1. Name of the proprietary product:
Ketamine Injection BP 50 mg/ml (Pal Ketamine Injection)

2 Qualitative and Quantitative Composition:
2.1 Qualitative Declaration

. Each ml contains:

Ketamine Hydrochloride BP

Eq. to Ketamine 50 mg

Water for Injection QS

2.2 Quantitative declaration:

Sr. No.	Ingredients	Specification	Qty./ml	Qty/Batch kg	Function
1	Ketamine Hydrochloride eq. to Ketamine	BP	50 mg	5.0	API
2	Sodium Edetate	BP	0.1 mg	0.01	Chelating Agent
3	Sodium Chloride	BP	1.6 mg	0.16	Tonicity
4	Water for Injection	BP	QS	QS to 100 ml	Vehicle

3. Pharmaceutical Form:
Solution for injection

4. Clinical Particulars:
4.1. Therapeutic Indications:
Ketamine is indicated in children and in adults.
Ketamine is recommended:
As an anaesthetic agent for diagnostic and surgical procedures. When used by intravenous or intramuscular injection, Ketamine is best suited for short procedures. With additional doses, or by intravenous infusion, Ketamine can be used for longer procedures. If skeletal muscle relaxation is desired, a muscle relaxant should be used and respiration should be supported.
For the induction of anaesthesia prior to the administration of other general anaesthetic agents.
To supplement other anaesthetic agents.
Specific areas of application or types of procedures:
When the intramuscular route of administration is preferred.
Debridement, painful dressings, and skin grafting in burned patients, as well as other superficial surgical procedures.
Neurodiagnostic procedures such as pneumoencephalograms, ventriculograms, myelograms, and lumbar punctures.
Diagnostic and operative procedures of the eye, ear, nose, and mouth, including dental extractions.

Note: Eye movements may persist during ophthalmological procedures.
Anaesthesia in poor-risk patients with depression of vital functions or where depression of vital functions must be avoided, if at all possible.
Orthopaedic procedures such as closed reductions, manipulations, femoral pinning, amputations, and biopsies.

Sigmoidoscopy and minor surgery of the anus and rectum, circumcision and pilonidal sinus.
Cardiac catheterization procedures.
Caesarean section; as an induction agent in the absence of elevated blood pressure.
Anaesthesia in the asthmatic patient, either to minimise the risks of an attack of bronchospasm developing, or in the presence of bronchospasm where anaesthesia cannot be delayed.

4.2. Posology and method of administration:
For intravenous infusion, intravenous injection or intramuscular injection.
NOTE: All doses are given in terms of ketamine base
Adults, elderly (over 65 years) and children:

For surgery in elderly patients ketamine has been shown to be suitable either alone or supplemented with other anaesthetic agents.

Preoperative preparations

Ketamine has been safely used alone when the stomach was not empty. However, since the need for supplemental agents and muscle relaxants cannot be predicted, when preparing for elective surgery it is advisable that nothing be given by mouth for at least six hours prior to anaesthesia.
Premedication with an anticholinergic agent (e.g. atropine, hyoscine or glycopyrolate) or another drying agent should be given at an appropriate interval prior to induction to reduce ketamine-induced hypersalivation.
Midazolam, diazepam, lorazepam, or flunitrazepam used as a premedicant or as an adjunct to ketamine, have been effective in reducing the incidence of emergence reactions.

Onset and duration

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 recommendation cannot be absolutely fixed. The dose should be titrated against the patient's requirements.
Because of rapid induction following intravenous injection, the patient should be in a supported position during administration. An intravenous dose of 2 mg/kg of bodyweight usually produces surgical anaesthesia within 30 seconds after injection and the anaesthetic effect usually lasts 5 to10 minutes. An intramuscular dose of 10 mg/kg of bodyweight usually produces surgical anaesthesia within 3 to 4 minutes following injection and the anaesthetic effect usually lasts 12 to 25 minutes. Return to consciousness is gradual.

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 1 mg/ml of ketamine in dextrose 5% or sodium chloride 0.9% is suitable for administration by infusion.

General Anaesthesia Induction

An infusion corresponding to 0.5 – 2 mg/kg as total induction dose.

Maintenance of anaesthesia

Anaesthesia may be maintained using a microdrip infusion of 10 - 45 microgram/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 (in terms of ketamine base). The average amount required to produce 5 to 10 minutes of surgical anaesthesia has been 2.0 mg/kg. It is recommended that intravenous administration be accomplished slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Dosage in Obstetrics

In obstetrics, for vaginal delivery or in caesarean section, intravenous doses ranging from 0.2 to 1.0 mg/kg are recommended (see section 4.6 Fertility, pregnancy and lactation).

Intramuscular Route

The initial dose of Ketamine administered intramuscularly may range from 6.5 mg/kg to 13 mg/kg (in terms of ketamine base). A low initial intramuscular dose of 4 mg/kg has been used in diagnostic manoeuvres and procedures not involving intensely painful stimuli. A dose of 10 mg/kg will usually produce 12 to 25 minutes of surgical anaesthesia.

Dosage in Hepatic Insufficiency:

Dose reductions should be considered in patients with cirrhosis or other types of liver impairment. (see section 4.4 Special Warnings and Special Precautions for Use)

Dosage in Obstetrics

Data are lacking for intramuscular injection and maintenance infusion of ketamine in the parturient population, and recommendations cannot be made. Available data are presented in Section 5.2.

Maintenance of general anaesthesia

Lightening of anaesthesia may be indicated by nystagmus, movements in response to stimulation, and vocalization. Anaesthesia is maintained by the administration of additional doses of Ketamine by either the intravenous or intramuscular route.

Each additional dose is from ½ 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 minutes 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 minutes 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 I.V. in an adult). A hypnotic dose of a thiobarbiturate (50 to 100 mg I.V.) 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

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Ketamine is contra-indicated in persons in whom an elevation of blood pressure would constitute a serious hazard (see section 4.8 Undesirable effects).

Ketamine should not be used in patients with eclampsia or pre-eclampsia, severe coronary or myocardial disease, cerebrovascular accident or cerebral trauma.

4.4. Special warnings and precautions for use

To be used only in hospitals by or under the supervision of experienced medically qualified anaesthetists except under emergency conditions.

As with any general anaesthetic agent, resuscitative equipment should be available and ready for use.

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.

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

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.

Although aspiration of contrast medium has been reported during Ketamine anaesthesia under experimental conditions (Taylor, P A and Towey, R M, Brit. Med. J. 1971, 2: 688), in clinical practice aspiration is seldom a problem.

In surgical procedures involving visceral pain pathways, Ketamine should be supplemented with an agent which obtunds visceral pain.

When Ketamine 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.

Ketamine should be used with caution in patients with the following conditions:

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

• Ketamine 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 use have been reported, particularly with extended use (>3 days) or drug abuse.

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

• Use with caution in patients with globe injuries and increased intraocular pressure (e.g. glaucoma) because the pressure may increase significantly after a single dose of ketamine.

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

• Use in caution in patients with acute intermittent porphyria.

• Use in caution in patients with seizures.

• Use in caution in patients with hyperthyroidism or patients receiving thyroid replacement (increased risk of hypertension and tachycardia)

• Use in caution in patients with pulmonary or upper respiratory infection (ketamine sensitises the gag reflex, potentially causing laryngospasm)

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

<u>Emergence Reaction</u>

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 Undesirable Effects).
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.
Cardiovascular
Because of the substantial increase in myocardial oxygen consumption, ketamine should be used in caution in patients with hypovolemia, dehydration or cardiac disease, especially coronary artery disease (e.g. congestive heart failure, myocardial ischemia and myocardial infarction). In addition ketamine should be used with caution in patients with mild-to-moderate hypertension and tachyarrhythmias.
Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.
Elevation of blood pressure begins shortly after the injection of Ketamine, 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 percent of preanaesthetic values. Depending on the condition of the patient, 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, acute kidney injury, hydronephrosis, and ureteral disorders have been reported in patients being given ketamine on a long term basis, especially in the setting of ketamine abuse. (These adverse reactions develop in patients receiving long term ketamine treatment after a time ranging from 1 month to several years). **Ketamine 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 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. Adverse effects have also been reported: see "Long-Term Use".
Ketamine dependence and tolerance may develop in individuals with a history of drug abuse or dependence. Therefore, ketamine should be prescribed and administered with caution.

4.5. Interaction with other medicinal products and other forms of interaction: Interactions resulting in a contraindication

Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketamine.
Diazepam is known to increase the half-life of ketamine and prolongs its pharmacodynamic effects. Dose adjustments may therefore be needed.
Ketamine is chemically incompatible with barbiturates and diazepam because of precipitate formation. Therefore, these should not be mixed in the same syringe or infusion fluid.
Ketamine may potentiate the neuromuscular blocking effects of atracurium and tubocurarine including respiratory depression with apnoea.
The use of halogenated anaesthetics concomitantly with ketamine can lengthen the elimination half-life of ketamine and delay recovery from anaesthesia. Concurrent use of ketamine

(especially in high doses or when rapidly administered) with halogenated anaesthetics can increase the risk of developing bradycardia, hypotension or decreased cardiac output.
The use of ketamine 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. Reduced doses of ketamine may be required with concurrent administration of other anxiolytics, sedatives and hypnotics.
Ketamine 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.
Concomitant use of antihypertensive agents and ketamine increases the risk of developing hypotension.
Sympathomimetics (directly or indirectly acting) and vasopressin may enhance the sympathomimetic effects of ketamine.
Concomitant use with ergometrine may lead to an increase in blood pressure.
When ketamine and theophylline or aminophylline are given concurrently, a clinically significant reduction in the seizure threshold may be observed. Unpredictable extensor-type seizures have been reported with concurrent administration of these agents.
Drugs that inhibit CYP3A4 enzyme activity generally decrease hepatic clearance, resulting in increased plasma concentration of CYP3A4 substrate medications, such as ketamine. Coadministration of ketamine with drugs that inhibit CYP3A4 enzyme may require a decrease in ketamine dosage to achieve the desired clinical outcome.
Drugs that induce CYP3A4 enzyme activity generally increase hepatic clearance, resulting in decreased plasma concentration of CYP3A4 substrate medications, such as ketamine. Coadministration of ketamine with drugs that induce CYP3A4 enzyme may require an increase in ketamine dosage to achieve the desired clinical outcome.

4.6. Fertility, pregnancy and lactation

Pregnancy

Ketamine crosses the placenta. This should be borne in mind during operative obstetric procedures in pregnancy. No controlled clinical studies in pregnancy have been conducted. The use in pregnancy has not been established and such use is not recommended, with the exception of administration during surgery for abdominal delivery or vaginal delivery.
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 observed at intravenous doses greater than 2 mg/kg.
Data are lacking for intramuscular injection and maintenance infusion of ketamine in the parturient population, and recommendations cannot be made.

Lactation

The safe use of ketamine during lactation has not been established, and such use is not recommended.

Fertility

Studies in animals have shown reproductive toxicity

4.7. Effects on the ability to drive and use machines not reported.

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.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:
• The medicine is likely to affect your ability to drive
• Do not drive until you know how the medicine affects you
• It is an offence to drive while under the influence of this medicine
• However, you would not be committing an offence (called 'statutory defence') if:
o The medicine has been prescribed to treat a medical or dental problem and
o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
o It was not affecting your ability to drive safely

4.8. Undesirable effects: Summary of the safety profile
The following Adverse Events have been reported:

MedDRA System Organ Class	**Frequency†**	**Undesirable Effects**
Immune system disorders	Rare	Anaphylactic reaction*
Metabolism and nutrition disorders	Uncommon	Anorexia
Psychiatric disorders	Common	Hallucination, Abnormal dreams, Nightmare, Confusion, Agitation, Abnormal behaviour
	Uncommon	Anxiety
	Rare	Delirium* Flashback*, Dysphoria*, Insomnia, Disorientation*
Nervous system disorders	Common	Nystagmus, Hypertonia, Tonic clonic movements
Eye disorders	Common	Diplopia
	Not Known	Intraocular pressure increased
Cardiac disorders	Common	Blood pressure increased, Heart rate increased
	Uncommon	Bradycardia, Arrhythmia
Vascular disorders	Uncommon	Hypotension
Respiratory, thoracic and Mediastinal disorders	Common	Respiratory rate increased
	Uncommon	Respiratory depression, Laryngospasm
	Rare	Obstructive airway disorder*, Apnoea*
Gastrointestinal disorders	Common	Nausea, Vomiting
	Rare	Salivary hypersecretion*
Hepatobiliary disorders	Not known	Liver function test abnormal, Drug-induced liver injury**
Skin and subcutaneous tissue disorders	Common	Erythema, Rash morbilliform

Renal and urinary disorders	Rare	Cystitis*, Haemorrhagic cystitis*
General disorders and administration site conditions	Uncommon	Injection site pain, Injection site rash

4.9. Overdose

Respiratory depression can result from an overdosage of ketamine hydrochloride. Supportive ventilation should be employed. Mechanical support of respiration that will maintain adequate blood oxygen saturation and carbon dioxide elimination is preferred to administration of analeptics.

Ketamine has a wide margin of safety; several instances of unintentional administration of overdoses of Ketamine (up to 10 times that usually required) have been followed by prolonged but complete recovery.

5. Pharmacological Particulars:

5.1. Pharmacodynamic properties Pharmacotherapeutic group: Other general anesthetics.

ATC Code: N01A X03

Ketamine is a rapidly acting general anaesthetic for intravenous or intramuscular use with a distinct pharmacological action. Ketamine hydrochloride produces dissociative anaesthesia characterised by catalepsy, amnesia, and marked analgesia which may persist into the recovery period. Pharyngeal-laryngeal reflexes remain normal and skeletal muscle tone may be normal or can be enhanced to varying degrees. Mild cardiac and respiratory stimulation and occasionally respiratory depression occur.

Mechanism of Action:

Ketamine induces sedation, immobility, amnesia and marked analgesia. The anaesthetic state produced by ketamine has been termed “dissociative anaesthesia” in that it appears to selectively interrupt association pathways of the brain before producing somesthetic sensory blockade. It may selectively depress the thalamoneocortical system before significantly obtunding the more ancient cerebral centres and pathways (reticular-activating and limbic systems). Numerous theories have been proposed to explain the effects of ketamine, including binding to N-methyl-D-aspartate (NMDA) receptors in the CNS, interactions with opiate receptors at central and spinal sites and interaction with norepinephrine, serotonin and muscarinic cholinergic receptors. The activity on NMDA receptors may be responsible for the analgesic as well as psychiatric (psychosis) effects of ketamine. Ketamine has sympathomimetic activity resulting in tachycardia, hypertension, increased myocardial and cerebral oxygen consumption, increased cerebral blood flow and increased intracranial and intraocular pressure. Ketamine is also a potent bronchodilator. Clinical effects observed following ketamine administration include increased blood pressure, increased muscle tone (may resemble catatonia), opening of eyes (usually accompanied by nystagmus) and increased myocardial oxygen consumption.

5.2. Pharmacokinetic properties

Absorption

Ketamine is rapidly absorbed following intra-muscular administration.

Distribution

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.

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 µ g/mL). Average delivery time for these parturients was 12 minutes from the time of ketamine injection to vaginal delivery of a newborn.
Biotransformation
Biotransformation takes place in liver. Termination of anaesthetic is partly by redistribution from brain to other tissues and partly by metabolism. CYP3A4 enzyme is the primary enzyme responsible for ketamine N-demethylation to norketamine in human liver microsomes; with CYP2B6 and CYP2C9 enzymes as minor contributors.
Elimination
Elimination half-life is approximately 2-3 hours, and excretion renal, mostly as conjugated metabolites.

5.3. Pre-clinical Safety: Dose

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies. The clinical significance of these non-clinical findings is not known.

6. Pharmaceutical Particulars:
6.1. List of Excipients:
EDTA Disodium, sodium chloride, Hydrochloric acid.

6.2. Incompatibilities: Nil

6.3. Shelf Life: 24 months.

6.4. Special Precautions for storage: Do not store above 30°C. Protect from light.
Keep the medicine out of reach of children. Do not Freeze

6.5. Nature and contents of container: 10 ml clear white ring snap off ampoules

6.6. Special precautions for disposal and other handling: No special requirements

7. Marketing authorisation holder
PAL PHARMACEUTICALS
NIGERIA 2 OGOJA AVENUE S/GARI KANO

8.
Manufacturer
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