



This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ZYAMIS (MIDAZOLAM) OROMUCOSAL SOLUTION

1. NAME OF THE MEDICINE

Midazolam

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZYAMIS midazolam 2.5 mg/0.25 mL oromucosal solution.

Each pre-filled, oral syringe (0.25 mL) contains midazolam maleate equivalent to 2.5 mg midazolam per 0.25 mL solution.

ZYAMIS midazolam 5 mg/0.5 mL oromucosal solution.

Each pre-filled, oral syringe (0.5 mL) contains midazolam maleate equivalent to 5 mg midazolam per 0.5 mL solution.

ZYAMIS midazolam 7.5 mg/0.75 mL oromucosal solution.

Each pre-filled, oral syringe (0.75 mL) contains midazolam maleate equivalent to 7.5 mg midazolam per 0.75 mL solution.

ZYAMIS midazolam 10 mg/1 mL oromucosal solution.

Each pre-filled, oral syringe (1 mL) contains midazolam maleate equivalent to 10 mg midazolam per 1 mL solution.

Excipients with known effect include ethanol, saccharin sodium and maltitol solution.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Oromucosal solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

ZYAMIS, as buccal midazolam, is indicated for the treatment of Generalised Convulsive Status Epilepticus (GCSE), in those over 6 months old.

4.2 Dose and method of administration

The initial prescription must be initiated by a specialist physician experienced in the treatment of epilepsy.

ZYAMIS, when used by parents/caregivers, must only be used where the patient has been diagnosed by a medical practitioner to have epilepsy.

The medicine contains no preservatives. The medicine is for single use in one patient only.

The standard doses are summarised in the table below:

Table 1: Proposed Dose of ZYAMIS (midazolam)

Age Range	Weight Range	Dose
> 6 months to < 1 year	7 to <12 kg	2.5 mg
1 year to < 5 years	12 kg to <21 kg	5 mg
5 years to < 10 years	21 kg to <29 kg	7.5 mg
10 years and above	≥29 kg	10 mg

The recommended dose for adults is 10 mg. A second dose should only be given in accordance with either the patient's individual written care plan or as authorised by the medical practitioner.

Carers should only administer a single dose of ZYAMIS. They should seek emergency medical assistance – telephone for an ambulance immediately – if the patient's seizure does not stop shortly after administering ZYAMIS.

Carer's must be thoroughly trained by the prescriber on how to act if a seizure continues after a single dose of ZYAMIS.

After receiving ZYAMIS, patients should be kept under supervision by a carer who remains with the patient.

A second or repeat dose when seizures re-occur after an initial response should not be given without prior medical advice. The increased possibility of respiratory depression should be considered.

Special Dosage Instructions

Obesity

No efficacy studies of midazolam in obese children have been reported. The elimination half-life of midazolam is prolonged in obese patients. The clearance is not altered.

Patients with renal impairment

No efficacy studies of midazolam in children with severe renal impairment have been reported. In patients with severe renal impairment, this may result in delayed elimination of midazolam. Multiple doses of midazolam in such patients may be accompanied by more pronounced and prolonged effects. However, in the setting of treatment of an acute epileptic seizure with a single or 2 doses of midazolam, accumulation of parent drug or metabolite is unlikely to occur.

Hepatic impairment

The clinical effects in patients with hepatic impairment may be stronger and prolonged. The dose of ZYAMIS may have to be reduced and vital signs should be monitored (see section 4.4 Special warnings and precautions for use, Use in hepatic impairment and 5.2 Pharmacokinetic properties). No efficacy studies of midazolam in children with chronic hepatic impairment have been reported.

Careful monitoring of the clinical effects and vital signs is recommended following administration of ZYAMIS in patients with hepatic impairment (See Section 4.4). Doses, especially repeated doses, may have to be reduced.

Critically Ill Patients

No efficacy studies of midazolam in critically ill children have been reported.

Cardiac Insufficiency

No efficacy studies of midazolam in children with cardiac insufficiency have been reported.

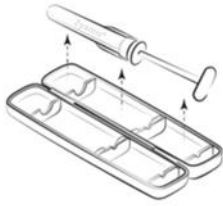
Method of Administration

ZYAMIS is for buccal use. It is only to be used in the mouth.

Precautions to be taken before handling or administering the medicinal product:

The amber sheath cap should be removed before use.

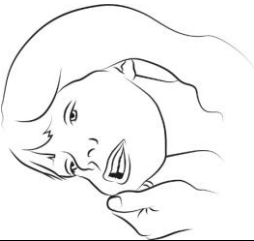
Using the pre-filled oral syringe provided, administer, over a period of 2-3 seconds, approximately half of the prescribed dose to each buccal cavity (space between the gum and the cheek). Laryngo-tracheal insertion should be avoided to prevent accidental aspiration of the solution. If it is particularly difficult to get the syringe into the buccal cavity, then administer the whole dose, over a period of 4-5 seconds, to one buccal cavity.

**Step 1**

Pull the tamper evident tab on the side of the polypropylene secondary packaging case, open it and take the syringe out.

**Step 2**

Holding the clear finger grips, unscrew the amber sheath cap in an anti-clockwise direction and remove the amber sheath cap.

**Step 3**

Gently roll the person onto one side (recovery position) if safe and practical to do so. Open their lips and place the tip of the syringe into the back of the space between the inside cheek and the lower gum (buccal cavity).

**Step 4**

Slowly administer approximately half of the solution to the buccal cavity on one side of the mouth, and then administer the remainder slowly to the other side, by pressing the syringe plunger until it stops. If it is particularly difficult to get the syringe into one buccal cavity, then administer the whole dose over a duration of 4 – 5 seconds into the other buccal cavity.

Step 5: Watch breathing and seizure activity while they remain lying on their side in the first aid position.

Step 6: Note the time that the seizure started, when the ZYAMIS was given and when the seizure stopped.

4.3 Contraindications

ZYAMIS should not be used in patients with myasthenia gravis, or those with hypersensitivity to benzodiazepines or any of their formulation excipients.

ZYAMIS should not be administered to patients in shock or coma, or in acute alcoholic intoxication with depression of vital signs.

Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma only if they are receiving appropriate therapy. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with Hypnovel; patients with glaucoma have not been studied.

4.4 Special warnings and precautions for use

Administration precautions

No needle, intravenous tubing or any other device for parenteral administration should be attached to the oral syringe. ZYAMIS is for oromucosal use only.

Care must be taken when administering the product to avoid the risk of the patient choking.

Vital signs should continue to be monitored during the recovery period.

Respiratory insufficiency

Midazolam should be used with caution in patients with limited pulmonary reserve because of the possibility that apnoea or respiratory depression may occur. Such patients are unusually sensitive to the respiratory depressant effect of midazolam.

Midazolam should be used with extreme caution in patients with sleep apnoea syndrome and patients should be regularly monitored.

Cerebral hypoxia or true paradoxical reactions

While the following reactions may be due to inadequate or excessive dosing, however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions: restlessness, agitation, irritability, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, combativeness, delusion, anger, aggressiveness, anxiety, nightmares, hallucinations, psychoses, inappropriate behaviour or other adverse behavioural effects have been reported.

Altered elimination of midazolam

Midazolam should be used with caution in patients with chronic renal insufficiency, impaired hepatic or cardiac function. Midazolam may accumulate in patients with chronic renal insufficiency, or impaired hepatic function (benzodiazepines may precipitate or exacerbate encephalopathy in patients with severe hepatic impairment), whilst in patients with impaired cardiac function it may cause decreased clearance of midazolam.

Debilitated patients

Debilitated patients are more prone to the central nervous system (CNS) effects of benzodiazepines. Particular care should be exercised in the use of ZYAMIS in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

Risk from concomitant use of opioids

Concomitant use of midazolam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as midazolam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe midazolam concomitantly with opioids, the lowest effective dose and the shortest possible duration of opioids should be used.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see Section 4.5).

Concomitant use of other central nervous system depressants

Concomitant use of barbiturates, alcohol or other central nervous system depressants increases the risk of under-ventilation or apnoea and/or cardio-ventricular depression and may contribute to a profound and/or prolonged drug effect that could result in coma or death.

Abuse Potential

As with other benzodiazepines, midazolam may have the potential to cause dependence, the risk of which increases with the duration of treatment.

Benzodiazepines, such as midazolam should be avoided in patients with a medical history of alcohol or drug abuse.

This should be considered when prescribing or dispensing of ZYAMIS (or midazolam) in situations where this is concern about and increase risk of misuse, abuse or diversion. All patients treated with benzodiazepines should be carefully monitored for signs of abuse or addiction.

Use in renal impairment

There is a greater likelihood of adverse drug reactions in patients with severe renal impairment (see section 4.2 Dose and method of administration, Special dosage instructions and 5.2 Pharmacokinetic properties, Pharmacokinetics in special populations).

Use in hepatic impairment

Hepatic impairment reduces the clearance of i.v. midazolam with a subsequent increase in terminal half-life. Therefore, the clinical effects may be stronger and prolonged. The required dose of midazolam may have to be reduced and proper monitoring of vital signs should be established (see section 4.2 Dose and method of administration, Special dosage instructions and 5.2 Pharmacokinetic properties, Pharmacokinetics in special populations).

Paediatric Use

Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/analgesic/sedation drug administration or other factors such as the surgery or underlying illness.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy. The clinical significance of these nonclinical finding is yet to be determined.

Excipient precautions

MALTITOL

This product contains maltitol solution. Patients with rare hereditary problems of fructose intolerance should not be given this medicine unless the benefits are considered to outweigh the risks.

SODIUM

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

There is a potentially relevant interaction between midazolam and compounds which inhibit or induce certain hepatic enzymes (particularly CYP3A). Data clearly indicate that these compounds influence the pharmacokinetics of midazolam and this may lead to altered degree and/or duration of action. At present, enzyme induction is known to occur *in vivo* with rifampicin, carbamazepine and phenytoin, and enzyme inhibition occurs with cimetidine, erythromycin, diltiazem, verapamil, ketoconazole, fluconazole, itraconazole, ritonavir and saquinavir.

During long-term midazolam infusions, a reduction of up to 50% of the initial dose followed by careful titration is recommended. Studies have shown that ranitidine has no influence on the pharmacokinetics of parenterally given midazolam.

Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to oromucosal or parenteral midazolam as CYP3A4 enzymes are also present in the upper gastro-intestinal tract. After buccal administration, only systemic clearance will be affected. After a single dose of oromucosal midazolam, the consequence on the maximal clinical effect due to CYP3A4 inhibition will be minor while the duration of effect may be prolonged. Hence, careful monitoring of the clinical effects and vital signs is recommended during the use of midazolam with a CYP3A4 inhibitor even after a single dose.

Simultaneous administration of cimetidine (but not ranitidine) has been reported to reduce clearance of midazolam.

Displacement of midazolam from its plasma protein binding sites by sodium valproate may increase the response to midazolam and, therefore, care should be taken to adjust the midazolam dosage in patients with epilepsy.

The effects of midazolam can be reversed by the benzodiazepine antagonist flumazenil.

Pharmacokinetic Drug-Drug Interaction (DDI)

Midazolam is almost exclusively metabolised by CYP3A (primarily CYP 3A4 and also CYP 3A5). Inhibitors and inducers of CYP3A have the potential to increase and decrease the plasma concentrations and, subsequently, the pharmacodynamic effects of midazolam. No mechanism other than modulation of CYP3A activity has been proven as a source for a clinically relevant pharmacokinetic DDI with midazolam. However, acute protein displacement from albumin is a theoretical possibility of drug interaction with drugs that have high therapeutic serum concentrations, as has been hypothesized for valproic acid (see below). Midazolam is not known to change the pharmacokinetics of other drugs.

When co-administered with a CYP3A-inhibitor, the clinical effects of midazolam may be stronger and also longer lasting and a lower dose may be required. Conversely, the effect of midazolam may be weaker and the duration of effect shorter when co administered with a CYP3A-inducer and a higher dose may be required. The tuberculostatic drug, rifampicin, belongs to the strongest inducers of CYP3A and its co-administration resulted in a decrease in the $AUC_{0-\infty}$ of IV midazolam by approximately 60%.

In case of CYP3A induction and irreversible inhibition (so-called mechanism based inhibition), the effect on the pharmacokinetics of midazolam may persist for a period of several days up to several weeks after administration of the CYP3A modulator. Examples of mechanism based CYP3A inhibitors include antibacterials (e.g. clarithromycin, erythromycin, isoniazid); anti- retroviral agents (e.g. HIV protease inhibitors, such as ritonavir (including ritonavir-boosted protease inhibitors), delavirdine); calcium channel blockers (e.g. verapamil, diltiazem); tyrosine kinase inhibitors (e.g. imatinib, lapatinib, idelalisib, or the oestrogen receptor modulator, raloxifene and several herbal constituents (e.g. bergamottin). In contrast to other mechanism based inhibitors, ethinyloestradiol combined with norgestrel or gestodene (used for oral contraception) and grapefruit juice (200 mL) did not modify exposure to midazolam to a clinically significant degree.

The range of the inhibiting/inducing potency of drugs is wide.

Drugs that inhibit CYP3A

Medicinal product interactions following buccal administration of midazolam are likely to be similar to those observed after intravenous midazolam rather than oral administration.

Patients receiving compounds which inhibit CYP3A should not be administered midazolam whenever possible. Otherwise, the dose of ZYAMIS should be adjusted and the patient kept under careful surveillance. In line with pharmacokinetic principles, clinical studies have shown that after a single IV dose of midazolam, in the presence of CYP3A inhibition, the change in maximal clinical effect due to CYP3A modulation will be minor, whereas the duration of effect may be prolonged. However, after prolonged dosing of midazolam, both the magnitude and duration of effect may be increased.

Azole antifungals

- *Ketoconazole and voriconazole*: Increased the $AUC_{0-\infty}$ of IV midazolam by 5-fold and 3-4 fold respectively, while the terminal half-life increased by approximately 3-fold.
- *Fluconazole and itraconazole*: Both increased the $AUC_{0-\infty}$ of IV midazolam, which was associated with a 2.4-fold and 1.5-fold increase in terminal half-life for itraconazole and fluconazole, respectively. A 100 – 300% increase in plasma midazolam at 48 hours after receiving fluconazole was commonly (3/10) seen in intensive care unit patients with a midazolam infusion. Orally, fluconazole increased C_{max} 1.7-fold and $AUC_{0-\infty}$ 3.6-fold, while for itraconazole they increased 2.5- and 6.6- fold, respectively.
- *Posaconazole*: Increased the $AUC_{(tf)}$ (AUC zero to last measurable concentration) of IV midazolam by 1.8-fold.

Macrolide antibiotics

- *Erythromycin*: Resulted in an increase in the $AUC_{(tf)}$ of IV midazolam and was associated with a 1.4 – 1.8-fold increase in the terminal half-life of midazolam.
- *Clarithromycin*: Increased the AUC of IV midazolam by approximately 2.5-fold and was associated with a 2.7-fold increase in terminal half-life.

Additional information from oral midazolam

- *Telithromycin* increased the plasma levels of oral midazolam 6-fold.
- *Roxithromycin* has less of an effect on the pharmacokinetics of midazolam than erythromycin or clarithromycin. After oral administration with roxithromycin the maximum plasma concentration (C_{max}) of midazolam increased approximately 40% compared with increases of 2.7-fold caused by erythromycin and 2.8-fold with clarithromycin, while the 40% increase in $AUC_{0-\infty}$ is matched by 4.4-fold and 7-fold increases, respectively. The mild effect on the terminal half-life of midazolam (~ 30%) indicates that the effects of roxithromycin on IV midazolam may be minor.

Intravenous anaesthetics

- Disposition of intravenous midazolam was also changed by intravenous propofol (AUC and half-life increased by 1.6 fold).

Protease inhibitors

- *Saquinavir and other HIV protease inhibitors*: If parenteral midazolam is co-administered with HIV protease inhibitors, treatment setting should follow the description in the section above for ketoconazole within azole antifungals.
- *HCV protease inhibitors*: Boceprevir and telaprevir reduce midazolam clearance. This effect resulted in a 3.4-fold increase of midazolam AUC after i.v. administration and prolonged its elimination half-life 4-fold.

Histamine receptor 2 antagonists

- *Cimetidine* increased the steady state plasma concentration of midazolam by 26%.

Calcium-channel blockers

- *Diltiazem*: After pre-treatment with lorazepam and a single dose of diltiazem, on cessation of an IV infusion of midazolam, the AUC from cessation for 23 h increased approximately 25% and the terminal half-life was prolonged approximately 43%.

Additional information from oral midazolam

- *Verapamil* increased the C_{max} of oral midazolam 2-fold, while $AUC_{0-\infty}$ increased 3- and 4-fold, respectively. The terminal-half-life of midazolam increased 41%.

Various drugs/Herbs

- *Atorvastatin*: Increased the AUC of IV midazolam by approximately 1.4-fold compared with control group.
- *Intravenous fentanyl* is a weak inhibitor of midazolam's elimination: AUC and half-life of i.v. midazolam were increased by 1.5-fold in presence of fentanyl.

Additional information from oral midazolam

- *Fluvoxamine*: Increased the $AUC_{0-\infty}$ and C_{max} of oral midazolam 40% and doubled the terminal half-life.
- *Nefazodone*: Increased the $AUC_{0-\infty}$ of oral midazolam 4.6-fold with an increase in C_{max} of 1.8-fold and in terminal half-life of 1.6-fold.
- Tyrosine kinase inhibitors have been shown either in vitro (imatinib, lapatinib or after oral administration in vivo (idelalisib) to be potent inhibitors of CYP3A4. After concomitant administration of idelalisib, oral midazolam exposure was increased on average 5.4-fold.
- NK1 receptor antagonists (aprepitant, netupitant, casoprepitant): Dose-dependently increased the AUC of oral midazolam up to approximately 2.5-3.5 fold and increased terminal half-life by approximately 1.5-2 fold.
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- Chlorzoxazone: Decreased the ratio of the CYP3A-generated metabolite α -hydroxymidazolam to midazolam, indicating a CYP3A-inhibiting effect of chlorzoxazone.
- For a number of drugs or herbal medicines, a weak interaction with midazolam's elimination was observed with concomitant changes in its exposure (< 2 -fold change in AUC) (bicalutamide, everolimus, cyclosporine, simeprevir, propiverine, berberine as also contained in goldenseal). These weak interactions are expected to be further attenuated after i.v. administration.

Drugs that induce CYP3A

- Rifampicin (600 mg o.d.) decreased the AUC of IV midazolam by approximately 60% after 7 days. The terminal half-life decreased by approximately 50 - 60%.
- Ticagrelor is a weak CYP3A activator in vitro but has only small effects on intravenously administered midazolam (-12%) and 4-hydroxy-midazolam (-23%) exposures.

Additional information from oral midazolam

- Carbamazepine and phenytoin: Repeat dosages of carbamazepine or phenytoin resulted in a decrease in the AUC and C_{max} of oral midazolam by over 90% and a shortening of the terminal half-life by almost 60%.
- The very strong CYP3A4 induction seen after mitotane or enzalutamide resulted in a profound and long-lasting decrease of midazolam levels in cancer patients. AUC of orally administered midazolam was reduced to 5% and 14% of normal values respectively.
- Clobazam and Efavirenz: are weak inducers of midazolam metabolism and reduce the AUC of the parent compound by approximately 30%. There is a resulting 4-5-fold increase in the ratio of the active metabolite (α -hydroxy-midazolam) to the parent compound but the clinical significance of this is unknown.
- Vemurafenib modulates CYP isozymes and inhibits CYP3A4 mildly: Repeat-dose administration resulted in a mean decrease of oral midazolam exposure of 39% (up to 80% in individuals).

Herbs and food

- *Echinacea purpurea root extract*: Decreased the AUC of IV midazolam 20% and was associated with a decrease in half-life of approximately 42%.
- *St John's wort*: Decreased the AUC of IV midazolam by approximately 20% and AUC of oral midazolam by 50% with C_{max} decreased by 40 - 50%. It was associated with a decrease in terminal half-life by approximately 16 - 19%.

Additional information from oral midazolam

- Quercetin (also contained in Gingko biloba) and Panax ginseng both have weak enzyme inducing effects and reduced exposure to midazolam after its oral administration to the extent of 20-30%.

Acute protein displacement

- *Valproic acid*: Increased concentrations of free midazolam due to displacement from plasma protein binding sites by valproic acid cannot be excluded although the clinical relevance of such an interaction is not known.

Pharmacodynamic Drug-Drug Interactions (DDI)

The co-administration of midazolam with other sedative/hypnotic agents, including alcohol, is likely to result in increased sedative/hypnotic effects. Examples include opiates/opioids (when they are used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines (used as anxiolytics or hypnotics), barbiturates, propofol, ketamine, etomidate, sedative antidepressants, antihistaminics and centrally acting antihypertensive drugs. Midazolam decreased the minimum alveolar concentration (MAC) of Halothane.

Enhanced effects such as sedation and cardio-respiratory depression may also occur when midazolam is co-administered with any centrally acting depressants including alcohol. Therefore, adequate monitoring of vital signs should be established. Alcohol should be avoided in patients receiving midazolam (see sections 4.4 Special warnings and precautions for use and 4.9 Overdose for warning of other CNS depressants, including alcohol).

Drugs increasing alertness/memory such as the acetylcholinesterase inhibitor physostigmine, reversed the hypnotic effects of midazolam. Similarly, 250 mg of caffeine partly reversed the sedative effects of midazolam.

Disulfiram: ZYAMIS contains a small amount of alcohol and therefore should not be co-administered with disulfiram.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

A reproduction study in male and female rats did not show any impairment of fertility at dosages up to 10 times the human IV dose of 0.35 mg/kg.

Use in Pregnancy: Category C

Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. Midazolam crosses the placenta and the administration of midazolam in the last weeks of pregnancy or at high doses during labour have resulted in neonatal CNS depression and can be expected to cause irregularities in the foetal heart rate, hypothermia, hypotonia, poor sucking and moderate respiratory depression due to the pharmacological action of the product. Moreover, infants born to mothers who received benzodiazepines chronically during the latter stage of pregnancy may have developed physical dependence, and may be at some risk of developing withdrawal symptoms in the postnatal period. Midazolam is therefore not recommended for obstetric use.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy.

Published studies in pregnant and juvenile animals demonstrate that the use of anaesthetic/analgesic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. These studies included anaesthetic agents from a variety of drug classes.

Teratological studies with midazolam in a number of animal species have not shown association between administration of the drug and disturbances of foetal development, nor has clinical experience so far yielded any evidence of such an association. Midazolam should not be used in the first three months of pregnancy.

An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested.

Use in Lactation

Midazolam passes in low quantities (0.6%) into breast milk. However, its effects on newborns are not known. Therefore, midazolam is not recommended for use in nursing mothers unless the benefits outweigh the risks.

4.7 Effects on ability to drive and use machines

Although highly unlikely that patients with the GCSE will be medically licensed to drive, patients should be warned to take extra care as a pedestrian and not to drive a vehicle or operate a machine until the patient has completely recovered from the effects of the drug, such as drowsiness. The physician should decide when activities such as driving a vehicle or operating a machine may be resumed. The patients' attendants should be made aware that the patients' anterograde amnesia may persist longer than the sedation and therefore, patients may not carry out instructions even though they appear to acknowledge them. If sleep duration is insufficient or alcohol is consumed, the likelihood of impaired alertness may be increased (see section 4.5 Interactions with other medicines and other forms of interactions).

4.8 Adverse effects (undesirable effects)

Table 2 lists the adverse reactions reported in the literature to occur when oromucosal midazolam was administered to children in clinical studies. The frequency of adverse reactions is classified as follows: Common: $\geq 1/100$ to $< 1/10$; Uncommon: $\geq 1/1,000$ to $< 1/100$; Very rare: $< 1/10,000$. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Tabulated list from literature studies of adverse reactions of buccal midazolam in children

System Organ Class	Frequency: Adverse Drug Reaction
Nervous system disorders	Common: Sedation, somnolence, depressed levels of consciousness Respiratory depression
Gastrointestinal disorders	Common: Nausea and vomiting
Skin and subcutaneous tissue disorders	Uncommon: Pruritus, rash and urticaria

Post-Marketing experience

Post-marketing experience has been reported during the period 10 Sep 2016 to 09 Sep 2019 for Midazolam 10 mg Oromucosal Solution. There were 90 non-serious and 83 serious AEs. This section provides a summary of where a minimum of two serious adverse reactions were reported during this time. The only non-serious adverse reactions reported more than twice during the 3-year interval included 'drug ineffective' (3 cases), 'drug interaction' (18 cases), 'product administered to patient of inappropriate age' (7 cases), and 'somnolence (18 cases). All the adverse reactions from post-marketing experience are classified as very rare ($<1/10,000$).

Cardiac Disorders: Very rare: Cardiac arrest, Tachycardia.

General Disorders and Administration Site Conditions: Very rare: Multiple organ dysfunction syndrome.

Immune System Disorders: Very rare: Anaphylactic reaction.

Injury, Poisoning and Procedural Complications: Very rare: Product administered to patient of inappropriate age.

Investigations: Very rare: Oxygen saturation decreased.

Nervous System Disorders: Very rare: Sedation, Seizure, Tremor, Unresponsive to stimuli.

Respiratory, Thoracic and Mediastinal Disorders: Very rare: Bronchospasm, Dyspnoea, Respiratory arrest, Respiratory depression.

Vascular Disorders Very rare: Hypotension.

The following additional adverse effects were reported subsequent to IV administration of midazolam.

Immune System Disorders: Generalised hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), angioedema, anaphylactic shock.

Psychiatric Disorders: Confusional state, disorientation, emotional and mood disturbances, hallucinations, dysphoria, changes in libido.

Paradoxical reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, nervousness, hostility, anger, aggressiveness, anxiety, nightmares, abnormal dreams, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, argumentativeness, nervousness, anxiety, irritability, tension, mood changes, restlessness, paroxysmal excitement and assault, have been reported, particularly among children and the elderly. In these cases, discontinuation of the drug should be considered.

Dependence: Use of midazolam, even in therapeutic doses, may lead to the development of physical dependence. Abuse has been reported in poly-drug abusers.

Nervous System Disorder: Prolonged sedation, decreased alertness, headache, dizziness, ataxia, dreaming during sleep, sleep disturbance, insomnia, athetoid movements, slurred speech, dysphonia, paraesthesia, postoperative sedation, anterograde amnesia, the duration and risk of which is directly related to the administered dose, with the risk increasing at higher doses. In isolated cases prolonged amnesia has been reported.

Convulsions have been reported in premature infants and neonates.

Cardiac Disorders: Severe cardio-respiratory adverse effects have occurred on rare occasions. These have included cardiac arrest, hypotension, bradycardia, vasodilating effects, bigeminy, premature ventricular contractions, tachycardia, nodal rhythm, cardiovascular collapse, and vasovagal episode. Life-threatening incidents are more likely to occur in adults over 60 years of age 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 (see section 4.4 *Special warnings and precautions for use*).

Respiratory Disorders: Severe cardio-respiratory adverse effects have occurred on rare occasions. These have included respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnoea. Life-threatening incidents are more likely to occur in adults over 60 years of age 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 (see section 4.4 *Special warnings and precautions for use*). Coughing, hiccoughs.

Gastrointestinal System Disorders: Nausea, vomiting, constipation, dry mouth, acid taste, retching, excessive salivation.

Skin and Appendages Disorders: Skin rash, urticaria, pruritus.

Ophthalmic Disorders: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, difficulty in focusing.

Miscellaneous: Yawning, lethargy, chills, weakness, continued phonation, ears blocked, loss of balance, light-headedness, toothache, faint feeling, haematoma.

Injury, Poisoning and Procedural Complications: There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic

beverages) and in the elderly.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Symptoms

Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. Overdose of midazolam is seldom life-threatening if the medicine is taken alone, but in mild cases, may lead to symptoms including drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, areflexia, apnoea, hypotonia, hypotension, respiratory depression, coma and very rarely death. Coma may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol. When combined with other CNS depressants, the effects of overdosage are likely to be severe and may prove fatal.

Treatment

Treatment of overdose is symptomatic; institute supportive measures as indicated by the patient's clinical state. If the overdosage is known to be small, observation of the patient and monitoring of their vital signs only may be appropriate. In adults or children who have taken an overdose of benzodiazepines within 1 - 2 hours, consider activated charcoal with airway protection if indicated.

If CNS depression is severe consider the use of flumazenil (Anexate), a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil may precipitate seizures and is contraindicated in the presence of medicines that reduce seizure threshold (e.g. tricyclic antidepressants) and epileptic patients who have been treated with benzodiazepines. Refer to the prescribing information for flumazenil (Anexate), for further information on the correct use of this medicine.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication.

For information on the management of overdosage, contact the Poisons Information Centre (phone: 13 11 26).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives (benzodiazepine derivatives), ATC code: N05CD08.

The active ingredient of ZYAMIS is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4] benzodiazepine maleate (midazolam).

Midazolam is a benzodiazepine from the imidazobenzodiazepine group.

Midazolam is available for use as the maleate salt. The free base is a lipophilic substance with low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring enables midazolam to form water-soluble salts with acids. These produce a stable solution suitable for buccal administration.

Mechanism of Action

Midazolam is a short-acting central nervous system depressant which induces sedation, hypnosis, amnesia and anaesthesia. Pharmacokinetic and pharmacodynamic data in chronic intravenous (IV) usage are not available beyond 15 days.

Pharmacodynamic effect

The mechanism of action of the benzodiazepines is under continuous investigation. Benzodiazepines appear to intensify the physiological inhibitory mechanisms mediated by gamma-aminobutyric acid (GABA), the most common inhibitory neurotransmitter in the brain.

Midazolam has a marked anticonvulsant effect with a non-linear relationship between concentration and effect without an apparent ceiling at higher concentrations.

The effects of midazolam on the CNS are dependent on the dose administered, the route of administration and the presence or absence of other premedications. Onset time of sedative effects after intramuscular (IM) administration is 15 min, with peak sedation occurring 30 - 60 min following injection.

Midazolam (10 mg) administered by the oromucosal route demonstrated a rapid (≤ 5 -10 minutes) neurophysiological effect as measured by EEG in healthy adults.

When used IV as a sedative for endoscopic or other short therapeutic or diagnostic procedures, the end point of slurred speech can be attained within 2.8 - 4.8 min, depending on the total dose administered and whether or not preceded by narcotic premedication. The time to induction of anaesthesia for surgical procedures is variable, occurring in approximately 1.5 min (0.3 - 8 min) when an opioid premedicant has been administered and in 2 - 2.5 min without premedication or with a sedative premedication. Approximately 2 h are required for full recovery from midazolam-induced anaesthesia; however duration of effect is dependent on the dose and other drugs used.

At doses sufficient to induce sedation, IV midazolam decreases the sensitivity of the ventilatory response to elevated carbon dioxide tension in normal subjects and in those with chronic obstructive lung disease, who are at risk of hypoxia. Sedation with midazolam has no adverse effects on pulmonary compliance and does not cause bronchoconstriction or significantly affect functional residual capacity or residual volume.

Although midazolam may cause modest decreases in mean arterial pressure, baroreceptor response is not affected and decreases in arterial pressure are accompanied by increases in heart rate. IV midazolam at doses of 0.15 - 0.2 mg/kg did not have deleterious effects on cardiac haemodynamics.

IV administration of midazolam does not alter intracranial pressure unless the patient is intubated. Cerebral blood flow may be reduced by up to 35%, which is of the same order as caused by equivalent doses of diazepam. The effect on cerebral metabolism is not clearly established.

Midazolam reduces the intraocular pressure to the same degree as thiopentone and diazepam.

Clinical trials

A randomised, open, active controlled clinical trial was conducted with 120 patients presenting with convulsions to an emergency department¹. They were treated with either buccal midazolam (60 in a dose of 0.2 mg/kg) or IV diazepam (60 in a dose of 0.3 mg/kg). The frequency of overall control of convulsive episodes within 5 minutes was 85% and 93.3% in the buccal midazolam and IV diazepam groups, respectively (no significant difference shown $P=0.142$). The mean time needed for controlling the convulsive episodes after administration of the drugs was significantly less with IV diazepam ($P < 0.001$). The mean time for initiation of treatment was significantly less with buccal midazolam ($P < 0.001$). The mean time for controlling the convulsive episodes after noticing them were significantly less with buccal midazolam than with IV diazepam ($P=0.004$), likely to be due to the longer time needed for initiating treatment with IV diazepam (time to prepare the injection and establish IV access). There were no significant side effects

¹ Talukdar B, Chakrabarty B. Efficacy of buccal midazolam compared to intravenous diazepam in controlling convulsions in children: a randomized controlled trial. *Brain Dev.* 2009; 31(10):744-9

reported for either group.

A second open randomized, controlled trial compared the efficacy and safety of ZYAMIS oromucosal solution and IV diazepam in the control of seizures in the emergency department of a children's hospital². A total of 92 children (age 6 months to 14 years) with seizures lasting longer than 5 minutes were treated with ZYAMIS (n=32; dose varied according to age from 2.5 to 10 mg) or IV diazepam (n=60; dose 0.3 mg/kg). A second dose was administered if the seizure continued at 5 minutes after the first dose. Cessation of seizures was achieved after a single dose within 5 minutes in 13/32 (40%) of buccal midazolam subjects compared to 24/60 (40%) of IV diazepam subjects (no significant difference shown P=0.9). Overall, cessation of seizures within 10 minutes after 1 or 2 doses was achieved in 22/32 (68.7%) buccal midazolam subjects compared to 42/62 (70%) of the IV diazepam subjects (no significant difference shown P=0.9). No serious side effects were observed in either group of patients, although significant agitation and mild hypotension were observed in both groups. 4 patients that received intravenous diazepam experienced apnoea compared to none in the buccal midazolam group.

5.2 Pharmacokinetic properties

Absorption

Absorption after oromucosal administration

Absorption of midazolam from the buccal mucosa is rapid. Maximum plasma concentrations are reached within 30 minutes. The absolute bioavailability of oromucosal midazolam is about 75% in healthy adults. The bioavailability of oromucosal midazolam has been estimated at 87% in children with severe malaria and convulsions.

Distribution

Midazolam is highly lipophilic and distributes extensively. The volume of distribution of midazolam at steady state is 0.6 – 1.9 L/kg.

Metabolism

Less than 0.03% is excreted in the urine as intact midazolam. The drug is rapidly metabolised to the active metabolite, 1-hydroxymethyl midazolam, which is conjugated with subsequent excretion in the urine. The concentration of midazolam is 10- to 30-fold greater than that of 1-hydroxymethyl midazolam. Based on a paediatric simulated population mean AUC ratio of the 1-hydroxymidazolam metabolite to midazolam, 40% of midazolam is converted into 1-hydroxymidazolam.

Excretion

In normal subjects the mean elimination half-life of midazolam is between 1.4 – 2.4 h and the clearance is in the range of 220 – 470 mL/min. Midazolam is mainly excreted by renal route: 60 – 80% of the administered dose of midazolam is excreted in urine as glucoconjugated α -hydroxymidazolam.

The elimination half-life of this metabolite is < 1 h.

Compounds that inhibit or induce cytochrome P450 3A4 (CYP3A) may alter patients' elimination of midazolam, and the dose may need to be adjusted accordingly (see section 4.5 Interactions with other medicines and other forms of interactions).

In children over 12 months, the half- life of parenteral midazolam was reported to be 0.8 to 1.8 hours³, which was similar to or less than that in adults. Plasma clearance in children over 12 months was 4.7 to 19.7 mL/min/kg which was similar to or higher than that in adults. The difference is consistent with an increased metabolic clearance in children⁴.

² Tonekaboni S., Shamsabadi FM, Anvari S, Mazrooei A, and Ghofrani M. A comparison of buccal midazolam and intravenous diazepam for the acute treatment of seizures in children. *Iran J Pediatr.* 2012; 22(3):303-308

³ Blumer, J.L. Clinical pharmacology of midazolam in infants and children. *Clin Pharmacokinet* **35**, 37–47 (1998)

⁴ J Hughes, A M Gill, H Mulhearn, E Powell, I Choonara. Steady-state plasma concentrations of midazolam in critically ill infants and children. *Ann Pharmacother.* 1996 Jan;30(1):27-30

Pharmacokinetics in Special Populations

Elderly

In adults over 60 years of age, the elimination half-life of midazolam may be prolonged up to four times.

Renal impairment

The free fraction of midazolam in chronic renal failure may be significantly higher than normal. After correcting for protein binding the pharmacokinetics of unbound midazolam is similar to that reported in healthy volunteers.

Hepatic impairment

The clearance in cirrhotic patients may be reduced and the elimination half-life may be longer when compared to those in healthy volunteers (see sections 4.2 Dose and method of administration, Special dosage instructions and 4.4 Special warnings and precautions for use).

Critically ill

Midazolam elimination half-life is prolonged in critically ill patients.

Cardiac insufficiency

Midazolam elimination half-life is prolonged in patients with congestive heart failure.

Obese

The elimination half-life of midazolam is prolonged in obese patients. The clearance is not altered.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Midazolam was not mutagenic in the Ames test in *S. typhimurium* with or without metabolic activation, in Chinese hamster lung cells (V79), human lymphocytes, or in vivo in the micronucleus test in mice.

Carcinogenicity

Midazolam maleate was administered with diet in mice and rats for 2 years at dosages of 1, 9 and 80 mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumours. In high dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumours. Dosages of 9 mg/kg/day of midazolam maleate do not increase the incidence of tumours. The pathogenesis of induction of these tumours is not known. These tumours were found after chronic administration, whereas human use is ordinarily single dose or of short duration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ZYAMIS midazolam (as maleate) Oromucosal Solution 2.5 mg/0.25 mL, 5 mg/0.5 mL, 7.5 mg/0.75 mL and 10 mg/1 mL, contains ethanol, saccharin sodium, glycerol, purified water, sodium hydroxide (for pH adjustment) and maltitol solution.

6.2 Incompatibilities

None.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25 °C. Do not refrigerate or freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

ZYAMIS midazolam (as maleate) 2.5 mg/0.25 mL, 5 mg/0.5 mL, 7.5 mg/0.75 mL and 10 mg/1 mL is presented in a 1 mL oral syringe with a Cyclic Olefin Polymer (COP) siliconised barrel and COP amber oversheath cap. The product is supplied as a single dose pack, each containing one pre-filled oral syringe in a polypropylene container.

The different presentations are identified with different colours of the label on the immediate packaging (syringe barrel) and the colour of the tamper evident container as described:

Each 0.25 mL pre-filled, oral syringe has a yellow syringe label and is packed in a yellow polypropylene container.

Each 0.5 mL pre-filled, oral syringe has a blue syringe label and is packed in a blue polypropylene container.

Each 0.75 mL pre-filled, oral syringe has a purple syringe label and is packed in a purple polypropylene container.

Each 1 mL pre-filled, oral syringe has an orange syringe label and is packed in an orange polypropylene container.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physiochemical properties

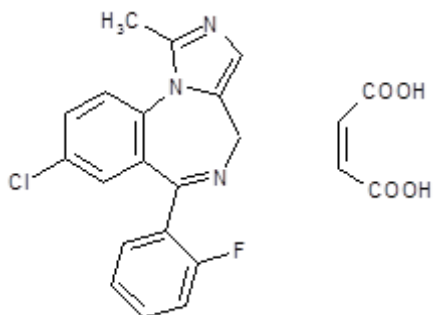
Midazolam maleate is a white or yellowish crystalline powder, slightly soluble in water, sparingly soluble in ethanol and freely soluble in methanol and 0.1M HCl.

ZYAMIS midazolam (as maleate) oromucosal solution is a slightly viscous, clear colourless to pale yellow solution for buccal administration presented in a pre-filled syringe.

pH 4.8-5.6.

Chemical structure

Its structural formula is:



Molecular formula: C₁₈H₁₃ClFN₃ · C₄H₄O₄

Relative molecular mass: 441.8 g/mol

CAS number

CAS Number: 59467-94-6

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription only medicine

8. SPONSOR

Clinect Pty Ltd,
120-132 Atlantic Drive,
Keysborough, VIC 3173,
Australia

Free Call Australia: 1800 899 005

9. DATE OF FIRST APPROVAL

22 April 2022

10. DATE OF REVISION

24 February 2023

Summary table of changes

Section Changed	Summary of new information
8	Update of Sponsor details