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). 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. If necessary, recording of vital functions can be performed in the usual manner. 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 ZENZIKET anaesthesia and decreases the incidence of emergence reactions.

ZENZIKET 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. In cases of prolonged administration (>3 days) or drug abuse, abnormal liver function tests have been observed. Hepatotoxicity has also been reported in patients with extended use (> 3 days). Dosage reductions should be considered in these patients.

The dosage of ZENZIKET may need to be decreased in the event of renal impairment.

ZENZIKET must be used with caution in patients with a history of severe anginal attacks.

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

Elevation of blood pressure begins shortly after the injection of ZENZIKET, reaches a maximum within a few minutes and usually returns to pre-anaesthetic values within 15 minutes after injection. The median peak rise of blood pressure in clinical studies has ranged from 20 to 25 % of pre-anaesthetic 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.

When ZENZIKET is administered to patients in a state of shock, the appropriate measures necessary for treating shock must be applied (correction of hypovolemia, oxygen administration). In extremely severe states of shock, when it is very difficult or impossible to measure blood pressure, extreme caution is required as with any other anaesthetic.

Antisecretory agents such as atropine must always be administered to prevent hypersalivation.

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

Use with caution in patients with acute 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 (ZENZIKET sensitises the gag reflex, potentially causing laryngospasm).

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

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

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

When ZENZIKET 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 ZENZIKET.

Drug abuse and dependence

There are reports of ketamine abuse, according to which ketamine may cause symptoms such as: hallucinations, dysphoria, states of anxiety, insomnia, disorientation and flashbacks. 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. For these reasons, the use of ZENZIKET should be closely supervised, and it should be prescribed and administered with caution.

Paediatric population

Paediatric neurotoxicity

In published animal experimentation studies, it has been shown that the administration for more than three hours of anaesthetics and sedatives that block NMDA receptors and/or potentiate GABA activity results in increased neuronal apoptosis in the developing brain and long-term cognitive deficits. The clinical significance of this observation in humans is not known. Based on supra-specific comparisons, however, it is assumed that the vulnerability time window for such changes has a correlation with exposures during the third trimester and the first months of life, but in humans, may also extend approximately until the end of the third year of life.

Anaesthetics and sedatives are a necessary part of the management of children who require surgery or other medical procedures or tests that cannot be postponed. In this context, no specific medicines have proven to be safer than others. In choosing when to perform the planned procedure requiring anaesthesia, the physician should evaluate the benefit of the procedure against the potential risks.

Information relating to the excipients included in ZENZIKET

ZENZIKET 10 mg/ml contains 26 mg sodium per 10 ml ampoule, equivalent to 1,3 % of the WHO recommended maximum daily dietary intake of 2 g of sodium per adult.

4.5 Interaction with other medicines and other forms of interaction

Concomitant administration of ZENZIKET and halogenated anaesthetics, such as ether, halothane and other cerebral depressants, may prolong the elimination half-life of ZENZIKET and delay the recovery phase. Prolonged recovery has also occurred when barbiturates and/or opioids have been given with ZENZIKET. The risk of bradycardia, of lowering blood pressure or decreased cardiac output may be increased, particularly with high doses or rapid administration combined with halogenated anaesthetics (see section 4.8).

The undesirable effects of ketamine, especially those of a psychotomimetic nature, are much less pronounced when it is used as part of an anaesthetic combination.

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

Concomitant administration of ZENZIKET and CNS-inhibiting medicines and substances (e.g., ethanol, phenothiazines, sedating H_1-blockers or skeletal muscle relaxers) may potentiate CNS sedation and/or increase the risk of respiratory depression (see section 4.8). A reduction in the ZENZIKET dose may be necessary if ketamine is used at the same time as other anxiolytics, sedatives and hypnotics. In particular, the combination with benzodiazepines or neuroleptics prolongs the effect of ketamine. It is known, for example, that diazepam increases the half-life of ketamine and prolongs its pharmacodynamic effect. Dose adjustments may therefore be necessary.

It has been reported that ketamine antagonises the hypnotic effect of thiopental.

ZENZIKET may prolong the effect of both non-depolarizing and depolarizing muscle relaxants.

Concomitant administration of ZENZIKET with antihypertensive agents increase the risk of developing hypotension.

Concomitant administration of ZENZIKET and theophylline or aminophylline may significantly lower the seizure threshold. Unpredictable extensor-type seizures have been reported with concurrent administration of these medicines with ketamine.

Concomitant administration of thyroid hormones, direct-acting or indirect-acting sympathomimetics and vasopressin may enhance the sympathomimetic effects of ZENZIKET and cause high blood pressure and tachycardia.

Concomitant use of ZENZIKET and ergometrine can cause high blood pressure. It is not recommended that ZENZIKET be combined with ergometrine.

Administration of ZENZIKET potentiates the anaesthetic effect of halothane, for which lower doses may therefore be sufficient.

Concomitant use of ZENZIKET and halothane may increase the risk of cardiac arrhythmias triggered by the adjuvant administration of epinephrine.

Medicines that inhibit the enzymatic activity of CYP3A4 generally reduce hepatic clearance. This leads to elevated plasma concentrations of CYP3A4 substrates such as ketamine. A reduction in the ZENZIKET dose may be necessary if ZENZIKET is used at the same time as medicines that inhibit the CYP3A4 enzyme.

Medicines that induce the enzymatic activity of CYP3A4 generally increase hepatic clearance. This leads to decreased plasma concentrations of CYP3A4 substrates such as ketamine. An increase in the ZENZIKET dose may be necessary to achieve the desired clinical outcome if ZENZIKET is used at the same time as medicines that induce the CYP3A4 enzyme.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established (see section 4.3).

ZENZIKET crosses the placenta.

Ketamine has not been adequately studied with regard to reproductive toxicity and there are no controlled studies in pregnant women.

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

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

There are no data on intramuscular use or maintenance of the anaesthetic effect in parturient women.

ZENZIKET must not be used during pregnancy.

Breastfeeding

Safety in lactation has not been established (see section 4.3). It is not known whether ketamine is excreted in breast milk. ZENZIKET must therefore not be used during breastfeeding.

Fertility

No fertility studies have been conducted in humans.

Studies in animals have shown reproductive toxicity.

4.7 Effects on ability to drive and use machines

ZENZIKET has a major influence on the ability to drive and use machines.

Particularly in situations where the patient may be discharged earlier than scheduled, the duration of the effect of ZENZIKET and other medicines administered during anaesthesia should be taken into account. Patients must be made aware that they should not drive, use dangerous machines or perform hazardous activities for 24 hours after anaesthesia, or even longer (depending on the dose of ZENZIKET and other medicines used).

If ZENZIKET is administered in an outpatient setting, patients must undergo post-anaesthetic monitoring and may only return home, accompanied by a responsible adult, when permitted by the attending physician.

4.8 Undesirable effects

The observations described below are partly explained by the mechanism of action of ketamine.

The transient increase in heart rate and blood pressure is a characteristic effect regularly observed with ketamine. The increase in blood pressure (at a constant differential pressure) occurs just after the injection, reaches its peak within a few minutes and generally returns to pre-anaesthetic values after 15 minutes. During clinical trials with ketamine, blood pressure increased on average from 20 % to 25 % compared to pre-anaesthetic values. Depending on the patient's condition, this increase in blood pressure may have a positive or adverse impact. Clinical studies currently available for ketamine have shown that, in patients for whom a decrease in blood pressure must be avoided as much as possible on account of their condition, maintenance of a stable or slightly raised blood pressure with ketamine represents an advantage.

If the cardio stimulant effect of ketamine must be avoided, pre-medication with intravenous diazepam at a dose of 0,2 – 0,25 mg/kg provides good results.

The adverse reactions of ketamine are listed below by organ system and frequency.

System organ class (MedDRA)	**Adverse event**	**Frequency**
Immune system disorders	Anaphylactic reaction.	Less frequent
Metabolism and nutrition disorders	Anorexia.	Less frequent
Psychiatric disorders	Hallucinations, vivid/abnormal dreams, nightmares, mental confusion, motor agitation, behavioural changes, agitation.	Frequent

	Anxiety, delirium, flashback, dysphoria, insomnia, disorientation.	Less frequent
Nervous system disorders	Tonic-clonic movements, hypertonia, increased intracranial pressure (unless adequate ventilatory support is available).	Frequent
	Vertigo.	Less frequent
Eye disorders	Diplopia, nystagmus, visual disturbances.	Frequent
	Increase in intraocular pressure, lacrimation.	Not known
Cardiac disorders	Hypertension, tachycardia.	Frequent
	Dysrhythmias, bradycardia.	Less frequent
Vascular disorders	Hypotension.	Less frequent
Respiratory, thoracic and mediastinal disorders	Elevated respiratory rate.	Frequent
	Laryngospasm (or other forms of airway constriction), respiratory depression, apnoea.	Less frequent
Gastrointestinal disorders	Nausea, vomiting.	Frequent
	Hypersalivation.	Less frequent
Hepato-biliary disorders	Medicine-induced liver injury (reported with extended use (> 3 days) or drug abuse).	Not known
Skin and subcutaneous tissue disorders	Erythema, morbilliform erythema.	Frequent
	Transient skin rashes.	Not known
Renal and urinary disorders	Cystitis, haemorrhagic cystitis.	Less frequent
General disorders and administration site conditions	Local pain sensitivity, redness/rash at the injection site.	Less frequent

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare 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

4.9 Overdose

Overdose and rapid IV injection may cause respiratory arrest, requiring ventilatory support until adequate spontaneous breathing is restored. Supportive ventilation and resuscitation equipment must always be available when general anaesthesia is administered.

If overdosage with ZENZIKET occurs, ventilation should be employed using mechanical support to maintain adequate blood oxygen saturation until adequate spontaneous breathing is restored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: 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 patients 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 patients was 12 minutes from the time of ketamine injection to vaginal delivery of a newborn.

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

ZENZIKET 10 mg/ml: Sodium chloride and water for injections.

ZENZIKET 50 mg/ml: Water for injections.

6.2 Incompatibilities

Due to chemical incompatibility (formation of a precipitate), do not combine barbiturates or diazepam and ZENZIKET in the same syringe or bag.

6.3 Shelf life

ZENZIKET 10 mg/ml: 36 months

ZENZIKET 50 mg/ml: 24 months

6.4 Special precautions for storage

Store at or below 30 °C. Do not refrigerate or freeze.

Store in original package in order to protect from light.

For storage conditions after dilution of the medicine, see section 6.3.

Keep out of the sight and reach of children.

6.5 Nature and contents of container

ZENZIKET 10 mg/ml is presented in 10 ml one point cut clear colourless Type I glass ampoules. Ampoules are packed into outer cardboard cartons in pack sizes of 10 ampoules per carton.

ZENZIKET 50 mg/ml is presented in 2 ml one point cut clear colourless Type I glass ampoules. Ampoules are packed into outer cardboard cartons in pack sizes of 10 ampoules per carton.

6.6 Special precautions for disposal and other handling

The preparations do not contain a preservative. For microbiological reasons, after opening, the ready to use preparations should be used immediately. Any remaining preparation must be discarded.

Once diluted, the preparation for infusion should not be stored. For microbiological reasons, after opening, the ready to use preparation should be used immediately after dilution.

ZENZIKET should not be resterilised in an autoclave.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Umsebe Healthcare

506 Sunclare Building

21 Dreyer Street, Claremont

Cape Town

7708

South Africa

Manufacturer: Sintetica SA

8. REGISTRATION NUMBERS

ZENZIKET 10 mg/ml: 56/2.1/0427

ZENZIKET 50 mg/ml: 56/2.1/0428

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 September 2023

10. DATE OF REVISION OF THE TEXT

28 June 2024

NAMIBIA:

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