

# NEW ZEALAND DATA SHEET

## HYPAM

*Triazolam Tablets 0.125mg, 0.25mg*



---

## Presentation

---

HYPAM 0.125mg tablets are oval, flat, bevelled edged white tablets marked TZ on one side and scored on the other.

HYPAM 0.25mg tablets are oval, flat, bevelled edged blue tablets marked TZ on one side and scored on the other.

Dimensions (both strengths): 7.9mm x 5.6mm

---

## Uses

---

### **Actions**

The exact mechanism of action of triazolam, like that of other benzodiazepines, is unclear. The actions of benzodiazepines appear to be restricted solely to the central nervous system, where they potentiate the inhibitory actions of the neurotransmitter gamma-aminobutyric acid. The pharmacologically active benzodiazepines bind to specific receptors found only in the brain.

### **Pharmacokinetics**

Triazolam has a desirable hypnotic pharmacokinetic profile.

Peak plasma concentration is reached in 1.0 to 1.5 hours. The mean minimum absorption of triazolam equals 82% based on actual excretion data and 91% based on excretion data normalised for 100% recovery. The elimination half-life is 2.3 hours (range 1.7 to 3.0 hours).

In the elderly the elimination half-life is unaltered. However, the peak plasma concentrations are significantly increased.

The two major metabolites of triazolam in man (a-hydroxytriazolam and 4-hydroxytriazolam) are found in small quantities and are relatively inactive. Only very low levels of free a-hydroxytriazolam and 4-hydroxytriazolam are present in the plasma. The plasma half-life of a-hydroxytriazolam glucuronide was 3.9 hours; that of 4-hydroxytriazolam glucuronide was 3.8 hours.

Triazolam and its metabolites are excreted primarily in the urine. The two primary metabolites accounted for 79.9% of urinary excretion. Urinary excretion appeared to be biphasic in its time course. Triazolam and its metabolites do not accumulate in the blood after multiple-dose administration.

In studies with patients with renal failure undergoing haemodialysis, triazolam elimination rate was not decreased and maximum concentration was not increased. Patients with hepatic dysfunction may have reduced triazolam clearance and increased peak plasma concentrations, and in this patient group consideration should be given to reduced dosages. The usual precautions in administering sedatives to patients with liver dysfunction should be observed.

### **Indications**

Triazolam is useful in the management of patients with transient up to 7 days, and short term 2 to 4 weeks, severe or disabling insomnia. It is also useful as a short term, intermittent adjunctive treatment in the management of selected patients with long term insomnia.

---

## Dosage and Administration

---

The lowest effective dose of triazolam should be used. Treatment with triazolam should not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient.

The starting dose in all patients should be 0.125mg; for many patients this dose immediately before retiring should be sufficient. A dose of 0.25mg should not be exceeded.

For elderly or debilitated patients and patients with disturbed liver/kidney function, the dose should not exceed 0.125mg before retiring. The 0.25mg dose should be used only for exceptional patients who do not respond to a trial of the lower dose.

In all patients the risk of several adverse reactions increases with the size of the dose administered.

---

## Contraindications

---

Triazolam is contraindicated in patients with known hypersensitivity to benzodiazepines or to any component of the product's formulation.

Triazolam should not be used as monotherapy to treat depression, or symptoms of anxiety associated with depression, due to a risk of suicide (see Warnings and Precautions).

Co-administration of triazolam with ketoconazole, itraconazole and nefazodone is contraindicated (see Interactions).

---

## Warnings and Precautions

---

Caution must be used in treating patients with impaired hepatic function, severe pulmonary insufficiency or sleep apnoea. In patients with compromised respiratory function, respiratory depression and apnoea have been reported infrequently.

In elderly and/or debilitated patients, it is recommended that treatment with triazolam tablets be initiated at 0.125mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. In other adults the recommended dose is 0.25mg (see Dosage and Administration).

Patients should be cautioned not to take triazolam in circumstances where a full night's sleep and clearance of the drug from the body are not possible before they would again need to be active and functional, e.g., an overnight flight of less than 7-8 hours, since amnestic episodes have been reported in such situations.

### Duration of treatment

For patients with anxiety and/or insomnia, the duration of treatment should not exceed 4 weeks (including the tapering off process). Continuous long term use is not recommended, but intermittent use may be appropriate. Where long-term therapy is considered essential, the patient should be regularly reviewed.

### Tolerance and Dependence

There is evidence that tolerance develops to the sedative effects of benzodiazepines. When triazolam is used at recommended doses for short term treatment, the dependence potential is low. However, as with all benzodiazepines, the risk of dependence increases with higher doses and long term use and is further increased in patients with a history of alcoholism or drug abuse.

### Withdrawal

Discontinuation of triazolam therapy may result in withdrawal or rebound phenomena. Withdrawal symptoms, including seizures, have been reported when patients abruptly discontinue multiple daily doses of triazolam. The triazolam dose should be tapered gradually to minimise the occurrence of withdrawal symptoms.

---

Symptoms of benzodiazepine withdrawal include anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances such as hypersensitivity to physical, visual, and auditory stimuli and abnormal taste, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia and orthostatic hypotension.

Rare and more serious symptoms include muscle twitching, confusional or paranoid psychosis, convulsions, hallucinations, and a state resembling delirium tremens. Broken sleep with vivid dreams and increased REM sleep may persist for some weeks after withdrawal of benzodiazepines.

## **Depression**

Depression has been reported with therapeutic use and withdrawal of benzodiazepine therapy. The disinhibiting effects of benzodiazepines may also play a role in the precipitation of suicide attempts or completed suicides. This occurs in a rare and unpredictable fashion. Therefore, triazolam should be used with caution and the prescription size should be limited in patients with signs and symptoms of a depressive disorder or suicidal tendencies.

## **Idiosyncratic reactions**

As with other benzodiazepines and CNS active drugs, three idiosyncratic symptom clusters, which may overlap, have been reported rarely with triazolam: amnesic symptoms (anterograde amnesia with appropriate or inappropriate behaviour); confusional states (disorientation, derealisation, depersonalization and/or clouding of consciousness); and an agitational state (restlessness, irritability and excitation).

Frequently, other factors may contribute to these idiosyncratic reactions e.g. concomitant intake of alcohol or other medicines, sleep deprivation, an abnormal premorbid state etc.

Triazolam should be discontinued if confusional or agitational reactions occur.

## **Abuse**

Due to the potential for abuse, triazolam should be used with caution in patients known to be addiction prone. In addition, repeat prescriptions should not be given without medical review.

## **Concomitant use with alcohol/CNS depressants**

The concomitant use of triazolam with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of triazolam which may include severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see Interactions).

## **Effects on ability to drive and use machines**

Patients should be cautioned about operating motor vehicles or other hazardous machinery the day after a night time dose of triazolam, until it is established that they do not exhibit daytime drowsiness or dizziness.

## **Pregnancy and Lactation**

The data concerning teratogenicity and effects on postnatal development and behaviour following benzodiazepine treatment are inconsistent. There is evidence from some early studies with other members of the benzodiazepine class *in utero* exposure may be associated with malformations. Later studies with the benzodiazepine class of drugs have provided no clear evidence of any type of defect. Infants exposed to benzodiazepines during late third trimester of pregnancy or during labour have been reported to exhibit either the floppy infant syndrome or neonatal withdrawal symptoms. If triazolam is used during pregnancy, or of the patient becomes pregnant while taking triazolam, the patient should be apprised of the potential hazard to the foetus.

Human studies have not been performed; however studies in rats have indicated that triazolam and its metabolites are secreted in milk. Triazolam should not be used by nursing mothers.

## **Paediatrics**

Safety and effectiveness in patients under the age of 18 have not been established.

---

## Adverse Effects

---

In placebo-controlled studies with triazolam, the most troublesome unwanted effect of the drug was sedation (drowsiness, somnolence, dizziness, ataxia, and/or inco-ordination), considered to be an extension of the pharmacologic activity of the drug. Less frequently encountered events include confusional states or memory impairment, CNS depression and visual disturbances.

In addition to the effects noted above, other events rarely reported during worldwide clinical use of triazolam include: aggressiveness, falling, transient insomnia after drug discontinuance, hallucinations, syncope and somnambulism.

Although the absolute occurrence of adverse effects with triazolam is low, there may be a dose relationship. The side effects of benzodiazepines which are extensions of their pharmacologic actions, e.g. drowsiness, dizziness, lightheadedness, or amnesia are clearly dose related. The relationship of dose with the risk of other adverse reactions has not been established. In accordance with good medical practice it is recommended that therapy be initiated at the lowest effective dose (see Dosage and Administration).

---

## Interactions

---

Benzodiazepines produce an additive effect when co-administered with alcohol or other CNS depressants (see Warnings and Precautions).

Pharmacokinetic interactions can occur when triazolam is administered along with drugs that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) may increase the concentration of triazolam and enhance its activity. Data from clinical studies with triazolam, *in vitro* studies with triazolam, and clinical studies with drugs metabolised similarly to triazolam provide evidence for varying degrees of interaction and possible interaction with triazolam for a number of drugs. Based on the degree of interaction and the type of data available, the following recommendations are made:

- The co-administration of triazolam with ketoconazole, itraconazole and nefazodone is contraindicated.
  - The co-administration of triazolam with other azole-type antifungals is not recommended.
  - Caution and consideration of dose reduction is recommended when triazolam is co-administered with cimetidine or macrolide antibiotics such as erythromycin, clarithromycin, and troleandomycin.
  - Caution is recommended when triazolam is co-administered with isoniazid, fluvoxamine, sertraline, paroxetine, diltiazem, and verapamil.
  - Interactions involving HIV protease inhibitors (e.g. ritonavir) and triazolam are complex and time dependent. Low doses of ritonavir resulted in a large impairment of triazolam clearance, prolonged its elimination half-life and enhanced clinical effects. However, upon extended exposure to ritonavir, CYP3A induction offset this inhibition. This interaction will require a dose-reduction or discontinuation of triazolam.
- 

## Overdosage

---

Symptoms of overdose with triazolam are extensions of its pharmacological action and include drowsiness, slurred speech, motor incoordination, coma, and respiratory depression. Serious sequelae are rare unless other drugs and/or ethanol are concomitantly ingested. Treatment of overdosage is primarily supportive of respiratory and cardiovascular function. The value of dialysis has not been determined. Flumazenil may be used as an adjunct to the management of respiratory and cardiovascular function associated with overdose.

---

## Pharmaceutical Precautions

---

Store below 25°C. Protect from light.

---

## Medicine Classification

---

Controlled Drug C5.

---

---

## Package Quantities

---

HYPAM 0.125mg tablets: Bottles of 100's and 500's

HYPAM 0.25mg tablets: Bottles of 100's and 500's

Not all pack sizes may be marketed.

---

## Further Information

---

### List of ingredients

Each HYPAM tablet contains the active ingredient, triazolam.

HYPAM 0.125mg tablets: lactose monohydrate, maize starch, microcrystalline cellulose, povidone, colloidal silicon dioxide, sodium lauryl sulphate, sodium starch glycollate and magnesium stearate.

HYPAM 0.25mg tablets: lactose monohydrate, maize starch, microcrystalline cellulose, povidone, colloidal silicon dioxide, sodium lauryl sulphate, sodium starch glycollate, magnesium stearate and indigo carmine (FD & C Blue No. 2).

HYPAM tablets do not contain gluten.

---

## Name and Address

---

Mylan New Zealand Limited  
PO Box 11-183  
Ellerslie  
AUCKLAND  
Telephone 09-579-2792

---

## Date of Preparation

---

7 February 2013