PRODUCT INFORMATION

Controlled Medicine

Prescribing Information (Summary of Products Characteristics)

1. NAME OF THE MEDICINAL PRODUCT

1.1 PRODUCT NAME

Ketamine Hydrochloride Injection USP 50 mg/ml, 10 ml

1.2 STRENGTH

50 mg/ml

1.3 PHARMACEUTICAL DOSAGE FORM

Solution for Injection Sterile

Description: Clear and colorless solution free from visible particles and fibers.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 QUALITATIVE DECLARATION

Ketamine Hydrochloride USP Equivalent to

Ketamine……..50 mg

Benzethonium Chloride USP……. 0.01% w/v

(As Preservative)

2.2 QUANTITATIVE DECLARATION

Each ml contains:

Ketamine Hydrochloride USP

Equivalent to Ketamine……..……50 mg

Benzethonium Chloride USP…….0.01% w/v

(As Preservative)

Water for Injections BP……...…….q.s.

3. PHARMACEUTICAL FORM

Solution for Injection Sterile

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

It 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.

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 to 10 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 4.5mg/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.

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.

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

Ketamine is contra-indicated in persons in whom an elevation of blood pressure would constitute a serious hazard. Ketamine hydrochloride is contraindicated in patients who have

shown hypersensitivity to the drug or its components. 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, 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 with caution in patients with acute intermittent porphyria.

Use with caution in patients with seizures.

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

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

Use with 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.

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.

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-tomoderate 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.

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. Ketamine is not indicated nor recommended for long term use.

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. Cases of cystitis including haemorrhagic cystitis have also been reported. If used on a daily basis for a few weeks, dependence and tolerance may develop, particularly in individuals with a history of drug abuse and dependence. Therefore the use of KETAMINE should be closely supervised and it should be prescribed and administered with caution.

4.5 Interaction with other medicinal products and other forms of interaction

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

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 H1-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.

When Ketamine 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 agents.

4.6 Fertility, pregnancy and lactation

Ketamine crosses the placenta. This should be borne in mind during operative obstetric procedures in pregnancy. With the exception of administration during surgery for abdominal delivery or vaginal delivery, no controlled clinical studies in pregnancy have been conducted. The safe use in pregnancy, and in lactation, has not been established and such use is not recommended.

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:

Immune system disorders

Rare: Anaphylactic reaction

Metabolism and nutrition disorders

Unknown: Anorexia

Psychiatric disorders

Common: Hallucination, Abnormal dreams, Nightmare, Confusion, Agitation, Abnormal behaviour.

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, Hepatobiliary disorders,

Not Known: Liver function test abnormal

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ketamine is a rapidly acting general anaesthetic for intravenous or intramuscular use with a distinct pharmacological action. Ketamine 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

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENT(S)

Benzethonium Chloride USP
Sodium Chloride USP
Disodium EDTA USP
Water for Injections BP

6.2 INCOMPATIBILITIES

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.

6.3 SHELF-LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light.

KEEP OUT OF REACH OF CHILDREN

6.5 NATURE AND CONTENTS OF CONTAINER

10 ml Amber Glass vial (USP Type- I) in a carton with insert.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Not Applicable

7. MARKETING AUTHORISATION HOLDER

SWISS PARENTRALS LTD.

808,809 & 810 Kerala Industrial Estate, G.I.D.C.,

Bavla, Dist. Ahmedabad – 382220, Gujarat, India.

8. MARKETING AUTHORISATION NUMBER

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9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION / APPROVAL OF THE TEXT

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11. LEGAL CATEGORY

Prescription only medicine.