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Halcion®

C IV

triazolam tablets, USP

PHARMACIA

Halcion triazolam tablets, USP

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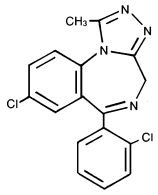
DESCRIPTION

HALCION Tablets contain triazolam, a triazolobenzodiazepine hypnotic agent.

Triazolam is a white crystalline powder, soluble in alcohol and poorly soluble in water. It has a molecular weight of 343.21.

The chemical name for triazolam is 8-chloro-6-(o-chlorophenyl)-1-methyl-4H-s-triazolo-[4,3-α][1,4] benzodiazepine.

The structural formula is represented below:



Each HALCION Tablet, for oral administration, contains 0.125 mg or 0.25 mg of triazolam. Inactive ingredients: **0.125 mg**—cellulose, corn starch, docusate sodium, lactose, magnesium stearate, silicon dioxide, sodium benzoate; **0.25 mg**—cellulose, corn starch,

docusate sodium, FD&C Blue No. 2, lactose, magnesium stearate, silicon dioxide, sodium benzoate.

CLINICAL PHARMACOLOGY

Triazolam is a hypnotic with a short mean plasma half-life reported to be in the range of 1.5 to 5.5 hours. In normal subjects treated for 7 days with four times the recommended dosage, there was no evidence of altered systemic bioavailability, rate of elimination, or accumulation. Peak plasma levels are reached within 2 hours following oral administration. Following recommended doses of HALCION, triazolam peak plasma levels in the range of 1 to 6 ng/mL are seen. The plasma levels achieved are proportional to the dose given.

Triazolam and its metabolites, principally as conjugated glucuronides, which are presumably inactive, are excreted primarily in the urine. Only small amounts of unmetabolized triazolam appear in the urine. The two primary metabolites accounted for 79.9% of urinary excretion. Urinary excretion appeared to be biphasic in its time course.

HALCION Tablets 0.5 mg, in two separate studies, did not affect the prothrombin times or plasma warfarin levels in male volunteers administered sodium warfarin orally.

Extremely high concentrations of triazolam do not displace bilirubin bound to human serum albumin *in vitro*.

Triazolam ^{14}C was administered orally to pregnant mice. Drug-related material appeared uniformly distributed in the fetus with ^{14}C concentrations approximately the same as in the brain of the mother.

In sleep laboratory studies, HALCION Tablets significantly decreased sleep latency, increased the duration of sleep, and decreased the number of nocturnal awakenings. After 2 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 and/or second night after drug discontinuance (first or second post-drug night), total time asleep, percentage of time spent sleeping, and rapidity of falling asleep frequently were significantly less than on baseline (predrug) nights. This effect is often called "rebound" insomnia.

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 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; the possibility of interaction with other psychoactive drugs or alcohol will be enhanced. In contrast, if half-lives are short, the 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 (ie, 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.

In a study of elderly (62-83 years old) versus younger subjects (21-41 years old) who received HALCION at the same dose levels (0.125 mg and 0.25 mg), the elderly experienced both greater sedation and impairment of psychomotor performance. These effects resulted largely from higher plasma concentrations of triazolam in the elderly.

INDICATIONS AND USAGE

HALCION is indicated for the short-term treatment of insomnia (generally 7-10 days). Use for more than 2-3 weeks requires complete reevaluation of the patient (see WARNINGS).

Prescriptions for HALCION should be written for short-term use (7-10 days) and it should not be prescribed in quantities exceeding a 1-month supply.

CONTRAINDICATIONS

HALCION Tablets are contraindicated in patients with known hypersensitivity to this drug or other benzodiazepines.

Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Transplacental distribution has resulted in neonatal CNS depression following the ingestion of therapeutic doses of a benzodiazepine hypnotic during the last weeks of pregnancy.

HALCION is contraindicated in pregnant women. If there is a likelihood of the patient becoming pregnant while receiving HALCION, she should be warned of the potential risk to the fetus. Patients should be instructed to discontinue the drug prior to becoming pregnant. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered.

HALCION is contraindicated with ketoconazole, itraconazole, and nefazodone, medications that significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP 3A) (see WARNINGS and PRECAUTIONS–Drug Interactions).

WARNINGS

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 behavior may be the consequence of an unrecognized psychiatric or physical disorder. These have also been reported to occur in association with the use of HALCION.

Because some of the adverse effects of HALCION appear to be dose related (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), it is important to use the smallest possible effective dose. Elderly patients are especially susceptible to dose related adverse effects.

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

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of benzodiazepine hypnotics including HALCION. Some of these changes may be characterized by decreased inhibition, eg, aggressiveness and extroversion that seem excessive, similar to that seen with alcohol and other CNS depressants (eg, sedative/hypnotics). Other kinds of behavioral changes have also been reported, for example, bizarre behavior, agitation, hallucinations, depersonalization. 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 behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Because of its depressant CNS effects, patients receiving triazolam 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 cautioned about the concomitant ingestion of alcohol and other CNS depressant drugs during treatment with HALCION Tablets.

As with some, but not all benzodiazepines, anterograde amnesia of varying severity and paradoxical reactions have been reported following therapeutic doses of HALCION. Data from several sources suggest that anterograde amnesia may occur at a higher rate with HALCION than with other benzodiazepine hypnotics.

Triazolam interaction with drugs that inhibit metabolism via cytochrome P450 3A:

The initial step in triazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP 3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of triazolam. Consequently, triazolam should be avoided in patients receiving very potent inhibitors of CYP 3A. With drugs inhibiting CYP 3A to a lesser but still significant degree, triazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with triazolam has been quantified with clinical data; for other drugs, interactions are predicted from *in vitro* data and/or experience with similar drugs in the same pharmacologic class.

The following are examples of drugs known to inhibit the metabolism of triazolam and/or related benzodiazepines, presumably through inhibition of CYP 3A.

Potent CYP 3A inhibitors: Potent inhibitors of CYP 3A that should not be used concomitantly with triazolam include ketoconazole, itraconazole, and nefazodone. Although data concerning the effects of azole-type antifun-

gal agents other than ketoconazole and itraconazole on triazolam metabolism are not available, they should be considered potent CYP 3A inhibitors, and their coadministration with triazolam is not recommended (see CONTRAINDICATIONS).

Drugs demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving triazolam (caution and consideration of dose reduction are recommended during coadministration with triazolam):

Macrolide Antibiotics—Coadministration of erythromycin increased the maximum plasma concentration of triazolam by 46%, decreased clearance by 53%, and increased half-life by 35%; caution and consideration of appropriate triazolam dose reduction are recommended. Similar caution should be observed during coadministration with clarithromycin and other macrolide antibiotics.

Cimetidine—Coadministration of cimetidine increased the maximum plasma concentration of triazolam by 51%, decreased clearance by 55%, and increased half-life by 68%; caution and consideration of appropriate triazolam dose reduction are recommended.

Other drugs possibly affecting triazolam metabolism: Other drugs possibly affecting triazolam metabolism by inhibition of CYP 3A are discussed in the PRECAUTIONS section (see PRECAUTIONS–Drug Interactions).

PRECAUTIONS

General: In elderly and/or debilitated patients it is recommended that treatment with HALCION Tablets be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination.

Some side effects reported in association with the use of HALCION appear to be dose related. These include drowsiness, dizziness, light-headedness, and amnesia.

The relationship between dose and what may be more serious behavioral phenomena is less certain. Specifically, some evidence, based on spontaneous marketing reports, suggests that confusion, bizarre or abnormal behavior, agitation, and hallucinations may also be dose related, but this evidence is inconclusive. In accordance with good medical practice it is recommended that therapy be initiated at the lowest effective dose (see DOSAGE AND ADMINISTRATION).

Cases of "traveler's amnesia" have been reported by individuals who have taken HALCION to induce sleep while traveling, such as during an airplane flight. In some of these cases, insufficient time was allowed for the sleep period prior to awakening and before beginning activity. Also, the concomitant use of alcohol may have been a factor in some cases.

Caution should be exercised if HALCION is prescribed to patients with signs or symptoms of depression that could be intensified by hypnotic drugs. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in these patients, and the least amount of drug that is feasible should be available to the patient at any one time.

The usual precautions should be observed in patients with impaired renal or hepatic function, chronic pulmonary insufficiency, and sleep apnea. In patients with compromised respiratory function, respiratory

depression and apnea have been reported infrequently.

Information for patients: The text of a patient package insert is printed at the end of this insert. To assure safe and effective use of HALCION, the information and instructions provided in this patient package insert should be discussed with patients.

Laboratory tests: Laboratory tests are not ordinarily required in otherwise healthy patients.

Drug interactions: Both pharmacodynamic and pharmacokinetic interactions have been reported with benzodiazepines. In particular, triazolam produces additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs which themselves produce CNS depression.

Drugs that inhibit triazolam metabolism via cytochrome P450 3A: The initial step in triazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP 3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of triazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs of this type).

Drugs and other substances demonstrated to be CYP 3A inhibitors of possible clinical significance on the basis of clinical studies involving triazolam (caution is recommended during coadministration with triazolam):

Isoniazid—Coadministration of isoniazid increased the maximum plasma concentration of triazolam by 20%, decreased clearance by 42%, and increased half-life by 31%.

Oral contraceptives—Coadministration of oral contraceptives increased maximum plasma concentration by 6%, decreased clearance by 32%, and increased half-life by 16%.

Grapefruit juice—Coadministration of grapefruit juice increased the maximum plasma concentration of triazolam by 25%, increased the area under the concentration curve by 48%, and increased half-life by 18%.

Drugs demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to triazolam or on the basis of in vitro studies with triazolam or other benzodiazepines (caution is recommended during coadministration with triazolam): Available data from clinical studies of benzodiazepines other than triazolam suggest a possible drug interaction with triazolam for the following: fluvoxamine, diltiazem, and verapamil. Data from *in vitro* studies of triazolam suggest a possible drug interaction with triazolam for the following: sertraline and paroxetine. Data from *in vitro* studies of benzodiazepines other than triazolam suggest a possible drug interaction with triazolam for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during coadministration of any of these drugs with triazolam (see WARNINGS).

Drugs that affect triazolam pharmacokinetics by other mechanisms:

Ranitidine—Coadministration of ranitidine increased the maximum plasma concentration of triazolam by 30%, increased the area under the concentration curve by 27%, and increased half-life by 3.3%. Caution is recommended during coadministration with triazolam.

Carcinogenesis, mutagenesis, impairment of fertility: No evidence of carcinogenic potential was observed in mice during a 24-month

study with HALCION in doses up to 4,000 times the human dose.

Pregnancy:

1. Teratogenic effects: Pregnancy category X (see CONTRAINDICATIONS).
2. 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.

Nursing mothers: Human studies have not been performed; however, studies in rats have indicated that HALCION and its metabolites are secreted in milk. Therefore, administration of HALCION to nursing mothers is not recommended.

Pediatric use: Safety and effectiveness of HALCION in individuals below 18 years of age have not been established.

Geriatric use: The elderly are especially susceptible to the dose related adverse effects of HALCION. They exhibit higher plasma triazolam concentrations due to reduced clearance of the drug as compared with younger subjects at the same dose. To minimize the possibility of development of oversedation, the smallest effective dose should be used (see CLINICAL PHARMACOLOGY, WARNINGS,PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

During placebo-controlled clinical studies in which 1,003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of triazolam, eg, drowsiness, dizziness, or light-headedness.

The figures cited below are estimates of untoward clinical event incidence among subjects who participated in the relatively short duration (ie, 1 to 42 days) placebo-controlled clinical trials of HALCION. 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. These figures cannot be compared with those obtained from other clinical studies involving related drug products and placebo, as each group of drug trials is conducted under a different set of conditions.

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. Even this use must be approached cautiously, as a drug may relieve a symptom in one patient while inducing it in others. (For example, an anticholinergic, anxiolytic drug may relieve dry mouth [a sign of anxiety] in some subjects but induce it [an untoward event] in others.)

	HALCION	PLACEBO
Number of Patients	1003	997
% Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5

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	HALCION	PLACEBO
Light-headedness	4.9	0.9
Coordination disorders/ataxia	4.6	0.8
Gastrointestinal		
Nausea/vomiting	4.6	3.7

In addition to the relatively common (ie, 1% or greater) untoward events enumerated above, the following adverse events have been reported less frequently (ie, 0.9% to 0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (ie, less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

In addition to these untoward events for which estimates of incidence are available, the following adverse events have been reported in association with the use of HALCION and other benzodiazepines: amnestic symptoms (anterograde amnesia with appropriate or inappropriate behavior), confusional states (disorientation, derealization, depersonalization, and/or clouding of consciousness), dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention. Other factors may contribute to some of these reactions, eg, concomitant intake of alcohol or other drugs, sleep deprivation, an abnormal premorbid state, etc.

Other events reported include: paradoxical reactions such as stimulation, mania, an agitational state (restlessness, irritability, and excitation), increased muscle spasticity, sleep disturbances, hallucinations, delusions, aggressiveness, falling, somnambulism, syncope, inappropriate behavior and other adverse behavioral effects. Should these occur, use of the drug should be discontinued.

The following events have also been reported: chest pain, burning tongue/glossitis/stomatitis.

Laboratory analyses were performed on all patients participating in the clinical program for HALCION. The following incidences of abnormalities were observed in patients receiving HALCION and the corresponding placebo group. None of these changes were considered to be of physiological significance.

	HALCION		PLACEBO	
Number of Patients	380		361	
% of Patients Reporting:	Low	High	Low	High
Hematology				
Hematocrit	*	*	*	*
Hemoglobin	*	*	*	*
Total WBC count	1.7	2.1	*	1.3
Neutrophil count	1.5	1.5	3.3	1.0
Lymphocyte count	2.3	4.0	3.1	3.8
Monocyte count	3.6	*	4.4	1.5
Eosinophil count	10.2	3.2	9.8	3.4
Basophil count	1.7	2.1	*	1.8
Urinalysis				
Albumin	—	1.1	—	*
Sugar	—	*	—	*
RBC/HPF	—	2.9	—	2.9

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	HALCION		PLACEBO	
WBC/HPF	—	11.7	—	7.9
Blood chemistry				
Creatinine	2.4	1.9	3.6	1.5
Bilirubin	*	1.5	1.0	*
SGOT	*	5.3	*	4.5
Alkaline phosphatase	*	2.2	*	2.6

*Less than 1%

When treatment with HALCION is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during therapy with HALCION and are of no known significance.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Triazolam is a controlled substance under the Controlled Substance Act, and HALCION Tablets have been assigned to Schedule IV.

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 HALCION. The more severe symptoms are usually associated with higher dosages and longer usage, although patients at therapeutic dosages given for as few as 1-2 weeks can also have withdrawal symptoms and in some patients there may be withdrawal symptoms (daytime anxiety, agitation) between nightly doses (see CLINICAL PHARMACOLOGY). 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 any patient with a history of seizure.

The risk of dependence is increased in patients with a history of alcoholism, drug abuse, or in patients with marked personality disorders. Such dependence-prone individuals should be under careful surveillance when receiving HALCION. As with all hypnotics, repeat prescriptions should be limited to those who are under medical supervision.

OVERDOSAGE

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).

Manifestations of overdosage with HALCION Tablets include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiratory depression and apnea have been reported with overdosages of HALCION. Seizures have occasionally been reported after overdosages.

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 a single benzodiazepine, including triazolam, and alcohol; benzodiazepine and alcohol levels seen in some of these cases have been lower than those usually associated with reports of fatality with either substance alone.

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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.

Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. 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.** The complete flumazenil package insert including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS should be consulted prior to use.

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 the intravenous infusion of norepinephrine bitartrate or metaraminol bitartrate. Hemodialysis and forced diuresis are probably of little value. 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 oral LD_{50} in mice is greater than 1,000 mg/kg and in rats is greater than 5,000 mg/kg.

DOSAGE AND ADMINISTRATION

It is important to individualize the dosage of HALCION Tablets for maximum beneficial effect and to help avoid significant adverse effects.

The recommended dose for most adults is 0.25 mg before retiring. A dose of 0.125 mg may be found to be sufficient for some patients (eg, low body weight). A dose of 0.5 mg should be used only for exceptional patients who do not respond adequately to a trial of a lower dose since the risk of several adverse reactions increases with the size of the dose administered. A dose of 0.5 mg should not be exceeded.

In geriatric and/or debilitated patients the recommended dosage range is 0.125 mg to 0.25 mg. Therapy should be initiated at 0.125 mg in these groups and the 0.25 mg dose should be used only for exceptional patients who do not respond to a trial of the lower dose. A dose of 0.25 mg should not be exceeded in these patients.

As with all medications, the lowest effective dose should be used.

HOW SUPPLIED

HALCION Tablets are available in the following strengths and package sizes:

0.125 mg (white, elliptical, imprinted HALCION 0.125):

Reverse numbered
Unit Dose (100) NDC 0009-0010-32

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10–10 Tablet Bottles	NDC 0009-0010-38
Bottles of 500	NDC 0009-0010-11

0.25 mg (powder blue, elliptical, scored, imprinted HALCION 0.25):

Reverse numbered Unit Dose (100)	NDC 0009-0017-55
10–10 Tablet Bottles	NDC 0009-0017-59
Bottles of 500	NDC 0009-0017-02

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

The text of the patient insert for HALCION is set forth below.

PATIENT INFORMATION

INTRODUCTION

HALCION is intended to help you sleep. It is one of several benzodiazepine sleeping pills that have generally similar properties. Anyone who is considering using one of these medications should be aware of both their benefits and several important risks and limitations, including diminishing effectiveness with continued use and the possible development of dependence (addiction) and possibly mental changes particularly when the drugs are used for more than a few days to a week. This patient information statement is intended to provide you with knowledge about this class of medications in general and about HALCION in particular that will be useful to guide you in the safe use of this product, BUT IT SHOULD NOT REPLACE A DISCUSSION BETWEEN YOU AND YOUR PHYSICIAN ABOUT THE RISKS AND BENEFITS OF HALCION.

This leaflet will focus on the beneficial and adverse effects of all members of this class of medications, as well as some specific information about HALCION. There are some differences among these products, and your physician may wish to discuss any specific advantages and disadvantages of particular members of this drug class with you.

EFFECTIVENESS OF BENZODIAZEPINE SLEEPING PILLS

Benzodiazepine sleeping pills are effective medications and are relatively free of serious problems when they are used for short-term management of sleep problems (insomnia). Insomnia is not always the same. It may be reflected in difficulty in falling asleep, frequent awakening during the night, and/or early morning awakening. Insomnia is often transient in nature, responding to brief treatment with sleeping pills. Use for more than a short while requires discussion with your physician about the risks and benefits of prolonged use.

SIDE EFFECTS

Common Side Effects

The most common side effects of benzodiazepine sleeping pills are related to the ability of the medications to make you sleepy; drowsiness, dizziness, light-headedness, and difficulty with coordination. Users must be cautious about engaging in hazardous activities requiring complete mental alertness, eg, operating machinery or driving a motor vehicle. Do not take alcohol while using HALCION. Benzodiazepine sleeping pills should not be used with other medications or substances that may cause drowsiness, without dis-

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cussing said use with your physician.

How sleepy you are the day after you use one of these sleep medications depends on your individual response and on how quickly the product is eliminated from your body. The larger the dose, the more likely an individual will experience next day residual effects such as drowsiness. For this reason, it is important to use the lowest effective dose for each individual patient. Benzodiazepines that are eliminated rapidly, eg, HALCION, tend to cause less next day drowsiness but may cause more withdrawal problems the day after use (see below).

Special Concerns

Memory Problems

All benzodiazepine sleeping pills can cause a special type of amnesia (memory loss) in which a person may not recall events occurring during some period of time, usually several hours, after taking a drug. This is ordinarily not a problem, because the person taking a sleeping pill intends to be asleep during this vulnerable period of time. It can be a problem when the drugs are taken to induce sleep while traveling, such as during an airplane flight, because the person may awake before the effect of the drug is gone. This has been called "traveler's amnesia". HALCION is more likely than other members of the class to cause this problem.

Tolerance/Withdrawal Phenomena

Some loss of effectiveness or adaptation to the sleep inducing effects of these medications may develop after nightly use for more than a few weeks and there may be a degree of dependence that develops. For the benzodiazepine sleeping pills that are eliminated quickly from the body, a relative deficiency of the drug may occur at some point in the interval between each night's use. This can lead to (1) increased wakefulness during the last third of the night, and (2) the appearance of increased signs of daytime anxiety or nervousness. These two events have been reported in particular for HALCION.

There can be more severe 'withdrawal' effects when a benzodiazepine sleeping pill is stopped. Such effects can occur after discontinuing these drugs following use for only a week or two, but may be more common and more severe after longer periods of continuous use. One type of withdrawal phenomenon is the occurrence of what is known as 'rebound insomnia'. That is, on the first few nights after the drug is stopped, insomnia is actually worse than before the sleeping pill was given. Other withdrawal phenomena following abrupt stopping of benzodiazepine sleeping pills range from mild unpleasant feelings to a major withdrawal syndrome which may include abdominal and muscle cramps, vomiting, sweating, tremor, and rarely, convulsions. These more severe withdrawal phenomena are uncommon.

Dependence/Abuse Phenomena

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 increasing doses, not so much for continued therapeutic effect, but rather, to avoid withdrawal phenomena and/or to achieve nontherapeutic effects. Individuals who have been dependent on alcohol or other

drugs may be at particular risk of becoming dependent on drugs in this class, but all people appear to be at some risk. This possibility must be considered before extending the use of these drugs for more than a few weeks.

Mental and Behavioral Changes

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of benzodiazepine sleeping pills. Some of these changes are like the release of inhibition seen in association with alcohol, eg, aggressiveness and extroversion that seem out of character. Others, however, can be more unusual and more extreme, such as confusion, bizarre behavior, agitation, hallucinations, depersonalization, and worsening of depression, including suicidal thinking. It is rarely clear whether such events are induced by the drug being taken, are caused by some 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. In any event, the most important fact is to understand that regardless of the cause, users of these medications should promptly report any mental or behavioral changes to their doctor.

Effects on Pregnancy

Certain benzodiazepines have been linked to birth defects when administered during the early months of pregnancy. In addition, the administration of benzodiazepines during the last weeks of pregnancy has been associated with sedation of the fetus. Consequently, the use of this drug should be avoided at any time during pregnancy.

Interactions with Other Medications

HALCION should not be taken with ketoconazole, itraconazole and nefazodone. Taking HALCION with certain other medications may cause increased levels of the drug in the blood and result in an excessive effect. Always tell your doctor about all medications you are taking.

SAFE USE OF BENZODIAZEPINE SLEEPING PILLS

To assure the safe and effective use of HALCION, you should adhere to the following cautions:

1. HALCION is a prescription medication and, therefore, should be used only as directed by your doctor. Follow your doctor's advice about how to take it, when to take it, and how long to take it. As with other prescription medication, HALCION should be taken only by the individual for whom it is prescribed.
2. Do not extend your use of HALCION beyond 7-10 days without first consulting your physician.
3. If you develop any unusual and disturbing thoughts or behavior during treatment with HALCION, you should discuss such problems with your physician.
4. Inform your physician about any alcohol consumption and medicine you are taking now, including drugs you may buy without a prescription. Do not use alcohol while taking HALCION.
5. Do not take HALCION in circumstances where a full night's sleep and elimination of the drug from the body are not possible

Halcion
brand of triazolam tablets, USP

before you would again need to be active and functional, eg, an overnight flight of less than 7-8 hours, because amnestic episodes have been reported in such situations.

6. Do not increase the prescribed dose except on the advice of your physician.
7. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.
8. Be aware that you may experience an increase in sleep difficulties (rebound insomnia) on the first night or two after discontinuing HALCION.
9. Inform your physician if you are planning to become pregnant, if you are pregnant, or if you become pregnant while you are taking this medicine. The use of HALCION should be avoided at any time during pregnancy.
10. Always tell your doctor about all medications you are taking.

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A subsidiary of Pharmacia Corporation
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Revised January 2003 812 110 831A
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