SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ketamine Propharm 10 mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains:

ketamine (as hydrochloride) equivalent to 10 mg ketamine base per ml.

Excipient with known effect: sodium.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As the sole anaesthetic agent for diagnostic and surgical procedures. When used by intravenous or intramuscular injection, Ketamine Propharm is best suited for short procedures. With additional doses, or by intravenous infusion, Ketamine Propharm 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

Preoperative preparations

While vomiting has been reported following ketamine administration, some airway protection may be afforded because of active laryngeal-pharyngeal reflexes. However, since aspiration may occur with ketamine and since protective reflexes may also be diminished by supplementary anesthetics and muscle relaxants, the possibility of aspiration must be considered. Ketamine is recommended for use in the patient whose stomach is not empty when, in the judgment of the practitioner, the benefits of the drug outweigh the possible risks.

Premedications with an anticholinergic agent (e.g., atropine, scopolamine, hyoscine, or glycopyrrolate) 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

Because of rapid induction following intravenous injection, the patient should be in a supported position during administration.

The onset of action of ketamine is rapid; an intravenous dose of 2 mg/kg of body weight usually produces surgical anaesthesia within 30 seconds after injection and the anaesthetic effect usually lasts 5 to 10 minutes. If a longer effect is desired, additional increments can be administered intravenously or intramuscularly to maintain anesthesia without producing significant cumulative effects.

Intramuscular doses, from experience primarily in pediatric patients, in a range of 9 mg/kg to 13 mg/kg usually produce surgical anesthesia within 3 to 4 minutes following injection, with the anesthetic effect usually lasting 12 to 25 minutes.

Dosage:

As with other general anesthetic agents, the individual response to ketamine is somewhat varied depending on the dose, route of administration, and age of patient, so that dosage recommendation cannot be absolutely fixed. The drug should be titrated against the patient's requirements.

Supplementary Agents:

Ketamine is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

The regimen of a reduced dose of ketamine supplemented with diazepam can be used to produce balanced anesthesia by combination with other agents such as nitrous

oxide and oxygen.

General Anesthesia Induction

Intravenous Route:

Adults: 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 minutes of surgical anaesthesia has been 2.0 mg/kg.

Alternatively, in adult patients an induction dose of 1.0 mg to 2.0 mg/kg intravenous ketamine at a rate of 0.5 mg/kg/min may be used for induction of anesthesia. In addition, diazepam in 2 mg to 5 mg doses, administered in a separate syringe over 60 seconds, may be used. In most cases, 15 mg of intravenous diazepam or less will suffice. The incidence of psychological manifestations during emergence, particularly dream-like observations and emergence delirium, may be reduced by this induction dosage program.

Rate of Administration: It is recommended that ketamine be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Intramuscular Route:

Adults: The initial dose of ketamine administered intramuscularly may range from 6.5 mg/kg to 13 mg/kg. 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 Precautions for Use –** General).

Maintenance of General Anaesthesia

The maintenance dose should be adjusted according to the patient's anesthetic needs and whether an additional anesthetic agent is employed.

Increments of one-half to the full induction dose may be repeated as needed for maintenance of anesthesia. However, it should be noted that purposeless and tonic-clonic movements of extremities may occur during the course of anesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anesthetic. It should be recognized that the larger the total dose of ketamine administered, the longer will be the time to complete recovery.

Adult patients induced with ketamine augmented with intravenous diazepam may be maintained on ketamine given by slow microdrip infusion technique at a dose 0.1 mg/minute to 0.5 mg/minute, augmented with diazepam 2 to 5 mg administered intravenously as needed. In many cases 20 mg or less of intravenous diazepam total for combined induction and maintenance will suffice. However, slightly more diazepam may be required depending on the nature and duration of the operation, physical status of the patient, and other factors. The incidence of psychological manifestations during emergence, particularly dream-like observations and emergence delirium, may be reduced by this maintenance dosage program.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Ketamine Propharm is contraindicated in persons in whom an elevation of

blood pressure would constitute a serious hazard (see section 4.8). Ketamine Propharm 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 Propharm, 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 Propharm 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 Propharm should be supplemented with an agent which obtunds visceral pain.

When Ketamine Propharm 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 Propharm 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 Propharm anaesthesia, Ketamine Propharm 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.

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.

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 Propharm, 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 Propharm 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”.

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 Propharm should be closely supervised and it should be prescribed and administered with caution.
Excipient information
Ketamine Propharm 10 mg/ml contains sodium. The sodium content is less than 1 mmol per dose, i.e "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketamine Propharm.

Diazepam is known to increase the half-life of ketamine and prolongs its pharmacodynamic effects. Dose adjustments may therefore be needed.

Ketamine Propharm 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 Propharm 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. Available data are presented in section 5.2.

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

Studies in animals have shown reproductive toxicity (see section 5.3).

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.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. 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:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

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*, Disorientation* Flashback*, Dysphoria*, Insomnia,
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 airways 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	Haemorrhagic cystitis*, ***, Cystitis*,
General disorders and administration site conditions	Uncommon	Injection site pain, Injection site rash

† Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Not known (frequency cannot be estimated from the available data)

* ADR identified during post-marketing use ** Extended period use (>3 days) or drug abuse

*** Long term use (1 month to several years), especially in the setting of ketamine abuse.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N01AX03, Pharmacotherapeutic group: Other general anaesthetics.
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 intramuscular 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 µg/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 Preclinical safety data

Animal research has shown that ketamine can induce NMDA antagonist-induced neuronal cell death in juvenile animals (apoptosis) when administered in high doses,

for prolonged periods, or both. In some cases this led to abnormalities in behaviour, learning and memory. The relevance of this finding to human use is unknown. 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 nonclinical findings is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
For single use only. Discard any unused product at the end of each operating session.

Shelf life after dilution

After dilution the solutions should be used immediately.
Chemical and physical in-use stability has been demonstrated for 48 hours at 25°C. However, from a 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

Store below 30°C.

6.5 Nature and contents of container

5 ml sealed glass ampoules type I containing 5 ml of solution as 10 mg ketamine base per ml. Each pack contains 10 ampoules.

6.6 Instructions for use/handling

I.V. infusion
Dilution: To prepare a dilute solution containing 1 mg of ketamine per mL, aseptically transfer 500 mg ketamine to 500 mL of 5% dextrose injection, or sodium chloride (0.9%) for injection, and mix well. The resultant solution will contain 1 mg of ketamine per mL. For shelf life after dilution please refer to section 6.3.

The fluid requirements of the patient and duration of anesthesia must be considered when selecting the appropriate dilution of ketamine.

7 License Holder:

Propharm Ltd. POB 4046, Ben-Gurion 23 Zichron Yaacov

8 Manufacturer:

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License Number: 172-43-36566-99

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