1.4 Product information

1.4.1 Summary of product characteristics (SmPC)

Please refer subsequent pages.

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of Medicinal Product

BENZOSED, 5 ml (Midazolam Injection BP)

2. Qualitative and quantitative composition

Each ml Contains:

Midazolam BP……. 1mg.

Water for Injections BP……q. s.

For the full list of excipients, see section 6.1

3. Pharmaceutical Form:
Solution for Injection
Clear colourless liquid

4. Clinical Particulars:

4.1 Therapeutic indications

Benzosed is indicated

(i) For preoperative sedation

(ii) For conscious sedation prior to short diagnostic or endoscopic procedures

(iii) For induction of general anaesthesia prior to administration of other anaesthetic agents

4.2 Posology and method of administration

Midazolam is a potent sedative agent and requires slow administration and individualization of dosage. Midazolam, at a concentration of 0.5 mg/ml, is compatible with 5% dextrose in water, 0.9% sodium chloride and lactated Ringer's solution. Infusion with 5% dextrose in water and 0.9% sodium chloride should be completed within 24 hours of preparation and with lactated Ringer's solution, it should be completed within 4 hours of preparation.

Usual Adult Dose

(i) Preoperative sedation: Intramuscular (IM) the recommended premedication dose of Benzosed for adult patients below the age of 60 years is 0.07 to 0.08 mg/ kg administered about 1 hour before surgery. The dose must be individualized and reduced when Benzosed is administered to patients with chronic obstructive pulmonary disease, patients more than 60 years of age and patients who have received concomitant narcotics or other CNS depressants and other high-risk surgical patients. For intramuscular use, Benzosed should be injected deep in a large muscle mass.

(ii) Conscious sedation : Intravenous (IV)

When used for conscious sedation, dosage must be individualized and titrated. Benzosed should not be administered by rapid or single bolus intravenous administration. Benzosed 1 mg / ml is recommended for conscious sedation to facilitate slower injection. Both, 1 mg/ml and 5 mg/ml formulations may be diluted with 0.9% Sodium chloride or 5% Dextrose in water.

Maintenance dose: Additional doses to maintain the desired level of sedation may be given in increments of 25% of the initial dose used to reach the sedative endpoint, but again only by slow titration, especially in the elderly and chronically ill or debilitated patient.

These additional doses should be given only, when a thorough clinical evaluation clearly indicates the need for additional sedation.

- **Healthy adults below the age of 60:** Titrate slowly to the desired effect, e.g., the initiation of slurred speech. No more than 2.5 mg should be given at first over a period of at least 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If further titration is necessary, continue to titrate using small increments to the appropriate level of sedation. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint.
- **Patients aged 60 or older, and debilitated or chronically ill patients:** As the danger of underventilation or apnoea is greater in elderly patients and those with chronic disease states or decreased pulmonary reserve and because the peak effect may take longer in these patients, increments should be smaller and the rate of injection slower. Some patients may respond to as little as 1mg. No more than 1.5 mg should be given over a period of not less than 2 minutes, waiting an additional 2 or more minutes to fully evaluate the sedative effect. If additional titration is necessary, it should be given at a rate of not more than 1 mg over a period of 2 minutes, waiting an additional 2 or more minutes each time to fully evaluate the sedative effect. Total doses greater than 3.5 mg are not usually necessary.

(iii) Introduction of anesthesia :

- **Unpremedicated Patients:**

a) In the absence of premedication, an average adult under age of 55 years will require an initial dose of 0.3-0.35 mg/kg for induction, administered over 20 to 30 seconds and allowing 2 minutes for effect. If needed, increments of approximately 25% of the patient's initial dose may be based to complete induction. In resistant cases, up to 0.6 mg/kg may be used for induction, but such large doses may prolong recovery.

b) Unpremedicated patients over the age of 55 years usually require less Benzosed for induction; an initial dose of 0.3 mg/kg is recommended. Unpremedicated patients with severe systemic disease or other debilitation usually require less Benzosed for induction. An initial dose of 0.2 to 0.25 mg/kg will usually suffice; in some cases, as little as 0.15 mg/kg may suffice.

- **Premedicated Patients:**

a) When the patient has received sedative or sedative or narcotic premedication, the range of recommended doses is 0.15 to 0.35 mg/kg.

b) In adults below the age of 55 years, a dose of 0.25 mg/kg, administered over 20 to 30 seconds and allowing 2 minutes for effect, will usually suffice.

c) An initial dose of 0.2 mg/kg is recommended for surgical patients over the age of 55 years.

4.3 Contraindications:

Midazolam is contraindicated in patients with a known hypersensitivity to benzodiazepines. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma only if they receive appropriate therapy.

4.4 Special warnings and precautions for use

Impairment of psychomotor skills may occur following midazolam sedation or anaesthesia and may persist for varying lengths of time, depending upon the combination of medications and total dosages administered. Possible adverse effects on patients' ability to drive or perform other tasks, requiring alertness and co-ordination, should be kept in mind when midazolam is administered for an outpatient procedure. It is recommended that the patient should not operate hazardous machinery or a motor vehicle until the effects of midazolam, such as drowsiness and amnesia have subsided, or until the day after anaesthesia and surgery, whichever is longer.

High risk surgical patients and elderly patients require lower doses, whether premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of midazolam. The initial dose should be reduced in patients with impaired renal function and in the elderly. Midazolam must never be used without individualization of dosage. Prior to intravenous administration of midazolam in any dose, the immediate availability of oxygen, resuscitative equipment and skilled personnel for the maintenance of a patent airway and support of ventilation should be ensured. Patients should be continuously monitored for early signs of underventilation or apnoea, which can lead to hypoxia/cardiac arrest unless effective counter measures are taken immediately. Vital signs should continue to be monitored during the recovery period. When used for conscious sedation, midazolam should not be administered by rapid or single bolus intravenous administration. Concomitant use of barbiturates, alcohol or other central nervous system depressants increases the risk of underventilation or apnoea and may contribute to prolonged drug effect.

4.5 Interaction with other medicinal products and other forms of interaction

Sedation with intravenous midazolam is accentuated by premedication, particularly with morphine, meperidine and fentanyl. Consequently, the dosage of midazolam should be adjusted according to the amount of premedication a administered. Following intramuscular administration of midazolam, moderate reduction in the required dose of thiopentone for induction has been noted**.** Hypotensive effects may be potentiated when medication viz. Beta blockers, Calcium channel blockers, Diuretics, ACE inhibitors, levodopa, magnesium sulphate, Nitrates and other hypotensive agents are used concurrently. Intravenous administration of midazolam decreases the minimum alveolar concentration of halothane required for general anaesthesia. Inhibition of the cytochrome P-450 enzyme system by cimetidine and ranitidine may cause a decrease in the hepatic metabolism of midazolam, which may result in delayed elimination and increased blood concentration.

4.6 Pregnancy and lactation

Pregnancy

Midazolam did not cause any impairment of fertility when given at doses upto 10 times the human dose of 0.35 mg/kg.

Nursing Mothers

Midazolam is secreted in human milk. It is not recommended for use in nursing mothers.

Paediatrics

Appropriate studies on the relationship of age to the effects of midazolam have not been performed in children upto 18 years of age. However, no paediatric specific problems have been documented to date.

Geriatrics

Elderly patients may require reduction of dosage because of age related decrease in renal function.

4.7 Effects on ability to drive and use machines.

Possible adverse effects on patients' ability to drive or perform other tasks, requiring alertness and co-ordination, should be kept in mind when midazolam is administered for an outpatient procedure. It is recommended that the patient should not operate hazardous machinery or a motor vehicle until the effects of midazolam, such as drowsiness and amnesia have subsided, or until the day after anaesthesia and surgery, whichever is longer.

4.8 Undesirable effects

Fluctuations in vital signs are the most frequently seen effects following parenteral administration of midazolam. Apnoea may occur in some patients following IV administration. Local effects at the IV site include pain during injection, redness and phlebitis. Other side effects that have been infrequently reported are hiccups, nausea, vomiting, headache, drowsiness, bronchospasm, retrograde amnesia, emergence delirium and prolonged emergence from anaesthesia.

Drug Abuse and Dependence:

Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is equivalent to that of diazepam.

4.9 Overdose

As there is insufficient human data on over dosage with midazolam, the manifestations of midazolam overdosage are expected to be similar to those observed with other benzodiazepines, including sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma and untoward effects on vital signs.

Treatment of over dosage

Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of

ventilation. An intravenous infusion should be started. If hypotension develops, treatment may include intravenous fluid therapy, repositioning, and judicious use of vasopressors appropriate to the clinical situation.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations where overdose with a benzodiazepine is known or suspected.

5.0 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives,

ATC code: N05CD08.

Mechanism of Action

Midazolam has anxiolytic, hypnotic, anticonvulsant, muscle relaxant and anterograde amnestic effects. The mechanism of action of midazolam is not clearly understood; however, it is probably similar to that of other benzodiazepines i.e., it potentiates the action of the inhibitory neurotransmitter GABA (gamma-amino butyric acid) by allosteric binding to the GABA receptors. It binds to an accessory site on the GABA receptor (benzodiazepine binding site) in such a way that the binding of GABA to the receptor is facilitated, thus opening the associated chloride channel and leading to hyperpolarization. Midazolam has a relatively high affinity (about twice that of diazepam) for the benzodiazepine binding site on the GABA receptor.

5.2 Pharmacokinetic properties

Midazolam is rapidly absorbed following intramuscular administration with a bioavailability greater than 90%. The peak effect of midazolam is reached within 15-60 minutes following intramuscular injection. Midazolam is widely distributed in the body including cerebrospinal fluid and brain. It is extensively bound to plasma proteins (97%). Midazolam is rapidly metabolised to 1-Hydroxy Methyl Midazolam and 4-Hydroxy Midazolam.

The pharmacological activity of these metabolites is negligible as compared to that of the parent compound. Midazolam is excreted mainly through the renal route as glucuronide conjugates. Less than 0.03%, of an intravenous dose is excreted unchanged. The elimination half-life of midazolam is about 2.5 hours.

5.3 Preclinical safety data

A marked increase in the incidence of hepatic tumors in female mice and an increase in benign thyroid follicular cell tumors in male mice were noted after chronic administration of midazolam at the dose of 80 mg/kg/day. Dosages of 9 mg/kg (25 times of the usual dose in humans) do not increase the incidence of these tumors. Midazolam did not have mutagenic activity in the Ames' test, Chinese hamster lung cell test, human lymphocytes or in the micronucleus test in mice.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium Chloride

Benzyl Alcohol

Disodium Edetate

Hydrochloric Acid *(for pH adjustment)*

Sodium Hydroxide Pellets *(for pH adjustment)*

Water for Injections

6.2 Incompatibilities:

Not Applicable

6.3 Shelf-life:

24 months

Shelf life after dilution study: 24 hours with 5% dextrose in water and 0.9% sodium chloride, 4 hours with lactated Ringer's solution at the below 30^{o} C.

Proposed shelf life (after first opening container): After first open use immediately

6.4 Special precautions for storage

Store below 30˚C, protected from light.

6.5 Nature and contents of container

Primary Packing: The product is available in 5 ml amber vial USP Type I with 20 mm bromo butyl rubber stopper and 20 mm brown flip off seal.

Secondary Packing: Further such 1 labelled vial packed in a printed carton along with package insert.

6.6 Special precautions for disposal:

Any unused BENZOSED from opened vials should be discarded.

7. MARKETING AUTHORISATION HOLDER

Troikaa Pharmaceuticals Ltd.

Troikaa House, Commerce House – 1, Satya Marg,

Bodakdev, Ahmedabad – 380 054, Gujarat, India

Phone: +91-79-26856242 / 43 / 44 / 45

Fax: +91-79-26856246

Email: regaffairs@troikaapharma.com prashantchudasama@troikaapharma.com

Manufacturing Site:

Troikaa Pharmaceuticals Ltd.

C-1, Sara Industrial Estate, Selaqui,

Dehradun-248197, Uttarakhand, India.

Telephone: +91-135-2699146, 2698819

Fax: +91-135-2698059

www.troikaa.com

Email: regaffairs@troikaapharma.com, prashantchudasama@troikaapharma.com

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS: Not applicable

9. DATE OF FIRST AUTHORISATION/RENEWALOF THE AUTHORISATION: Not applicable

10. DATE OF REVISION OF TEXT: Not applicable