SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Midazolam 1mg/ml Injection in a Prefilled Syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Midazolam 1mg/ml Prefilled Syringe contains 1mg of the active ingredient Midazolam.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion
(Sterile Solution for Slow Intravenous Infusion)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As intravenous sedative cover before and during minor medical, dental and surgical procedures such as gastroscopy, endoscopy, cytoscopy, bronchoscopy and cardiac catheterisation.

For sedation by intravenous injection (either continuous infusion or intermittent bolus injection) in critically ill patients in intensive care.

As an alternative intravenous agent for the induction of anaesthesia in high risk and elderly patients, especially where cardiovascular stability is of particular importance. Induction is more reliable when heavy opiate premedication has been administered or when Midazolam Injection is given with a narcotic analgesic such as fentanyl.

4.2. Posology and Method of Administration

One or more intravenous injections over a single operating session.

Adults: An assessment should be made of the degree of sedation necessary for the planned procedure.
The dose should be titrated against the response of the patient. The desired titration end point will depend upon the procedure. Full sedation will be

evident by drowsiness, slurred speech but response to commands will be maintained.
As a guide it is recommended that initially 2mg be administered intravenously over 30 seconds.
If after 2 minutes, sedation is not adequate, incremental doses of 0.5 - 1mg should be given.
Usual dosage range 2.5 - 7.5mg total dose (equivalent to around 0.07mg/kg body weight). Dosages greater than 5.0mg are not usually necessary.

Elderly: THE ELDERLY ARE MORE SENSITIVE TO THE EFFECTS OF BENZODIAZEPINES. IN THESE PATIENTS DOSES GREATER THAN 3.5MG ARE NOT USUALLY NECESSARY AND LOW DOSES AS LITTLE AS 1-2MG (1-2ML) MAY BE ADEQUATE, THE INITIAL DOSE SHOULD NOT EXCEED 1-1.5MG (1-1.5ML).

Children: Midazolam Injection has not been evaluated for use as an intravenous sedative in children.

Combination therapy: Where analgesia is provided by a narcotic analgesic, the latter should be administered first, the dose of Midazolam should then be carefully titrated and low doses 1-2mg (1-2ml) may be adequate. In the elderly, smaller doses as little as 0.5mg-1ml (0.5-1.0ml) may be adequate.

Mode of administration: For the administration of Midazolam the patient should be placed in a supine position and remain there throughout the procedure. Resuscitation facilities should always be available and a second person fully trained in the use of such equipment, should always be present. It is recommended that patients should remain under medical supervision until at least 1 hour has elapsed from the time of injection. They should always be accompanied home by a responsible adult.
Patients who have received only Midazolam IV sedation prior to minor procedures, should be warned not to drive or operate machinery for 12 hours.
Where Midazolam is used concurrently with other central nervous system depressants (e.g. potent analgesics) recovery may be prolonged. Patients should therefore be assessed carefully before being allowed to go home or resume normal activities.

Sedation in the critically ill patient: Midazolam can be given intravenously by two methods for this purpose, either by continuous infusion or by intermittent bolus dose. Both have their own advantages and disadvantages and the appropriate method of giving Midazolam will need to be determined for each patient.
The dose of Midazolam needed to sedate critically ill patients varies considerably between patients. The dose of Midazolam should be titrated to the desired state of sedation. This will depend on the clinical need, physical status, age and concomitant medication.
Midazolam can also be given in combination with an opioid. The opioid may be used for its analgesic effects or as an antitussive agent to help the patient tolerate the tracheal tube and ventilatory support.
Patients receiving Midazolam for sedation in the intensive care situation should receive ventilatory support.

Safety of the use of Midazolam for periods of over 14 days in duration has not been established in clinical trials.
After prolonged iv administration of Midazolam, abrupt discontinuation may be accompanied by withdrawal symptoms, therefore a gradual reduction of Midazolam is recommended.

Potential drug interactions: The critically ill patient is exposed to many drugs. Because of this, there is a potential for drug interactions. (See interactions section under Contra-indications, warnings, etc.)

Sedation by intermittent bolus dose in intensive care Midazolam only: The exact dose of Midazolam needs to be titrated to the individual patient response. Small doses of Midazolam 1.0 – 2.0mg (1-2ml) can be given, and repeated, until the required degree of sedation is reached.

Midazolam and an opioid: When Midazolam and an opioid are used together, the opioid should be given first. Both drugs need to be titrated to the individual patient's response and to the level of sedation thought to be necessary. Small doses of Midazolam 1-2mg can be given, and repeated, until the required degree of sedation is reached. In the elderly, smaller doses as little as 0.5-1.0mg (0.5-1.0ml) may be adequate.
The use of these two groups of drugs can increase the risk of respiratory depression. If the patient is being given ventilatory support, using a mode that depends upon some spontaneous effort by the patient, then the minute volume may decrease.

Sedation by continuous infusion in intensive care Midazolam only:
Adults and children: Loading dose: For patients already sedated or anaesthetised after an operation, a loading dose of midazolam is unnecessary. In other situations a loading dose of 0.03 – 0.3 mg/kg is recommended depending on the level of sedation required. This should be given over a five minute period. The loading dose should be reduced or omitted in hypovolaemic, vasoconstricted or hypothermic patients.
Maintenance dose: A dose between 0.03 – 0.2 mg/kg/hour is recommended, starting at the lower dose.
The dose should be reduced in hypovolaemic, vasoconstricted or hypothermic patients.

Midazolam and an opioid: When opioid analgesics are used, the rate of infusion of Midazolam should be titrated carefully to the sedative needs of the patient. Low doses of Midazolam, 0.01 to 0.1mg/kg/hour may be used to start. The use of these two groups of drugs an increase the risk of respiratory depression. If the patient is being given ventilatory support, using a mode that depends upon some spontaneous effort by the patient, then the minute volume may decrease.

Whenever a continuous infusion of Midazolam is used (with or without an opioid analgesic), its need should be assessed on a daily basis in order to reduce the risk of accumulation and prolonged recovery. Each day, the infusion of Midazolam should be stopped or its rate reduced and the patient

seen to recover from its effect. If recovery is prolonged (>2 hours) a lower dose should be used when it is restarted. A sedation score should be used routinely.
When Midazolam has been given for a number of days and then gradually withdrawn, patients may be awake but show no signs of residual sedation for the next 12 to 24 hours. This can cause difficulties because patients may not cough and expectorate will when weaned from ventilatory support. However, while recovering from the effects of Midazolam, patients may not be sufficiently sedated to tolerate ventilatory support. In such circumstances sedation may be provided with a shorter acting agent while there is recovery from the effects of Midazolam.

The recommended concentration of a solution for infusion in a critically ill adult patient is 1mg/ml.

Intravenous induction of anaesthesia: One or more bolus intravenous injections over a single anaesthetic session.

Adults: The dose should be titrated against the individual response of the patient. Midazolam should be given by slow intravenous injection until there is a loss of eyelid reflex, response to commands and voluntary movements. In anticipating the required dose of Midazolam, both the premedication already given and the age of the patient are important. Young, fit unpremedicated patients may need at least 0.3mg/kg body-weight, whereas patients premedicated with an opiate usually need only 0.2mg/kg body-weight.

Elderly: THE ELDERLY ARE MORE SENSITIVE TO THE EFFECTS OF BENZODIAZEPINES. INDUCTION MAY BE ADEQUATE WITH 0.1MG/KG BODY-WEIGHT IN UNPREMEDICATED PATIENTS AND 0.2MG/KG BODY-WEIGHT IN UNPREMEDICATED PATIENTS.

Children over 7 years: Midazolam has been shown to be an effective agent for induction of anaesthesia in children over 7 years of age, at a dose of 0.15mg/kg body-weight.

Intramuscular premedication: Adults: A single intramuscular injection of 0.07 – 0.1 mg/kg body-weight, given 30-60 minutes before anaesthesia, has been shown to be adequate in most cases. The usual dose is about 5mg.
Atropine or hyoscine hydrobromide may be given concomitantly, bearing in mind that hyoscine hydrobromide will enhance and prolong the sedative and amnesic effects of Midazolam.

Elderly: THE ELDERLY ARE MORE SENSITIVE TO THE EFFECTS OF BENZODIAZEPINES AND IN THESE PATIENTS A LOWER DOSE OF 2.5MG MAY BE ADEQUATE.

Children: Midazolam has not been evaluated for use as an intramuscular premedicant in children.

4.3. Contra-indications

- Known Benzodiazepine sensitivity.
- Pregnancy - unless the benefits outweigh the possible risks.
- Hypersensitivity to the active substance, other benzodiazepines or any of the excipients.
- Myasthenia Gravis
- Severe respiratory insufficiency
- Sleep apnoea syndrome
- Severe liver failure
- Acute intoxication with alcohol, hypnotics, neuroleptics, antidepressants or lithium
- Acute narrow angle glaucoma

4.4. Special Warnings and Precautions for Use

Midazolam is a potent sedative agent and there is a wide variation in susceptibility to its effects. Deaths have been reported to the UK Committee on Safety of Medicines associated with respiratory and cardiovascular depression. It is therefore essential that the drug is only used intravenously by those skilled in resuscitation and tracheal intubation. A means of ventilating the lungs and full resuscitative apparatus must always be available when the drug is given intravenously. Flumazenil as an antidote should also be available.

Patients with chronic respiratory disease may be particularly sensitive to the respiratory depressant effects of intravenous midazolam and exhibit a more marked and prolonged depression than healthy subjects.

In hypovolaemia, vasoconstriction or hypothermia, the dose should be reduced, or the initial dose omitted.

Low doses may be adequate if an opioid analgesic is also used.

After prolonged administration of Midazolam, abrupt discontinuation may be accompanied by withdrawal symptoms, therefore a gradual reduction of Midazolam is required.

Elderly patients tend to be particularly sensitive to midazolam.

Liver disease may delay elimination of midazolam, thus prolonged sedation may result as this may be accompanied by withdrawal symptoms.

Midazolam should be given with care with compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 IIA) as these compounds influence the pharmacokinetics of Midazolam and may lead to prolonged sedation.

4.5. Interactions with other Medicaments and other forms of Interaction

Alcohol
The sedative effects may be enhanced when Midazolam Injection is used in combination with alcohol. This affects the ability to drive or use machines. Concomitant use with alcohol is therefore not recommended for at least 8 hours after administration of Midazolam.

Opioids, barbiturates, sedatives and anaesthetics
Midazolam will also potentiate the central depressant effects of opioids, barbiturates, and other sedatives and anaesthetics; profound and prolonged respiratory depression may result. Severe hypotension has occurred when midazolam was used along with high dose fentanyl.

Ketamine
Midazolam will attenuate the increase in heart rate and arterial blood pressure produced by anaesthetic doses of ketamine and will also reduce the psychotic sequelae following ketamine anaesthesia.

Erythromycin
The metabolism of midazolam is inhibited by erythromycin, this results in increased plasma-midazolam concentration, with profound sedation.

Antifungals
Itraconazole, ketoconazole and possibly fluconazole increase plasma concentrations of midazolam, prolonging the sedative effect.

Diltiazem and Verapamil
Diltiazem and verapamil inhibit the metabolism of midazolam, resulting in increased plasma-midazolam concentration, with increased sedation.

Rifampicin
The metabolism of midazolam is increased by rifampicin, because rifampicin induces certain P450 enzymes that are responsible for the oxidation of the midazolam.

There is a potentially relevant between Midazolam and compound that inhibit certain hepatic enzymes (particularly cytochrome P450 IIIA). Data clearly indicate that these compounds influence the pharmacokinetics of Midazolam and may lead to prolonged sedation. At present this interaction is known to occur with cimetidine, erythromycin, diltiazem, verapamil, ketoconazole and itraconazole. These is also a theoretical possibility that, by competitive inhibition of P450 IIA, Midazolam could potentiate the effects of other drugs which are metabolised by this isoenzyme e.g. cyclosporin, nifedipine. Therefore patients receiving the above compounds or others which inhibit P450 IIA together with Midazolam should be monitored carefully for the first

few hours after administration of Midazolam (Studies show that Ranitidine has no influence on the pharmacokinetics of parenterally given Midazolam).

The following drugs may enhance the sedative effect of benzodiazepine drugs such as midazolam:

Antihistamines	Lofexidine
Antipsychotics	Baclofen
Alpha-blockers	Nabilone
Disulfiram	Cimetidine

4.6. Pregnancy and Lactation

Pregnancy: Animal experiments have not indicated any teratogenic risk with Midazolam but evaluation in human pregnancy has not been undertaken. Therefore, Midazolam should not be used during pregnancy, especially in the first trimester, unless this is considered essential by the physician.
The administration of high single doses of benzodiazepines in the last trimester of pregnancy has been reported to product irregularities in the foetal heart rate, and hypotonia, poor sucking and hypothermia in the neonate. Midazolam should not therefore be used during the last trimester

Lactation: Midazolam may pass into breast milk and caution should be exercised with its use in lactating mothers.

4.7. Effects on Ability to Drive and Use Machines

Sedation, amnesia and impaired muscular function may adversely affect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased (see also Interactions), therefore after the administration of Midazolam the patient should avoid driving or using machinery for 12 hours, or longer if prolonged sedation or when used with other CNS depressants. This time should be increased if prolonged sedation occurs or when Midazolam is used with other CNS depressants.

4.8. Undesirable Effects

Midazolam can cause respiratory and cardiovascular depression, ventricular irritability and a change in the baroreflex control of heart rate. There is a wide variation in susceptibility to its effects, the elderly being particularly sensitive. Respiratory depression, respiratory arrest, hypotension and even death have been reported following its use, usually during conscious sedation.

Adverse effects following intravenous midazolam include agitation, involuntary movements, confusion, slurred speech, blurred vision, lethargy,

and dizziness and occur in less than 1% of patients receiving midazolam parenterally. Nausea and vomiting occur in 2-3% of patients following intravenous use.

Paradoxical reactions e.g. agitation, restlessness and disorientation have been reported, although this is rare.

Hallucinations, some of a sexual nature, have been reported

Pain on injection is rare following intravenous midazolam, while thrombosis and thrombophlebitis occur in less than 1% of cases and is less common than with diazepam with organic solvents.

Like other anaesthetics, midazolam is known to depress renal blood flow and renal function.

4.9. Overdose

The results of an overdose of midazolam are likely to be an extension of the usual pharmacological effects of the benzodiazepines with sedation, confusion, somnolence, impaired co-ordination, diminished reflexes, and coma. The effects are rapidly reversed with flumazenil, although central depression may return after use of the latter, because of its shorter duration of action. Patients requiring such intervention should, therefore, be monitored closely in hospital.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Midazolam is an imidazo benzodiazepine with properties very similar to those of other benzodiazepines. Thus it binds to benzodiazepine receptors in various regions of the CNS such as the spinal cord, brain stem, cerebellum, limbic system and the cerebral cortex.

Benzodiazepines like midazolam block EEG arousal from stimulation of the brainstem reticular formation. Midazolam acts as a CNS depressant on CNS reflexes via the brain stem reticular formation. Midazolam produces anterograde amnesia similar to that produced by diazepam but neither benzodiazepine produces retrograde amnesia.

Midazolam produces sedation, anxiolysis and hypnosis.

5.2. Pharmacokinetic Properties

After rapid injection of midazolam 0.15mg/kg intravenously, plasma levels at 5 minutes can vary from 291 to 425µg/l and due to its rapid distribution had fallen to approximately 10% of these values within 2 hours.

Following intravenous administration, it is rapidly and widely distributed, with a steady-state volume of distribution of 39-68L (0.8-1.7 l/Kg). The kinetics are adequately described by a two-compartment model with an elimination half-life of 2-3 hours; this is prolonged in the elderly and half lives of over 10 hours have been reported. The t½β is short compared with other benzodiazepines. Total body clearance is 6.4-11.1 ml/min/Kg (plasma clearance 268-630 ml/min). There is no evidence of any significant enterohepatic circulation.

Midazolam is extensively bound to plasma proteins (94-98%) and small changes in protein binding will produce large changes in the amount of available free drug, which has important consequences in clinical practice. The free fraction is higher in patients with chronic renal failure.

Less than 1% of midazolam is excreted unchanged in the kidneys and the drug is cleared virtually entirely by liver metabolism. The half-life of midazolam is prolonged in those with liver disorders; thus the elimination of midazolam is delayed. Prolonged sedation has resulted from use of the drug in severely ill patients with reduced hepatic blood flow.

Midazolam is oxidised by a member of the P450 IIIA sub-family and thus concentrations of the drug may be reduced in patients receiving inducers of these microenzymes, such as macrolide antibiotics (e.g. rifampicin) and anticonvulsants (e.g. phenytoin). L-hydroxymethylmidazolam, the major metabolite is less active than midazolam and has a half-life of about one hour. Midazolam metabolites are excreted in the urine, mainly as glucuronide conjugates.

5.3. Preclinical Safety Data

There are no pre-clinical safety data of relevance to the prescriber that are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric Acid
Sodium Chloride
Sodium Hydroxide
Water for Injections

6.2. Incompatibilities

Midazolam is incompatible with certain parenteral solutions, causing precipitation. A white precipitate forms immediately on mixing dimenhydrinate, pentobarbital sodium, perphenazine, prochlorperazine edisylate or ranitidine. Y-site injection of midazolam with Foscarnet Sodium causes gas production; with Methotrexate Sodium a yellow precipitate is produced; with Sodium Bicarbonate, and with Thiopental Sodium, a white precipitate forms immediately.
The medicinal product must not be diluted with other solutions for parenteral use other than those mentioned in section 6.6, instructions for use/handling. Compatibility must be checked before administration, if intended to be mixed with other drugs.

6.3 Shelf life

2 Years

6.4. Special Precautions for Storage

Do not store above 25°C
Keep container in the outer carton

6.5 Nature and contents of container

Sterile aqueous solution for injection in borosilicate glass (type I) 5ml and 10ml pre-filled syringes with a chlorobutyl elastomer syringe piston. Also available as a cyclo-olefin copolymer plastic 50ml pre-filled syringe with a halobutyl elastomer piston and tip cap.

6.6. Instruction for Use and Handling

Midazolam solution is stable, both physically and chemically, for up to 24 hours at room temperature when mixed with 500ml infusion fluids, containing Dextrose 4% with Sodium Chloride 0.18%, Dextrose 5% or Sodium Chloride 0.9%.
Midazolam solution is stable, both physically and chemically, for up to 1 hour at room temperature when mixed in the same syringe with Atropine Sulphate Injection 500 micrograms/ml, or Hyoscine Hydrobromide Injection 0.4 mg/ml.
There is no evidence of adsorption of Midazolam onto the plastic of infusion apparatus or syringes.
Use once only and discard container and any remaining solution in appropriate manner.

7 MARKETING AUTHORISATION HOLDER

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