NEW ZEALAND DATA SHEET

HYPAM

1. Product Name

HYPAM, 0.125 mg, 0.25 mg, tablets.

2. Qualitative and Quantitative Composition

Each HYPAM tablet contains 0.125 mg or 0.25 mg of triazolam.

Excipients with known effect: lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

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

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

Dimensions (both strengths): 7.9 mm x 5.6 mm.

The score line is not intended for breaking the tablet.

4. Clinical Particulars

4.1 Therapeutic 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.

4.2 Dose and method of administration

Dose

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

For elderly or debilitated patients and patients with disturbed liver/kidney function, the dose should not exceed 0.125 mg before retiring. The 0.25 mg 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.

4.3 Contraindications

Triazolam should not be used as monotherapy to treat depression, or symptoms of anxiety associated with depression, due to a risk of suicide (see section 4.4).

- Pregnancy
- Depressed patients with suicidal tendencies
- Myasthenia gravis
- Co-administration with nefazodone, ketoconazole, itraconazole, and HIV protease inhibitors (see section 4.4)
- Lactation
- Hypersensitivity to benzodiazepines or any of the excipients contained in triazolam tablets (see section 6.1)

4.4 Special warnings and precautions for use

Because some of the adverse effects of triazolam appear to be dose-related (see section 4.2), it is important to use the smallest possible effective dose, especially in the elderly (see special populations, elderly).

In general, benzodiazepines should be prescribed for short periods only. Triazolam is indicated in the short-term treatment of insomnia (generally 7-10 days). Use of triazolam for more than 2-3 weeks requires complete re-evaluation of the patient. Continuous long-term use of triazolam is not recommended. There is evidence that tolerance develops to the sedative effect 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 (see dependence).

After as little as one week of therapy with recommended doses, withdrawal symptoms can appear following cessation of treatment, e.g., rebound insomnia following cessation of a hypnotic benzodiazepine. Caution patients 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. Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Severe anaphylactic and anaphylactoid reactions

Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics. Some patients have had additional symptoms such as dyspnoea, throat closing, or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with triazolam should not be re-challenged with the drug.

Sleep disturbance

Sleep disturbance may be the presenting manifestation of a physical and/or psychiatric disorder. Consequently, a decision to initiate symptomatic treatment of insomnia should only be made after the patient has been carefully evaluated.

The failure of insomnia to remit after 7-10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.

Worsening of insomnia or the emergence of new abnormalities of thinking or behaviour may be the consequence of an unrecognised psychiatric or physical disorder. These have also been reported to occur in association with the use of triazolam.

Psychiatric effects

An increase in daytime anxiety has been reported for triazolam after as few as 10 days of continuous use. In some patients this may be a manifestation of interdose withdrawal (see section 5.1). If increased daytime anxiety is observed during treatment, discontinuation of treatment may be advisable.

A variety of abnormal thinking and behaviour changes have been reported to occur in association with the use of benzodiazepine hypnotics including triazolam. Some of these changes may be characterised by decreased inhibition, e.g., aggressiveness and extroversion that seem excessive, similar to that seen with alcohol and other CNS depressants (e.g., sedative/hypnotics). Other kinds of behavioural changes have also been reported, for example, bizarre behaviour, agitation, hallucinations, depersonalisation. In primarily depressed patients, the worsening of depression, including suicidal thinking, has been reported in association with the use of benzodiazepines.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviours listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioural sign or symptom of concern requires careful and immediate evaluation.

As with all patients taking CNS-depressant medications, patients receiving triazolam should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from triazolam therapy (see section 4.7). Patients should also take care as pedestrians. Abilities may be impaired on the day following use. Patients should be advised that their tolerance for alcohol and other CNS-depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of triazolam.

"Sleep-driving" and other complex behaviours

Complex behaviours such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported. These events can occur in sedative-hypnotic-naive as well as in sedative-hypnotic-experienced persons. Although behaviours such as sleep-driving may occur with sedative-hypnotics alone at therapeutic doses, the use of alcohol and other CNS depressants with sedative-hypnotics appears to increase the risk of such behaviours, as does the use of sedative-hypnotics at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of sedative-hypnotics should be strongly considered for patients who report a "sleep-driving" episode.

There have been reports of people getting out of bed after taking a sedative-hypnotic and driving their cars while not fully awake, often with no memory of the event. If a patient experiences such an episode, it should be reported to his or her doctor immediately, since "sleep-driving" can be dangerous. This behaviour is more likely to occur when sedative-hypnotics are taken with alcohol or other central nervous system depressants or when sedative-hypnotics are used at doses exceeding the maximum recommended dose.

Other complex behaviours (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with "sleep-driving", patients usually do not remember these events.

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, dependence and withdrawal

There is evidence that tolerance develops to the sedative effects of benzodiazepines. Tolerance as defined by a need to increase the dose in order to achieve the same therapeutic effect seldom occurs

in patients receiving the recommended dose under medical supervision. Tolerance to benzodiazepines may develop from continued therapy. Tolerance to sedation may occur with benzodiazepines, especially in those with drug seeking behaviour. Tolerance may develop during 1 to 2 weeks of therapy. The use of benzodiazepines may lead to dependence as defined by the presence of a withdrawal syndrome on discontinuation of the medicine. 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, or in patients with marked personality disorders. Regular monitoring in such patients is essential.

Rapid dosage reduction or abrupt discontinuation of triazolam therapy may result in withdrawal or rebound phenomena. The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency. More serious manifestations of withdrawal are more common in patients who have received excessive doses over a prolonged period, or in patients who have been dependent on alcohol or other narcotic drugs in the past. Withdrawal symptoms may occur with abrupt cessation of benzodiazepines following normal therapeutic doses given for short periods of time. Withdrawal symptoms, including seizures, have been reported when patients abruptly discontinue multiple daily doses of triazolam. Particular care should be taken in patients with epilepsy, and other patients who have had a history of seizures, alcohol or drug dependence. The triazolam dose should be tapered gradually to minimise the occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected.

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.

Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia and anxiety mean an increase in the severity of these symptoms beyond pre-treatment levels following the cessation of benzodiazepines. Rebound phenomena in general possible reflect the re-emergence of pre-existing symptoms combined with withdrawal symptoms described earlier. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 to 4 hours) may experience relatively mild rebound symptoms between their regular doses. Withdrawal/rebound symptoms may follow the use of high doses for relatively short periods.

In some cases, patients taking benzodiazepines have developed protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months.

Depression, psychosis and schizophrenia

Triazolam is not recommended as primary therapy for patients with depression and psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated. 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: amnestic 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.

Paradoxical reactions

Paradoxical reactions such as acute rage, stimulation or excitement may occur; should such reactions occur, triazolam should be discontinued.

Impaired respiratory function

Caution in the use of triazolam is recommended in patients with respiratory depression or sleep apnoea. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased oxygen tension. In patients with compromised respiratory function, respiratory depression and apnoea have been reported infrequently.

Hypotension

Although hypotension may occur only rarely, benzodiazepines should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in the elderly patient.

Abuse

Abuse of benzodiazepines has been reported. Due to the potential for abuse, triazolam should be used with caution in patients with a history of alcohol or drug abuse, dependence on CNS depressants, those known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescriptions without adequate medical supervision.

Before prescribing and throughout treatment, assess each patient's risk for abuse, misuse, and addiction. Use of benzodiazepines, particularly patients at elevated risk, necessitates counselling about the risks and proper use.

Acute narrow-angle glaucoma

Caution should be used in the treatment of patients with acute-narrow glaucoma (because of atropine-like side effects).

Epilepsy

Abrupt withdrawal of benzodiazepines in persons with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures.

Patients with convulsive disorder should not be abruptly withdrawn from triazolam.

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 section 4.5).

Concomitant use with opioids

Concomitant use of benzodiazepines, including triazolam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe triazolam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when triazolam is used with opioids (see section 4.5).

Special populations

Paediatric

Benzodiazepines and other hypnotic drugs may impair mental alertness in children. Safety and effectiveness in patients under the age of 18 have not been established.

Elderly or debilitated patients

Such patients may be particularly susceptible to the sedative effects of benzodiazepines and associated giddiness, ataxia and confusion, which may increase the possibility of a fall. For this reason, the dosage should be limited to the smallest effective amount to preclude such effects (see section 4.2).

The systemic availability of oral triazolam is increased in elderly patients probably due to a diminished first-pass hepatic metabolism.

Renal impairment

Patients with impaired renal function should use benzodiazepine medication with caution and a reduction in dosage, or decision not to prescribe, may be necessary in such patients.

Hepatic impairment

Patients with impaired renal or liver function should use benzodiazepine medication with caution and a reduction in dosage, or decision not to prescribe, may be necessary in such patients. In rare instances some patients taking benzodiazepines have developed blood dyscrasias, and some have had elevations of liver enzymes. As with other benzodiazepines, periodic blood counts and liver function tests are recommended. Caution must be used in treating patients with impaired hepatic function, severe pulmonary insufficiency, or sleep apnoea.

4.5 Interaction with other medicines and other forms of interaction

Benzodiazepines, including triazolam, produce additive CNS depressant effects when co-administered with alcohol or other medication which themselves produce CNS depression, e.g., barbiturates, sedatives, tricyclic antidepressants, non-selective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines, narcotic analgesics and anaesthetics (see section 4.4).

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 pharmacokinetics of triazolam may be altered by co-administration of grapefruit juice (see section 5.2).
- The anticholinergic effects of other drugs, including atropine and similar drugs, antihistamines and antidepressants may be potentiated when taken in conjunction with benzodiazepines.
- Interactions have been reported between some benzodiazepines and anticonvulsants, with changes in the serum concentration of the benzodiazepine or the anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together, and that serum level monitoring of the anticonvulsant be performed more frequently.
- 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 disulfiram, isoniazid, fluvoxamine, sertraline, paroxetine, diltiazem, and verapamil.
- Interactions involving HIV protease inhibitors (e.g. ritonavir) and triazolam are complex and time dependent. Short-term low doses of ritonavir resulted in a large impairment of triazolam clearance, prolonged its elimination half-life and enhanced clinical effects. The co-administration of triazolam
  with HIV protease inhibitors is contraindicated (see section 4.3).
- The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Minor EEG changes, usually low voltage fast activity, of no known clinical significance, has been reported with benzodiazepine administration.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C

Triazolam is contraindicated in pregnant women.

Benzodiazepines cross the placenta and may cause hypotonia, respiratory depression and hypothermia in the newborn infant. Continuous treatment during pregnancy and administration of high doses in connection with delivery should be avoided. Withdrawal symptoms in newborn infants have been reported with this class of drug.

Non-teratogenic effects

It is to be considered that the child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity has been reported in an infant born of a mother who had been receiving benzodiazepines.

Radioactive studies in pregnant mice have demonstrated that the drug and its metabolites cross the placenta and are present at maternal concentrations in the foetuses. In rats or rabbits, triazolam 10 mg and 30 mg per kg per day given during gestation is considered to be associated with retarded or impaired skeletal formation. In rabbits given 5 mg per kg per day, the viability and weight gain of the neonates was impaired. These findings do not exclude the possibility of embryotoxicity and teratogenicity in pregnant women.

Breast-feeding

Triazolam is contraindicated in breast feeding mothers.

Human studies on the excretion of triazolam in breast milk have not been performed. Studies in rats have, however, indicated that triazolam and its metabolites are excreted in breast milk. Benzodiazepines generally show increased toxicity in neonates, and the excretion of benzodiazepines in breast milk may cause drowsiness and/or feeding difficulties in the infant.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Patients receiving triazolam should be warned not to operate dangerous machinery or motor vehicles until it is known that they are fully awake and no longer feeling drowsy.

There have been reports of people driving their cars while not fully awake after taking a sedative-hypnotic, often with no memory of the event. Due to the risk to the patient and the community, discontinuation of triazolam therapy should be strongly considered if a patient experiences such an episode**.**

4.8 Undesirable 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).

Post-marketing experience

Immune system disorder

Hypersensitivity reactions including angioneurotic oedema, anaphylactoid reaction, allergic oedema and anaphylactic shock have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Because of the potency of triazolam, some manifestations of overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg)

Symptoms

Symptoms of overdose with triazolam are extensions of its pharmacological action, including respiratory depression and degrees of central nervous system depression, ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion, slurred speech, motor incoordination and lethargy. In more serious cases symptoms may include ataxia, hypotonia, hypotension, respiratory depression, apnoea, hypothermia, rhabdomyolysis, coma and very rarely

death. Seizures have occasionally been reported after overdosages. In terms of duration, most obtunded patients become arousable within 12 to 36 hours following an acute overdose. Serious sequelae are rare unless other drugs and/or alcohol are concomitantly ingested. Benzodiazepine and alcohol levels seen in some cases have been lower than those usually associated with reports of fatality with either substance alone.

Treatment

In the management of overdosage with any medication it should be borne in mind that multiple agents may have been taken.

Triazolam plasma concentrations are not clinically useful and specific lab work (CBC, electrolytes, urinalysis) is not needed unless otherwise indicated.

Treatment of overdosage is primarily supportive of respiratory and cardiovascular function. Activated charcoal may reduce absorption of the drug and it is most effective when administered within one hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

The benzodiazepine antagonist flumazenil may be useful in hospitalised patients for the reversal of acute benzodiazepine effects. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. Please consult the flumazenil product information prior to use.

Haemoperfusion, haemodialysis and forced diuresis are generally not useful in benzodiazepine intoxication.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: hypnotics and sedatives, ATC code: N05CD05

Mechanism of action

The type and duration of hypnotic effects and the profile of unwanted effects during administration of benzodiazepine drugs may be influenced by the biologic half-life of administered drug, the dose given, and any active metabolites formed. When half-lives are long, or the dosage increased, drug or metabolites may accumulate during periods of nightly administration and be associated with impairments of cognitive and motor performance during waking hours; the possibility of interaction with other psychoactive drugs or alcohol will be enhanced. In contrast, if half-lives are short, or dosage reduced, drug and metabolites will be cleared before the next dose is ingested, and carry-over effects related to excessive sedation or CNS depression should be minimal or absent. However, during nightly use for an extended period, pharmacodynamic tolerance or adaptation to some effects of benzodiazepine hypnotics may develop. If the drug has a short half-life of elimination, it is possible that a relative deficiency of the drug or its active metabolites (i.e., in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepine hypnotics: 1) increased wakefulness during the last third of the night, and 2) the appearance of increased daytime anxiety after 10 days of continuous treatment.

Clinical efficacy and safety

Triazolam is a potent short-acting hypnotic agent. In sleep laboratory studies in man, triazolam reduced sleep latency, increased duration of sleep and decreased the number of nocturnal awakenings compared to baseline. Other manifestations of effect included incoordination, impaired equilibrium, ataxia, muscle weakness, and amnesia. The duration and intensity of the CNS depression was dose-related. At usual therapeutic doses there was no significant respiratory or cardiovascular depression.

After two weeks of consecutive nightly administration, the drug's effect on total wake time is decreased, and the values recorded in the last third of the night approach baseline levels. On the first night after drug discontinuance (first post-drug night), total time asleep, percentage of time spent sleeping, and rapidity of falling asleep frequently were significantly less than on baseline (pre-drug) nights. This effect is often called "rebound" insomnia.

5.2 Pharmacokinetic properties

Absorption

Triazolam has a desirable hypnotic pharmacokinetic profile.

Following an oral dose of 0.88 mg of triazolam^{14}C in man, the mean peak plasma concentration of triazolam occurred at a mean time of 1.5 ± 0.7 hours. Triazolam levels decreased with a mean apparent plasma half-life ($t_{1/2}$) of 2.7 ± 0.5 hours. Triazolam is extensively and rapidly metabolised. Metabolite levels peaked at 1.6 ± 0.7 hours, decreased by a biphasic process, with a mean apparent half-life for the initial phase of 3.4 ± 0.9 hours and 7.8 ± 1.5 hours for the terminal phase. The mean recovery of ^{14}C by 240 hours was 89.6% (81.8% of urine and 7.9% of faeces).

Distribution

In vitro, triazolam is loosely bound (89%) to human serum proteins, and is rapidly dissociated, as shown by a relatively short plasma half-life of 2.7 hours. Although triazolam might be expected to dissociate rapidly, the serum concentration of free drug at any given time was extremely low (approximately 4%). Binding to serum albumin amounted to 49%. Triazolam, equivalent to or greater than 100 times the therapeutic dose, does not displace bilirubin bound to human serum albumin *in vitro.*

The systemic availability of oral triazolam is increased in geriatric patients, probably due to a diminished first-pass hepatic metabolism (see section 4.4).

Biotransformation

The major metabolites are a-hydroxymethyl triazolam (8-chloro-6-(o-chlorophenyl)-1-hydroxymethyl-4H-S-triazolo-[4,3-a][1,4] benzodiazepine), and 4-hydroxy triazolam (8-chloro-6-(o-chlorophenyl)-4-hydroxy-1-methyl-4H-S-triazolo-[4,3-a][1,4] benzodiazepine). These two metabolites accounted for 69% and 11% respectively of the urinary excretion in man. The pharmacological activity of triazolam metabolites has not been determined in man.

Pharmacokinetic interactions can occur when triazolam is administered along with drugs that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly CYP3A4) may increase the concentration of triazolam and enhance its activity. Specific examples, documented with evidence from clinical pharmacokinetic studies, include the following: cimetidine, erythromycin (a macrolide antibiotic), nefazodone, ketoconazole, and itraconazole. Inhibition of the metabolism of other benzodiazepines metabolised by pathways similar to those for triazolam has been reported for a number of drugs, for example, diltiazem and verapamil. There is the possibility of similar interactions with triazolam.

In a clinical pharmacokinetic study conducted in healthy volunteers, co-administration of grapefruit juice increased the maximum plasma concentration of triazolam by 25%, increased the area under the curve by 48% and increased half-life by 18% (see section 4.5).

Elimination

Excretion of ^{14}C in urine, faeces, and urine plus faeces appeared to be biphasic. The excretion half-times for urine plus faeces, corresponding to the initial and terminal excretion phases, were 3.4 ± 0.5 hours and 30 ± 8 hours. Only small amounts (approximately 2%) of unmetabolised triazolam appear in the urine.

6. Pharmaceutical Particulars

6.1 List of excipients

HYPAM tablets also contain:

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25°C. Protect from light.

6.5 Nature and contents of container

HDPE bottle with a child-resistant closure. Bottles of 100 and 500 tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Controlled drug C5.

8. Sponsor Details

Viatris Ltd
PO Box 11183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

27 April 1990

10. Date of Revision of the Text

24 March 2022

Summary table of changes

Section	Summary of new information
4.4	Updated information on abuse, dependence, tolerance and withdrawal.