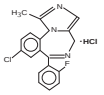
IDZO® 5mg/5ml Injection
(Midazolam)

Preservative free

For I.M./I.V. use or rectal application

DESCRIPTION:
Midazolam, the active ingredient of IDZO®, is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables the active ingredient of midazolam to form water soluble salts with acids. These produce a stable injection solution. Midazolam hydrochloride has the molecular weight of 362.24 and the following structural formula:



COMPOSITION:
IDZO® 5mg/5ml Injection
Each 5ml contains:
Midazolam 5mg

CLINICAL PHARMACOLOGY:
Mechanism of Action
Midazolam is a short-acting benzodiazepine central nervous system (CNS) depressant: The effects of midazolam on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other medications. Onset time of sedative effects after IM administration in adults is 15 minutes, with peak sedation occurring 30 to 60 minutes following injection. Onset time of sedative effects in the paediatric population begins within 5 minutes and peaks at 15 to 30 minutes depending upon the dose administered

PHARMACOKINETICS:
Absorption after Intramuscular Injection: Absorption of midazolam from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. Bioavailability is over 90% Absorption after Rectal Administration: Midazolam is absorbed quickly. After rectal administration, the area under the plasma concentration-time curve in children is comparable to that of adults. Bioavailability is about 50%

DISTRIBUTION:
When midazolam is injected intravenously, the plasma concentration-time curve shows two distinct phases of distribution. The volume of distribution calculated under steady-state conditions is 50-60 L

METABOLISM:
Midazolam is completely and rapidly metabolized in the body. The fraction extracted by the liver is 40-50%. The primary metabolite is alpha hydroxymidazolam, which can be found in the plasma

ELIMINATION:
In healthy volunteers, the elimination half-life is between 1.5 and 3.5 hours. Plasma clearance is in the range of 300-500 ml/min. When midazolam is given by I.V. infusion, its elimination kinetics do not differ from those following bolus injection. The elimination half-life of the main metabolite, alpha hydroxyl midazolam, is shorter than that of the parent substance. Immediately after its formation, it is conjugated with glucuronic acid (inactivation), and 50-70% of the dose is then eliminated by the kidneys

INDICATIONS:
Midazolam Injection, USP is indicated: Intramuscularly or intravenously for preoperative sedation/anxiolysis/amnesia;
Intravenously as an agent for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suture of lacerations and other procedures either alone or in combination with other CNS depressants;
Intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotics premedication, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous midazolam can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia);
Continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting

DOSAGE AND ADMINISTRATION:
Standard Dosage
In the case of elderly patients with organic cerebral changes or impaired cardiac and respiratory function, the dosage should be determined with caution, the special factors relating to each patient being taken into consideration. Intravenous injections must be given slowly (approximately 2.5mg in ten seconds for induction of anesthesia and 1mg in 30 seconds for basal sedation). The drug takes effect about two minutes after the injection is started
Premedication Before an Operation
Intramuscular Administration
In patients suffering from pain before an intervention: Administration alone or in combination with anticholinergics and possibly analgesics
Adults: 0.07-0.1mg/kg bodyweight I.M., according to age and general condition of the patient. Usual dose about 5mg
Children: Proportionately higher doses are required than in adults in relation to bodyweight (0.15-0.20mg/kg)
Elderly and debilitated patients: 0.025-0.05 mg/kg I.M. The doses should be administered 30 min. before induction of anesthesia
Rectal Administration in Children
For Preoperative Sedation: Rectal administration of the ampoule solution by means of a plastic applicator fixed on the end of a syringe, 0.35-0.45mg/kg 20-30 min. before induction of general anesthesia. If the volume to be administered is too small, water may be added up to a total volume of 10ml
Basal Sedation and Sedation in Intensive Care Units (ICU)
Intravenous Basal Sedation: For basal sedation in diagnostic or surgical interventions carried out under local anesthesia: The initial dose is 2.5mg for 5-10 min. before the beginning of the operation. Further doses of 1mg may be given as necessary. A total dose greater than 5mg is not usually necessary to reach the desired endpoint. In cases of severe illness, particularly if the patient is in poor general condition or of advanced age, the initial dose must be reduced to 1-1.5mg. Total doses greater than 3.5mg are not usually necessary
Intravenous Sedation in ICU: For sedation in ICU, the dosage should be individualized and midazolam titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication
Loading dose: 0.03-0.3mg/kg. Maintenance dose: 0.03-0.2mg/kg/hr.
The dosage should be reduced or the loading dose should even be omitted in hypovolemic, vasoconstricted and hypothermic patients
Induction and Maintenance of Anesthesia
Intravenous Injection
Induction: The dose is 10-15mg I.V. A sufficiently deep level of sleep is generally achieved after 2-3 min.
Maintenance: For maintenance of the desired level of unconsciousness, further small doses should be injected I.V. The dose and the intervals between doses vary according to the individual patient's reaction, Alternatively, midazolam can be administered by continuous infusion
Intravenous Continuous Infusion
For intravenous anesthesia combined with ketamine: 0.03-0.1mg/kg/hr.; narcotics: 0.03-0.3mg/kg/hr. High-risk surgical patients, elderly and debilitated patients require lower dosages
Intramuscular Administration in Children
A combination of sleep inducing and amnesia-inducing midazolam with ketamine (ataranalgesia) is recommended. Midazolam I.M.: 0.15 to 0.20mg/kg, in combination with ketamine I.M. A sufficiently deep level of sleep is generally achieved after 2-3 min. When midazolam is given with potent analgesics, the latter should be administered first so that the sedative effects of midazolam can be safely titrated on top of any sedation caused by the analgesic

ADVERSE REACTIONS:
Changes in arterial blood pressure, pulse rate and breathing are usually slight. As a rule, the systolic blood pressure falls by a maximum of 15%, while the pulse rate simultaneously shows a corresponding rise. Severe cardiorespiratory side effects have occurred on rare occasions. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest. Such life threatening incidents are more likely to occur in elderly patients and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered. Therefore, midazolam ampoules should be used only when resuscitation facilities are available. In isolated cases, generalized hypersensitivity including anaphylactoid reactions and skin reactions have been reported. In rare cases paradoxical reactions such as agitation, hyperactivity and aggressivity have occurred; involuntary movements (including tonic/clonic convulsions and muscle tremor) have also been observed. Should such reactions occur, the response to each dose of midazolam should be evaluated before proceeding. Anterograde amnesia of short duration may occur. After prolonged I.V. administration of midazolam, abrupt discontinuation of the product may be accompanied by withdrawal symptoms. Therefore, a gradual reduction of midazolam is recommended. After rectal administration, a slightly euphoric condition of short duration was observed in individual children. In isolated cases bouts of double vision lasting several minutes were reported. However, this had no effect on preparation for anesthesia

WARNING AND PRECAUTIONS:
Special caution should be exercised when administering midazolam parenterally to patients representing a higher risk group: Elderly and debilitated patients, patients with obstructive pulmonary disease, with chronic renal failure or with congestive heart failure. These higher risk surgical patients require lower and individualized dosages and should be continuously monitored for early signs of alterations of vital functions. Patients with chronic renal failure, impaired hepatic function and congestive heart failure may eliminate midazolam more slowly. Convulsions have been reported in premature infants and neonates. As with other parenteral hypnotic agents, venous access must be maintained when midazolam is administered intravenously (at least for the duration of the procedure in the case of basal sedation). Midazolam ampoules should be used only when resuscitation facilities are available. After receiving midazolam parenterally, patients should not be discharged from hospital or consulting room for at least three hours and then only if accompanied by an attendant. They should be warned not to drive a vehicle or operate a machine for at least twelve hours. Particular care is needed when administering midazolam to a patient with myasthenia gravis, owing to preexisting muscle weakness. (See Drug Interactions section concerning concurrent use of erythromycin or cimetidine)

PREGNANCY AND LACTATION:
There is strong evidence that benzodiazepine use during pregnancy is associated with risks for the human fetus. Midazolam like other drugs should therefore not be used in the first three months of pregnancy unless considered absolutely necessary by the physician. Special care must be taken when benzodiazepines are used during labor and delivery, as high single doses may produce irregularities in the fetal heart rate and hypotonia as well as poor sucking, respiratory depression, withdrawal symptoms and hypothermia in the neonate. Midazolam may pass into breast milk and caution should be exercised with its use in nursing mothers

SPECIAL DOSAGE INSTRUCTIONS:
Compatibility with infusion solutions: The midazolam ampoule solution can be diluted with sodium chloride 0.9%, dextrose 5% and 10%, levulose 5%, Ringer's solution and Hartmann's solution in a mixing ratio of 15mg midazolam per 100-1000ml infusion solution. These solutions remain physically and chemically stable for 24 hours at room temperature (or three days at 5°C)

DRUG INTERACTIONS:
In vitro data show that the hydroxylation of midazolam is inhibited by numerous agents that specifically inhibit the cytochrome P-4503A isoenzyme, resulting in a potentiation of midazolam's effects. These findings have been clinically confirmed for erythromycin, diltiazem, verapamil, ketoconazole, itraconazole and cimetidine, but not for cyclosporin, nitrendipine or ranitidine (after parenteral administration). Midazolam enhances the central sedative effect of neuroleptics, tranquilizers, antidepressants, sleep inducing agents, analgesics, antiepileptics and anesthetics. This potentiation can be of advantage therapeutically in certain cases. Special attention must be paid to the possibility of potentiation in patients at particular risk. In some cases the mutual potentiation of alcohol and midazolam can produce unforeseeable reactions. (No alcoholic beverages should be allowed for at least twelve hours after parenteral administration)

CONTRAINDICATIONS:
Midazolam must not be given to patients who are hypersensitive to benzodiazepines

OVER DOSAGE:
The symptoms of midazolam over dosage are mainly an intensification of the therapeutic effects (sedation, muscle weakness, profound sleep) or paradoxical excitation. In most cases only observation of vital functions is required. Extreme over dosage may lead to coma, areflexia, cardiorespiratory depression and apnea, requiring appropriate countermeasures (ventilation, cardiovascular support). The effects of overdoses can be very well controlled with the benzodiazepine antagonist flumazenil

STABILITY:
See expiry on the pack

PRESENTATION:
IDZO® 5mg/5ml Injection in a pack of 5's

INSTRUCTIONS:
Keep out of reach of children
Avoid exposure to heat, light and freezing
Store between 15 to 30°C
Improper storage may deteriorate the medicine
Injection should not be used if container is leaking, solution is cloudy or it contains undissolved particle(s)

How to break OPC ampoules:

اِڈزو® ۵ ملی گرام/ ۵ ملی لیٹر انجکشن
(میڈازولم)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں
بچوں کی پہنچ سے دور رکھیں
دوا کو دھوپ، گرمی اور منجمد ہونے سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی
انجکشن کے ایک ہونے، ہُوا نہ ہونے یا اس میں
کوئی غیر حل پزیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

R.N-01/HA/11/18

220 mm

71 mm