

HALCION®
Triazolam - 0.125mg, and 0.25mg, tablets

Presentation

HALCION 0.125mg tablets are lavender coloured, flat, elliptical tablets scored on one side, coded "Upjohn 10".

HALCION 0.25mg tablets are powder blue coloured flat, elliptical tablets scored on one side, coded "Upjohn 17".

Dimensions (all strengths): Length 8.0mm, width 5.7mm, thickness 2.1mm.

Uses

Actions

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

Pharmacokinetics

HALCION has a desirable hypnotic pharmacokinetic profile.

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

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

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

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

In studies with patients with renal failure undergoing haemodialysis, triazolam elimination rate was not decreased and maximum concentration was not increased. Patients with hepatic dysfunction may have reduced triazolam clearance and increased peak plasma concentrations,

and in this patient group consideration should be given to reduced dosages. The usual precautions in administering sedatives to patients with liver dysfunction should be observed.

Indications

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

Dosage and Administration

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

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

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

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

Contraindications

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

Warnings and Precautions

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

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

Patients should be cautioned not to take HALCION 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.

When HALCION is used at recommended doses for short-term treatment, the dependence potential is low. However, as with all benzodiazepines, the risk dependence increases with higher doses and long-term use and is further increased in patients with a history of alcoholism or drug abuse.

Withdrawal symptoms, including seizures have been reported when patients abruptly discontinue multiple daily doses of HALCION.

Although benzodiazepines are not depressogenic, they may be associated with mental depression which may or may not be associated with ideas of suicide or actual suicide attempts. This occurs in a rare and unpredictable fashion. Therefore, HALCION 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.

As with other benzodiazepines and CNS active drugs, three idiosyncratic symptom clusters, which may overlap, have been reported rarely with HALCION: amnesic symptoms (anterograde amnesia with appropriate or inappropriate behaviour); confusional states (disorientation, derealisation, depersonalisation and/or clouding of consciousness); and an agitational state (restlessness, irritability and excitation). Frequently, other factors may contribute to these idiosyncratic reactions, eg. concomitant intake of alcohol or other medicines, sleep deprivation, an abnormal premorbid state etc.

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

Preganancy and Lactation

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

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

Paediatrics

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

Adverse Effects

In placebo-controlled studies with HALCION, 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 HALCION include: aggressiveness, falling, transient insomnia after drug discontinuance, hallucinations, syncope and somnambulism.

Although the absolute occurrence of adverse effects with HALCION 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 section).

Interactions

Benzodiazepines produce an additive effect when co-administered with alcohol or other CNS depressants.

Pharmacokinetic interactions can occur when triazolam is administered along with drugs that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P4503A4) may increase the concentration of triazolam and enhance its activity. Data from clinical studies with triazolam, in vitro studies with triazolam, and clinical studies with drugs metabolised similarly to triazolam provide evidence for varying degrees of interaction and possible interaction with triazolam for a number of drugs. Based on the degree of interaction and the type of data available, the following recommendations are made:

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

Overdosage

Symptoms of overdose with HALCION are extensions of its pharmacological action and include drowsiness, slurred speech, motor inco-ordination, coma, and respiratory depression. Serious sequela are rare unless other drugs and/or ethanol are concomitantly ingested. Treatment of overdosage is primarily supportive of respiratory and cardiovascular function. The value of

dialysis has not been determined. Flumazenil may be used as an adjunct to the management of respiratory and cardiovascular function associated with overdose.

Pharmaceutical Precautions

Store at or below 25 degrees C.

Medicine Classification

Controlled Drug C5.

Package Quantities

HALCION is available as tablets of 0.125mg and 0.25mg strengths in bottles of 100.

Further Information

Nil

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