PRODUCT MONOGRAPH

MYLAN-TRIAZOLAM

triazolam USP

0.125 mg, 0.25 mg Tablets

USP

Hypnotic

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PRODUCT MONOGRAPH

NAME OF DRUG

MYLAN-TRIAZOLAM

(triazolam)
0.125 mg, 0.25 mg Tablets USP

THERAPEUTIC CLASSIFICATION

Hypnotic

ACTIONS

MYLAN-TRIAZOLAM (triazolam) is a benzodiazepine hypnotic with a very short elimination half- life (about 3 hours).

In sleep laboratory studies of one to 21 days duration, triazolam significantly decreased sleep latency, increased the duration of sleep and decreased the number of nocturnal awakenings. However, after two weeks of consecutive nightly administration, the drug's effect on total wake time was decreased, and the values recorded in the last third of the night approached baseline levels. On the first and/or second night after drug discontinuance (first or second post-drug night), total time asleep, and percentage of time spent sleeping frequently were significantly decreased, and sleep latency significantly increased when compared to baseline (predrug) nights. This effect is referred to as **"rebound" insomnia**.

The duration of hypnotic effect and the profile of unwanted effects may be influenced by the alpha (distribution) and beta (elimination) half-lives of the administered drug and any active metabolites formed. When half-lives are long, the drug or metabolites may accumulate during periods of nightly administration and be associated with impairments of cognitive and motor performance during waking hours. If half-lives are short, the drug and metabolites will be cleared before the next dose is ingested, and carry-over effects related to sedation or CNS depression should be minimal or absent. However, during nightly use and for an extended period, pharmacodynamic tolerance or adaptation to some effects of benzodiazepine hypnotics may develop. If the drug has a very short elimination half-life, it is possible that a relative deficiency (i.e., in relation 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 day-time anxiety (see WARNINGS).

When sedation and psychomotor performance were compared in healthy elderly and young subjects, in response to 0.125 and 0.25 mg doses of triazolam, the degree of sedation was greater and the impairment of psychomotor performance more pronounced in the elderly. The age-dependent difference was closely associated with the correspondingly higher plasma triazolam concentrations measured in elderly subjects.

Patients with severe liver disease also demonstrated greater psychomotor impairment than control subjects or patients with minimal liver dysfunction.

Pharmacokinetics

Triazolam is rapidly absorbed and peak plasma levels are reached within 2 hours following oral administration. Peak plasma concentration (C_{max}) and area under the plasma-concentration curve (AUC) increase in proportion to the dose, while the time to peak plasma concentration (T_{max}), elimination half-life ($t_{1/2\beta}$), and clearance are independent of dose. Triazolam has a short half-life; the range is reported to be 1.5 to 5.5 hours.

Triazolam is metabolised via hepatic microsomal oxidation. The hydroxylated metabolites, which are inactive, are excreted primarily in the urine as conjugated glucuronides. The two primary metabolites account for approximately 80% of urinary excretion.

Repeated administration of triazolam for 7 days does not lead to accumulation and does not alter the rate of elimination.

Pharmacokinetics in the elderly: the kinetics of triazolam are significantly influenced by age (see table). Following single oral doses of 0.125 mg and 0.25 mg of triazolam, peak plasma concentrations and area under the curve were significantly higher and clearance significantly lower in elderly subjects (mean age: 69 years) than in younger ones (mean age: 30 years). Age, however, did not influence the time to peak plasma levels and differences in elimination half-life were small.

Mean (± standard deviation) pharmacokinetic parameters following single oral doses of triazolam in young and elderly volunteers.

	Triazolam 0.125 mg		Triazolam 0.25 mg	
	Young (n=26)	Elderly (n=21)	Young (n=26)	Elderly (n=21)
C_{max} (ng/ml)	1.08±0.08	1.67±0.16*	2.02±0.15	3.06±0.22*
T_{max} (hr)	0.88+0.08	0.95±0.11	0.96±0.10	0.88±0.07
AUC (ng/ml.hr)	3.85±0.45	6.24±0.82*	7.01±0.68	12.03±1.11*
$T_{1/2\beta}$ (hr)	2.94±0.4	3.03±0.25	2.43±0.16	3.00±0.24*
Clearance (ml/min/kg)	11.4±2.2	6.8±0.9*	10.5±1.0	5.8±0.4*

* $p<0.05$

Pharmacokinetics in patients with renal failure: following oral administration of triazolam, 0.5 mg, peak plasma triazolam concentrations were lower in eleven patients with renal failure undergoing dialysis (4.04 ± 1.83 ng/mL) than in patients with normal renal function (6.54 ± 1.70 ng/mL). Other pharmacokinetic parameters were not significantly different between patients with impaired and normal renal function.

Pharmacokinetics in patients with hepatic failure: following oral administration of triazolam, 0.25 mg, triazolam clearance was reduced in eight subjects with biopsy- proven cirrhosis (4.99 ± 3.14 mL /min/kg) as compared to seven normal subjects (6.69 ± 2.52 mL/min/kg). Peak plasma levels and time to peak concentration were not different between the groups. The reduction in triazolam clearance in subjects with cirrhosis correlated with the severity of liver dysfunction.

A summary of the results of a comparative, randomized, crossover, bioavailability study of MYLAN-TRIAZOLAM Tablets 0.25 mg and the reference drug HALCION(R) (triazolam tablets) 0.25 mg is found on the following table.

Parameter	**Test** **TRIAZOLAM** Geometric Mean, Arithmetic Mean, (C.V.)	Reference **HALCION**[(R)] Geometric Mean, Arithmetic Mean, (C.V.)	**Ratio of** Means (%)
AUC_T	21.1	19.8	107
(ng•h/mL)	22.7 (42)	22.1 (51)	
AUC_1	22.5	21.1	107
(ng.h/mL)	24.6 (47)	24.1 (57)	
	4.9	4.6	107
(ng/mL)	5.1 (28)	4.8 (29)	
T_{max} (h)	0.94 (0.36)	1.20 (0.46)	---
$T_{1/2}$ (h)	2.72 (0.76)	2.69 (0.79)	---

For the T_{max} and $T_{1/2}$ parameters, these are the arithmetic means (standard deviation).

INDICATIONS AND CLINICAL USE

MYLAN-TRIAZOLAM (triazolam) is indicated for the symptomatic relief of transient and short-term insomnia in patients who have difficulty falling asleep. Triazolam is not recommended for early morning awakenings.

Treatment with triazolam should usually not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete reevaluation of the patient.

The use of hypnotics should be restricted for insomnia where disturbed sleep results in impaired daytime functioning.

CONTRAINDICATIONS

MYLAN-TRIAZOLAM (triazolam) is contraindicated in patients with known hypersensitivity to this drug or other benzodiazepines.

Triazolam is contraindicated in patients who in the past manifested paradoxical reactions to alcohol and/or sedative medications, and in subjects with a history of substance or alcohol abuse.

Triazolam is contraindicated in pregnant women. Benzodiazepines may cause fetal damage when administered during pregnancy. During the first trimester of pregnancy, several studies have suggested an increased risk of congenital malformations associated with the use of benzodiazepines. During the last weeks of pregnancy, ingestion of therapeutic doses of a benzodiazepine hypnotic has resulted in neonatal CNS depression due to transplacental distribution. If triazolam is prescribed to women of child-bearing potential, the patient should be warned of the potential risk to a fetus and advised to consult her physician regarding the discontinuation of the drug if she intends to become pregnant.

Triazolam is contraindicated in patients who have myasthenia gravis or a history of uncorrected narrow-angle glaucoma.

WARNINGS

General: 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.

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

Memory disturbance

Anterograde amnesia of varying severity has been reported following therapeutic doses of benzodiazepines including triazolam. Anterograde amnesia is a dose-related phenomenon and elderly subjects may be at a particular risk. Data from several sources suggest that anterograde amnesia and next day memory loss may occur at a higher rate with triazolam than with other benzodiazepines.

Cases of transient global amnesia and "traveller's amnesia" have also been reported in association with triazolam, the latter in individuals who have taken the drug to induce sleep while travelling. Transient global amnesia and traveller's amnesia are unpredictable and not necessarily dose-related phenomena. Patients should be warned not to take triazolam under circumstances in which a full night's sleep and clearance of the drug from the body are not possible before they need again to resume full activity (e.g., an overnight flight of less than 7-8 hours).

Abnormal thinking and psychotic behavioral changes have been reported to occur in association with the use of benzodiazepine hypnotics including triazolam. Some of the changes may be

characterized by decreased inhibition, e.g., aggressiveness or extroversion that seem excessive, similar to that seen with alcohol and other CNS depressants (e.g., sedative/hypnotics). Particular caution is warranted in patients with a history of violent behaviour. Psychotic behavioral changes that have been reported include bizarre behaviour, hallucinations, and depersonalization. Abnormal behaviours associated with triazolam have been reported more with chronic use or high doses.

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. Nevertheless, the emergence of any new behavioural sign or symptom of concern requires careful and immediate evaluation.

Confusion: the benzodiazepines affect mental efficiency, e.g., concentration, attention and vigilance. The risk of confusion is greater in the elderly and in patients with cerebral impairment.

Anxiety, restlessness: an increase in daytime anxiety (interdose rebound anxiety) and/or restlessness have been observed during treatment with triazolam. This may be a manifestation of interdose withdrawal, due to the very short elimination half-life of the drug.

Depression: caution should be exercised if triazolam is prescribed to patients with signs or symptoms of depression that could be intensified by hypnotic drugs. Suicidal tendencies e.g., intentional overdose, is more common in these patients thus the least amount of drug that is feasible should be available to them at any one time.

Complex sleep-related behaviours: Complex sleep-related 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 in patients who have taken triazolam. Other potentially dangerous behaviours have been reported in patients who got out of bed after taking a sedative-hypnotic and were not fully awake, including preparing and eating food, making phone calls, leaving the house, etc. As with "sleep-driving", patients usually do not remember these events. The use of alcohol and other CNS-depressants with triazolam appears to increase the risk of such behaviours, as does the use of triazolam at doses exceeding the maximum recommended dose. MYLAN-TRIAZOLAM is not to be taken with alcohol. Caution is needed with concomitant use of other CNS depressant drugs. Due to the risk to the patient and the community, discontinuation of MYLAN-TRIAZOLAM should be strongly considered for patients who report any such complex sleep-related behaviours.

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, including triazolam. Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angiodema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with MYLAN-TRIAZOLAM should not be rechallenged with the drug.

PRECAUTIONS

Drug Interactions: Triazolam produces additive CNS depressant effects when co-administered with alcohol, antihistamines, anticonvulsants, or psychotropic medications which themselves can produce CNS depression.

Pharmacokinetic interactions can occur when triazolam is administered along with drugs that interfere with its metabolism. Examples include cimetidine or erythromycin which when co-administered with triazolam cause an approximate doubling of the plasma levels and elimination half-life of triazolam. Consequently, consideration of dose reduction may be appropriate when patients are treated concomitantly with triazolam and either cimetidine or erythromycin.

Drug abuse, dependence and withdrawal: Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting, sweating, dysphoria, perceptual disturbances and insomnia) have occurred following abrupt discontinuance of benzodiazepines, including triazolam. The more severe symptoms are usually associated with higher dosages and longer usage, although patients given therapeutic dosages for as few as 1-2 weeks can also have withdrawal symptoms, including daytime anxiety, between nightly doses (see ACTIONS and WARNINGS). Consequently, abrupt discontinuation should be avoided and a gradual dosage tapering schedule is recommended in any patient taking more than the lowest dose for more than a few weeks. The recommendation for tapering is particularly important in patients with a history of seizures.

The risk of dependence is increased in patients with a history of alcoholism, drug abuse, or in patients with marked personality disorders (see CONTRAINDICATIONS). Interdose daytime anxiety and rebound anxiety may increase the risk of dependency in triazolam-treated patients. As with all hypnotics, repeat prescriptions should be limited to those who are under medical supervision.

Patients with specific conditions: Triazolam should be given with caution to patients with impaired hepatic or renal function, severe pulmonary insufficiency, or sleep apnea. Respiratory depression and apnea have been reported in patients with compromised respiratory function.

Patients requiring mental alertness: Because of triazolam' s CNS depressant effect, patients receiving the drug should be cautioned against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be warned against the concomitant ingestion of triazolam and alcohol or CNS depressant drugs.

Use in pregnancy: For teratogenic effects see CONTRAINDICATIONS. Non-teratogenic effects: a child born to 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 to a mother who had been receiving benzodiazepines.

Use in nursing mothers: Human studies have not been performed but studies in rats have shown that triazolam and its metabolites are secreted in the milk. Therefore, administration of triazolam to nursing mothers is not recommended.

Use in children: The safety and effectiveness of triazolam in children below the age of 18 have not been established.

Use in the elderly: Elderly patients are especially susceptible to dose-related adverse effects, such as drowsiness, dizziness, or impaired coordination. Therefore, the lowest possible dose should be used in these subjects.

ADVERSE REACTIONS

The most frequent adverse reactions associated with the use of triazolam are extensions of the pharmacological effects of the drug, e.g., sedation (morning drowsiness, somnolence), dizziness, nervousness/irritability and impaired coordination.

The most serious adverse reactions which may occur include memory impairment, abnormal thinking/ behavior, confusion, anxiety, and depression (see WARNINGS).

The incidence of adverse reactions among patients receiving triazolam or placebo is listed in the table. The figures cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those in clinical trials. Comparison of the cited figures, however, can provide the prescriber with some basis for estimating the relative contributions of drug and nondrug factors to the untoward event incidence rate in the population studied.

PERCENT OF PATIENTS REPORTING ADVERSE REACTIONS (≥0.5%)

The adverse reaction profile of triazolam observed in controlled clinical trials illustrates the dose-dependency of most of the adverse reactions. **At present, the higher dose range is not recommended (see DOSAGE AND ADMINISTRATION section).**

Body system	Adverse Reaction	Triazolam 0.1-0.3 mg N=1002	Triazolam 0.4-0.6 mg N=2370	Placebo N=2036
CNS	drowsiness/ sedation	9.5	18.6	14.5
	headache	5.9	8.1	6.2
	Dizziness	4.4	9.0	5.8
	nervousness/irritability	3.7	4.6	6.4
	impaired coordination	1.7	4.3	1.2
	insomnia	1.0	1.2	2.8
	confusion	0.7	1.0	0.5
	mood changes	0.7	0.8	0.7
	depression	0.5	1.1	0.7
METABOLIC/ NUTRITION	memory impairment	0.2	1.0	0
	appetite change	0	0.5	0.6
SPECIAL SENSES	visual disturbance	0.4	0.7	0.2
	taste alteration	0.4	0.6	0.3
CARDIOVASCULAR	palpitations	0.5	0.4	0.4
RESPIRATORY	respiratory infection	1.1	1.7	0.9
GASTROINTESTINAL	nausea/vomiting	2.9	3.8	3.5
	dry mouth	0.5	0.9	1.4
	abdominal pain/ discomfort	0.4	0.6	0.5
	diarrhea	0.2	0.8	0.4
MUSCULOSKELETAL	musculoskeletal/ joint pain	0.8	0.9	0.7

The adverse reactions reported in the table were observed in controlled clinical trials conducted by The Upjohn Company.

Rare (i.e., less than 0.5%) adverse reactions include dysesthesia/ paresthesia, dream abnormalities, drug abuse/habituation, drug withdrawal symptoms, hallucinations, muscle tone disorder, tremor, tinnitus, hearing impairment, eye irritation/redness, edema, chest pain, hot/cold flashes, hypertension, syncope, dyspnea, constipation, flatulence, oral irritation, micturition difficulties, dermatitis, diaphoresis, muscular cramps, muscular weakness, malaise, sexual dysfunction. Elevated levels of SGOT, bilirubin, and alkaline phosphatase have also been noted.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Manifestations of MYLAN-TRIAZOLAM (triazolam) overdosage include extensions of its pharmacological effects, namely somnolence, confusion, impaired coordination, slurred speech, and ultimately coma. Respiratory depression and apnea have been reported with overdosages of triazolam.

Death has been reported in association with overdoses of triazolam by itself, as it has with other benzodiazepines. In addition, fatalities have been reported in patients who have overdosed with a combination of alcohol and a single benzodiazepine, including triazolam. In some of these cases, blood levels of the benzodiazepine and alcohol were lower than those usually associated with reports of fatalities with either substance alone.

As in all cases of drug overdosage, respiration, pulse and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. An adequate airway should be maintained. Intravenous fluids may be administered. As with the management of intentional overdosage with any drug, the physician should bear in mind that multiple agents may have been ingested by the patient.

The benzodiazepine antagonist, flumazenil ('Anexate'), is a specific antidote in known or suspected benzodiazepine overdose. (For conditions of use see 'Anexate' Product Monograph).

Experiments in animals have indicated that cardiopulmonary collapse can occur with massive intravenous doses of triazolam. This could be reversed with positive mechanical respiration and intravenous infusion of norepinephrine bitartrate or metaraminol bitartrate. Hemodialysis and forced diuresis are probably of little value.

For management of a suspected drug overdose, contact your regional Poison Control Centre Immediately.

DOSAGE AND ADMINISTRATION

The lowest effective dose of MYLAN-TRIAZOLAM (triazolam) should be used. Treatment with triazolam should usually not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete reevaluation 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. In most adults, a dose of 0.25 mg should not be exceeded. A dose of 0.5 mg should be used only for exceptional patients who do not respond adequately to a trial of the lower dose since the risk of several adverse reactions increases with the size of the dose administered.

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.

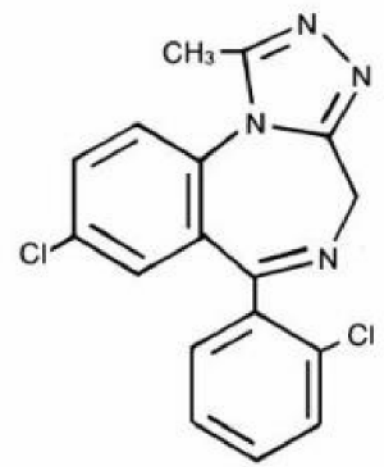
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: triazolam

Chemical Name: 4H-(1,2,4)Triazolo[4,3-a)[1,4] benzodiazepine, 8-chloro-6-(2-chlorpheny1)-1-methyl.

Structural Formula:



Molecular Formula: $C_{17}H_{12}Cl_2N_4$

Molecular Weight: 343.22

Description: Triazolam is a white, crystalline powder which is soluble in chloroform; slightly soluble in alcohol; practically insoluble in ether and in water. It has a melting point of 233 to 235°C.

Composition:
MYLAN-TRIAZOLAM Tablets 0.125 mg and 0.250 mg are manufactured using the active ingredient Triazolam, USP.

Storage Recommendations:
MYLAN- TRIAZOLAM Tablets 0.125 mg and 0.250 mg should be stored in a tight, light resistant package between 15 and 30°C (59 and 86°F).

AVAILABILITY OF DOSAGE FORMS

MYLAN-TRIAZOLAM 0.125 mg tablets are mauve, oval shaped, flat bevelled edged, marked "TZ" on one side and scored on the other side.

MYLAN-TRIAZOLAM 0.250 mg tablets are blue, oval shaped, flat bevelled edged, marked "TZ" on one side and scored on the other side.

MYLAN-TRIAZOLAM 0.125 mg and 0.250 mg tablets are available in blister packages of 7 tablets per blister strip. MYLAN-TRIAZOLAM will be supplied as 70 tablets per carton.

INFORMATION FOR THE PATIENT

What is the most important information I should know about MYLAN-TRIAZOLAM?
There have been reports of people getting out of bed while not fully awake after taking MYLAN-TRIAZOLAM and doing activities that they did not know they were doing. The next morning, they did not remember doing those activities. This unusual behaviour is more likely to occur when MYLAN-TRIAZOLAM is taken with alcohol or other drugs that can make you sleepy such as those for the treatment of depression or anxiety. The activities you may do in these situations can put you and people around you in danger. Reported activities included driving a car ("sleep-driving"), leaving the house, making and eating food, talking on the phone, etc.

Important:

1. Do not take more MYLAN-TRIAZOLAM than prescribed
2. Do not take MYLAN-TRIAZOLAM if you drink alcohol
3. Talk to your doctor about all of your medicines, including over-the-counter medicines and herbal products.
   Your doctor will tell you if you can take MYLAN-TRIAZOLAM with your other medicines.
4. You and people close to you should watch for the type of unusual behaviour described above. If you find out that you have done *any* such activities for which you have no memory you should call your doctor immediately.

INTRODUCTION

MYLAN-TRIAZOLAM is intended to help you sleep. It is one of several benzodiazepine sleeping pills that have generally similar properties.

If you are prescribed one of these medications, you should consider both their benefits and risks. Important risks and limitations include the following:

- the longer you use the medication, the less effective it may become,

- you may become dependent on the medication,

- the medication may affect your mental alertness or memory, particularly when not taken as prescribed.

In order to guide you in the safe use of the product, this leaflet will inform you about this class of medication in general, and about MYLAN-TRIAZOLAM in particular.

BUT THIS LEAFLET SHOULD NOT REPLACE A DISCUSSION BETWEEN YOU AND YOUR DOCTOR ABOUT THE RISKS AND BENEFITS OF MYLAN-TRIAZOLAM.

SAFE USE OF MYLAN-TRIAZOLAM SLEEPING PILLS

- MYLAN-TRIAZOLAM is a prescription medication, intended to help you sleep. Follow your doctor's advice about how to take MYLAN-TRIAZOLAM, when to take it, and how long to take it. DO NOT TAKE MYLAN-TRIAZOLAM if it is not prescribed for you.

- DO NOT TAKE MYLAN-TRIAZOLAM for more than 7-10 days without first consulting your doctor.

- DO NOT TAKE MYLAN-TRIAZOLAM when a full night's sleep is not possible before you would again need to be active and functional; e.g. an overnight flight of less than 8 hours. Memory lapses may occur in such situations. Your body needs time to eliminate the medication from your system.

- DO NOT TAKE MYLAN-TRIAZOLAM at any time during pregnancy. Tell your doctor if you are planning to become pregnant, if you are pregnant, or if you become pregnant while taking this medication.

- Tell your doctor about any alcohol consumption (present or past) or any medicine you are taking now, including drugs you can buy without a prescription. DO NOT CONSUME ALCOHOL WHILE TAKING MYLAN-TRIAZOLAM.

- DO NOT INCREASE THE PRESCRIBED DOSE.

- DO NOT DRIVE A CAR or operate potentially dangerous machinery until you experience how this drug will affect you.

- If you develop any unusual disturbing thoughts or behaviour while using MYLAN-TRIAZOLAM, discuss the matter immediately with your doctor.

-You may experience an increase in sleep difficulties (rebound insomnia) and/or increased daytime anxiety (rebound anxiety) for one or two days after discontinuing MYLAN-TRIAZOLAM.

In the event of overdosage, contact your doctor, hospital emergency department or regional Poison Control Centre Immediately.

Effectiveness of Benzodiazepine Sleeping Pills

Benzodiazepine sleeping pills are effective medications and are relatively free of serious problems when used for the short-term management of insomnia. Symptoms of insomnia may vary: you may have difficulty in falling asleep, or awaken often during the night, or awaken early in the morning, or you may have all three symptoms.
Insomnia may last only for a short time and may respond to brief treatment. The risks and benefits of prolonged use should be discussed with your doctor.

SIDE EFFECTS

Common Side Effects
Benzodiazepine sleeping pills may cause drowsiness, dizziness, lightheadedness, and difficulty with coordination. Users must be cautious about engaging in hazardous activities requiring complete mental alertness, e.g. operating machinery or driving a motor vehicle.

Avoid alcohol while using MYLAN-TRIAZOLAM. DO NOT USE benzodiazepine sleeping pills along with other medications without first discussing this with your doctor.

How sleepy you are the day after you use one of these sleeping pills depends on your individual response and on how quickly your body gets rid of the medication. The larger the dose, the more likely that you will experience drowsiness, etc., the next day. For this reason, it is important that you use the lowest effective dose. Benzodiazepines, which are eliminated rapidly (like MYLAN-TRIAZOLAM), tend to cause less drowsiness the next day, but may cause withdrawal problems the day after use (see below).

Serious Side Effects
Rare cases of severe allergic reactions have been reported. Symptoms may include swelling of the tongue or throat, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking MYLAN-TRIAZOLAM.

SPECIAL CONCERNS

Memory Problems
All benzodiazepine sleeping pills can cause a special type of memory loss (amnesia); you may not recall events that occurred during some period of time, usually several
hours, after taking the drug. This lapse is usually not a problem, because the person taking the sleeping pill intends to be asleep during this critical period of time. But it can be a problem if you take the medication to induce sleep while travelling, such as during an airplane flight, because you may wake up before the effect of the drug is gone. This has been called “traveller's amnesia”. MYLAN-TRIAZOLAM is more likely than other benzodiazepine sleeping pills to cause this problem.

Tolerance/Withdrawal Symptoms

After nightly use for more than a few weeks these drugs may lose some of their effectiveness. You may also develop a degree of dependence.

For benzodiazepine sleeping pills that the body eliminates quickly, there may be a deficiency of the drug in the body at some point between each night's use. This can lead to (1) being awake during the last third of the night, and (2) increased daytime anxiety or nervousness. These side effects have been reported in particular with triazolam.

More severe "withdrawal" effects can occur when patients stop taking benzodiazepine sleeping pills. The effects may occur following use for only a week or two but may be more common and severe after long periods of continuous use. One type of withdrawal symptom is known as "rebound insomnia", i.e. on the first few nights after stopping the medication, insomnia may be worse than before the sleeping pill was given.

Other withdrawal symptoms following abrupt stopping of sleeping pills may range from unpleasant feelings to a major withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremor, and rarely, convulsions. The severe symptoms are uncommon.

Dependence/Abuse

All benzodiazepine sleeping pills can cause dependence (addiction) especially when used regularly for more than a few weeks, or at higher doses. Some people develop a need to continue taking these drugs, either at the prescribed dose or at higher doses - not for continued therapeutic effect, but to avoid withdrawal symptoms or to achieve nontherapeutic effects.

Individuals who depend on alcohol or other drugs may be at particular risk of becoming dependent on drugs of this class. But ALL PEOPLE ARE AT SOME RISK. Consider this matter before you take these medications beyond a few weeks.

Mental and Behavioural Changes

A variety of abnormal thinking and behaviour changes may occur when you use benzodiazepine sleeping pills. Some of these changes include aggressiveness and extroversion which seem out of character. Other changes, however, can be more unusual and extreme such as confusion, strange behaviour, restlessness, hallucinations, feeling like you are not yourself, and worsening depression, including suicidal thinking.

It is rarely clear whether such symptoms are caused by the medication, or by an underlying illness, or are simply spontaneous happenings. In fact, worsened insomnia may in some cases be associated with illnesses that were present before the medication was used.

IMPORTANT NOTE: Regardless of the cause, if you take these medications, report any mental or behavioral changes promptly to your doctor.

Effects on Pregnancy

Certain benzodiazepine sleeping pills have been linked to birth defects when taken during the early months of pregnancy. In addition, benzodiazepine sleeping pills taken during the last weeks

of pregnancy have been known to sedate the baby. Therefore, **AVOID USING THIS MEDICATION DURING PREGNANCY**.

PHARMACOLOGY

Triazolam antagonized chemically induced seizures in mice, rats, and cats, but like other benzodiazepines, it was much less effective against electroshock-induced seizures.
In tests measuring potential muscle-relaxant activity, triazolam antagonized strychnine lethality, inhibited the traction response in mice, and depressed spinal reflexes in the decerebrate cat.

Triazolam was found to potentiate a number of central nervous system depressant agents, as measured by the loss of righting reflex in mice. No loss of righting reflex was noted with triazolam alone, except at toxic doses.

Triazolam significantly lowered the LD50's of chlorpromazine, diphenylhydantoin, glutethimide, and pentobarbital, while having little or no effect on the LD50's of a number of other drugs.

Triazolam was more active than diazepam in antagonizing foot-shock-induced aggressive behaviour in mice, in inhibiting aggressive behaviour in monkeys, and in suppressing conflict behaviour in rats. Cross dependence studies with barbiturates, direct physical dependence studies, and self-administration studies indicated little potential for physical dependence with triazolam in the animal systems tested.

Triazolam produced changes in EEG activity of monkeys characteristic of those seen with other benzodiazepines.

Triazolam did not influence plasma warfarin levels or alter prothrombin time in rats or dogs.

Triazolam crossed the blood-brain barrier in mice after intraperitoneal administration. Brain levels of norepinephrine and dopamine in mice were essentially unchanged by either triazolam or diazepam. Both slowed the utilization of dopamine by the brain and also decreased the incorporation of C^{14} tyrosine into norepinephrine and dopamine. Triazolam had no significant effect on serotonin turnover.

Triazolam and diazepam caused similar changes in cardiovascular and pulmonary parameters of cats and dogs at considerably higher doses than those producing central nervous system effects.

Pharmacokinetics:
Triazolam, administered orally to man as a compressed tablet, had a minimal absorption of 82% and a peak plasma level at 1.5 hours. Triazolam had a half-life of 2.7 hours and this was consistent with the absence of accumulated triazolam in the plasma 24 hours after each dose for seven consecutive 1 mg doses. Studies of blood and plasma indicated no accumulation of triazolam related material in the formed elements of the blood.

At 37°C, triazolam was 89% bound in human serum. Binding to albumin accounted for only a portion of the total binding observed, since binding in a physiological concentration of human serum albumin amounted to only 49%.

Urine from humans dosed orally with triazolam -^{14}C contained small amounts of unmetabolized triazolam as well as 6 metabolites. The two metabolites found in highest concentration in human urine were 1,-hydroxy-triazolam and 4-hydroxy-triazolam which accounted for 69% and 11% of the urinary radioactivity respectively.
In man, approximately 85% of drug related materials following oral administration of triazolam -^{14}C was excreted in the urine whereas approximately 8% was excreted in the faeces. Biliary excretion appeared relatively unimportant in man. Urinary excretion of drug-related materials was quite rapid in man and could be described by two exponentials. The initial excretion rate was equivalent to a mean excretion half-time of about 6 hours and the mean excretion half-time for the terminal excretion phase was about 36 hours.

The pharmacokinetics of triazolam were also examined in the rat and dog. Twelve metabolites were found in rat, and 10 metabolites in dog urine. All metabolites found in human urine were also present in rat urine, indicating a qualitative similarity of triazolam metabolism in human and rat. The two major human metabolites were also the major urinary metabolites in the dog, but not the rat. In the rat, triazolam-related materials were excreted primarily in the faeces, whereas the urinary and fecal excretion were approximately equivalent in the dog. The elimination kinetics of the rat were similar to those of man, whereas in the dog they were more complex.

Tissue distribution of ^{14}C-triazolam radioactivity was studied in the mouse by whole-body section autoradiography. Following oral or intravenous administration, triazolam and/or its metabolites were rapidly and widely distributed throughout the body. The concentration of drug-related material in most organs and tissues had reached a maximum within 1 hr. of dosing, and decreased rapidly thereafter. The ^{14}C concentration in the brain was reasonably well reflected by the blood ^{14}C concentration.

When triazolam was given to pregnant mice two days before term, drug-related material was found uniformly distributed in the fetus with concentrations approximately the same as in the brain of the mother. When ^{14}C-triazolam was given orally to lactating rats, triazolam appeared mainly as metabolites in the milk samples obtained at 6 and 24 hours post-administration.

TOXICOLOGY

Acute Toxicity:
The oral LD_{50}'s in the rat were found to be greater than 5000 mg/kg. The oral LD_{50} in the mouse was greater than 5000 mg/kg. Signs of toxicity included lethargy, ataxia, reduced motor activity, piloerection, ptosis, hunched back and abdominal distention.

Necropsy of the two rats who died revealed reddening of the pyloric antrum in one case and gaseous distention of the GI tract in the other.

Necropsy of the one mouse that died revealed no visible tissue abnormalities.

Necropsy of animals killed routinely at the conclusion of the study revealed no visible abnormality.

Subacute and Chronic Toxicity:
Triazolam was administered orally or intravenously to rats for periods of 14 days, 86 days and 2 years. In the two 14-day studies (0, 500 and 1000 mg/kg/day p.o.; 0, 0.5, 1.0 and 2.0 mg/kg/day i.v.), triazolam produced sedation, drowsiness and ataxia. In the 86- day study (0, 30, 100 and 300 mg/kg/day p.o.), sedation was observed after dosing. However, toward the end of the study, only the 300 mg/kg rats appeared to be affected. The higher doses produced increased kidney and adrenal weights in both sexes and increased liver weights in females. In the two-year study (0, 10, 30 and 100 mg/kg/day p.o.), the pharmacologic effects noted were drowsiness, increased aggressiveness in females and some unsteadiness. Male rats receiving the two higher dose levels had shorter mean survival times than did low dose and control animals. These early deaths were associated with urinary calculi and chronic progressive nephrosis. The overall incidence of chronic progressive nephrosis was the same for all males, but developed early in rats receiving the higher triazolam doses.

Seven treated rats developed large thrombi, mainly in the heart. Similarly, 10 treated animals had microscopic foreign body granulomas in their lungs. Triazolam tended to aggravate the incidence and extent of hepatic necrosis. Serum cholesterol levels increased slightly with increasing doses.

Dogs were administered triazolam for periods of 9 days, 13 days, 3 months and one year. In the 9-day study (0 and 100-300 mg/kg/day p.o.), anxiety, ataxia and sedation were seen for the first two days and polydypsia was the only consistent observation throughout the study. In the 13-day study (0, 0.1, 0.5 and 1.0 mg/kg/day i.v.), triazolam produced relaxation and ataxia and a dose-related increase in SGOT, cholesterol and BUN. One dog in the mid-dose group had marked elevation of liver enzymes, hepatocellular degeneration with focal necrosis and raised BSP. In the 3-month study (0, 0.5, 10 and 50 mg/kg/day p.o.), indications of tolerance development were seen and the dose was altered on the thirteenth day (0, 10, 30 and 100 mg/kg/day). Hyperactivity, hyperexcitability, ataxia, sedation and polydypsia were observed. Despite increased food consumption, treated dogs showed lower weight gain than controls. Dogs treated with the two higher triazolam doses had elevated alkaline phosphatase and slightly increased liver weights.

Two out of four dogs at the highest dose had reduced liver glycogen and one had a suggestion of bile duct proliferation. In the one-year study (0, 3, 10 and 30 mg/kg/day p.o. 6 days/wk), triazolam caused ataxia, ptosis, hyperactivity, increased food consumption and loose stools. Dogs in all treated groups had raised alkaline phosphatase levels and decreased prothrombin times. Liver weights were increased in the mid-dose group. At the two higher dose levels, elevation of platelet and leukocyte counts was observed. One high-dose dog was sacrificed at one year after being moribund and convulsing for 24 hours and was found to have acute myocardial degeneration.

Reproduction and Teratology Studies:

Significant drug-related abnormalities were not seen in the offspring of female rats treated orally with 2 and 5 mg/kg/day of triazolam in the diet prior to mating and throughout the subsequent pregnancy. Similarly, the same regimen administered to males prior to mating had no effect on the pregnancies sired by those males.

Triazolam given orally to pregnant rats from day 6 through day 15 at dosage levels of 10 and 30 mg/kg/day did not adversely affect the reproductive parameters studied with the exception of a slight increase in the average number of resorption sites per litter at the 30 mg/kg level. Some skeletal growth retardation occurred at the 30 mg level as indicated by a higher incidence of 5th metacarpals absent and minor sternebrae variations (mostly incomplete ossification). One fetus from the 30 mg level exhibited a hypoplastic mandible and premaxilla. Another fetus from the same litter lacked all ribs and vertebrae below the 3rd thoracic vertebrae with the exception of one sacral vertebra.

Triazolam administered orally to pregnant rabbits at 10 and 30 mg/kg/day on gestation days 6 through 18 did not adversely affect the reproductive parameters studied. The results of examinations for visceral and skeletal malformations in triazolam treated rabbits revealed minor alterations in rib numbers accompanied by a low incidence of rib and sternebrae malformations suggesting teratogenic activity in this species. The lowest dose level at which the alterations occurred with triazolam was 10 mg/kg/day.

Treatment of pregnant rabbits on gestation days 6 through 18 by gastric intubation of triazolam at 0.2, 0.5, 2 and 5 mg/kg/day or diazepam at 8, 20, 25 and 50 mg/kg/day did not affect the reproductive parameters studied.

The incidence of anatomical variations and abnormalities observed were comparable to current or previous control groups with this strain of rabbit or were considered spontaneous due to their isolated nature. No dose-related teratogenic activity was observed following treatment with triazolam or diazepam under the conditions of this study.

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