Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Halcion 125 micrograms Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 125 micrograms of Triazolam.

Excipients with known effect:
This medicinal product contains 72 mg of lactose monohydrate and 0.15 mg of sodium benzoate in each tablet.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Lavender elliptical tablet with 'Upjohn 10' on one-side, plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Insomnia
Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

The dosage of triazolam should be individualised for a maximum beneficial effect and to help avoid significant adverse effects. It is recommended to find the lowest effective dose, particularly in geriatric or debilitated patients.
The risk of dependence may increase with dose and duration of treatment; therefore, the lowest effective dose and duration should be used and the need for continued treatment reassessed frequently (see section 4.4.).

Abrupt discontinuation or rapid dosage reduction of triazolam after continued use may precipitate withdrawal reactions, which can be life threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue triazolam or reduce the dosage (see section 4.4.).

Duration of Treatment
Treatment should be as short as possible. Generally the duration of treatment varies from a few days to two weeks with a maximum, including tapering-off process, of four weeks. In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status.

Method of Administration
Halcion should be taken just before going to bed.

Posology

Insomnia:
The usual dose is 250 micrograms (0.25 mg) at night. Dosage should be adjusted on the basis of the individual patient response to achieve effect without overdosage. The lowest effective dose should be used. In patients previously untreated with hypnotics, initial dosage should be 125 micrograms (0.125 mg). A maximum dose of 250 micrograms (0.25 mg) should not be exceeded because of risk of unacceptable CNS adverse effects. Patients with renal impairment may be administered triazolam in the usual dose range; as appropriate.

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.

In the elderly, debilitated or patients with impaired hepatic function initial dosage should be 125 micrograms (0.125 mg) to decrease the possibility of development of over sedation, dizziness, or impaired coordination. It is seldom necessary to exceed

that dose. A maximum dose of 250 micrograms (0.25 mg) should not be exceeded. In other adults the recommended dose is 0.25 mg (see section 4.4).
Triazolam is not recommended for use in children and adolescents below the age of 18 years due to insufficient data on safety and efficacy.

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

4.3 Contraindications

Triazolam is contraindicated:

- In patients with a known hypersensitivity to benzodiazepines, triazolam or to any component of this medicine,listed in section 6.1.
- In patients with myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome, severe hepatic insufficiency.
- When co-administered with strong CYP 3A inhibitors like ketoconazole, itraconazole, nefazodone, and efavirenz or HIV protease inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required.

Caution must be used in treating patients with mild to moderate hepatic insufficiency. In patients with compromised respiratory function, respiratory depression and apnea have been reported infrequently.

Benzodiazepines produce an additive effect when co-administered with alcohol or other CNS depressants. Concomitant intake with alcohol is not recommended. Triazolam should be used with caution when combined with CNS depressants (see section 4.5).

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

Tolerance
Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Dependence
Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse.

Withdrawal reactions
Once dependence has developed, abrupt termination of treatment or rapid dosage reduction will be accompanied by withdrawal symptoms which can be life threatening. These can range from mild dysphoria, insomnia and headaches, to a major syndrome which may include muscle pain, abdominal and muscle cramps, vomiting, sweating, tremor, convulsions,extreme anxiety, tension, restlessness, confusion and irritability. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations, delirium tremens, depression, mania, psychosis,epileptic seizures, and suicidality.

Rebound insomnia
Rebound insomnia is a transient syndrome wherein the indication for treatment (insomnia) that led to treatment with a benzodiazepine recurs, with greater severity than at baseline, on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Drug abuse
Drug abuse is a known risk for benzodiazepines, and patients should be monitored accordingly when receiving triazolam. Benzodiazepines may be subject to diversion. There have been reports of overdose related deaths when benzodiazepines are

abused with other CNS depressants including opioids, other benzodiazepines, alcohol and/or illicit substances. These risks should be considered when prescribing or dispensing triazolam. To reduce these risks the lowest effective dose should be used, and patients should be advised on the proper storage and disposal of unused drug to prevent diversion (e.g. through friends and relatives).

Duration of treatment
Triazolam should primarily be used for occasional short-term treatment of insomnia, for up to 7-10 days in general. Use for more than two weeks requires a complete re-evaluation of the patient.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued.

There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

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, triazolam should be used with caution and the prescription size should be limited in patients with signs and symptoms of a depressive disorder or suicidal tendencies.

Amnesia
Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see also section 4.8).

Caution must be used in elderly and debilitated patients.
In elderly and/or debilitated patients, it is recommended that treatment with triazolam be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. In other adults the recommended dose is 0.25 mg (see section 4.2).
Because triazolam can cause sedation (drowsiness, somnolence, dizziness, ataxia, and/or incoordination) and CNS depression, patients, particularly the elderly, are at higher risk of falls.

Paediatric population
Triazolam is not recommended for use in children and adolescents below the age of 18 years due to insufficient data on safety and efficacy.

Psychiatric and paradoxical reactions
Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the medicinal product should be discontinued. They are more likely to occur in children and the elderly.

Specific patient groups
A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

Complex sleep behaviour-related events 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 are not fully awake after taking a sedative-hypnotic, including triazolam. These and other complex sleep behavior-related events may occur with

sedative-hypnotics, including triazolam, alone at therapeutic doses. The use of alcohol and other CNS depressants with sedative-hypnotics appears to increase the risk of such behaviors, as does the use of sedative-hypnotics at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of sedative-hypnotics should be strongly considered for patients who report such events (see section 4.8).

Severe anaphylactic and anaphylactoid reactions, including rare fatal cases of anaphylaxis, have been reported in patients receiving triazolam. 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 (see section 4.8).

Information about Excipients

Halcion contains lactose monohydrate (72 mg per tablet). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Halcion contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Halcion contains sodium benzoate (see section 2). Benzoates may increase unconjugated bilirubin levels by displacing bilirubin from albumin, which may increase neonatal jaundice. Neonatal hyperbilirubinaemia may lead to kernicterus (non-conjugated bilirubin deposits in the brain tissue) and encephalopathy.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Compounds that induce CYP3A4 may decrease the concentration of triazolam and diminish its activity.

Data from clinical studies with triazolam, in vitro studies with triazolam, and clinical studies with drugs metabolized 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 strong CYP 3A inhibitors like ketoconazole, itraconazole, and nefazodone is contraindicated.
- Interactions involving HIV protease inhibitors (eg, ritonavir) and triazolam are complex and time dependent. Short-term low doses of ritonavir resulted in a large impairment of triazolam clearance (less than 4% of the control values), prolonged its elimination half-life and enhanced clinical effects. The co-administration of triazolam with HIV protease inhibitors is contraindicated (see section 4.3).
- The co-administration of triazolam with other azole-type antifungals is not recommended.
- Caution and consideration of dose reduction is recommended when triazolam is coadministered 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.
- Oral contraceptives and imatinib may lead to enhanced clinical effects of triazolam due to the inhibition of the CYP3A4 isoenzyme. Caution is therefore recommended in case of concomitant use with triazolam.
- Rifampicin and carbamazepin cause CYP3A4 induction. Therefore, the effect of triazolam may be diminished significantly during therapy with rifampicin or carbamazepin.
- Efavirenz inhibits the oxidative metabolism of triazolam and may cause life-threatening effects, such as prolonged sedation ad respiratory depression. As a precaution, concomitant treatment is therefore contraindicated.
- Aprepitant: enhancement of the clinical effects may occur in cases of concomitant use with triazolam due to the inhibition of the enzyme CYP3A4. This interaction may require a dose-reduction of triazolam.
- Benzodiazepines produce an additive CNS depressant effect, including respiratory depression, when co-administered with opioids, alcohol or other CNS depressants (see section 4.4). Concomitant intake with alcohol is not recommended. Triazolam should be used with caution when combined with CNS depressants. Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic products, anaesthetics and sedative antihistamines. In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence. (See section 4.4).
- Increased bioavailability of triazolam has been shown when taken concomitantly with grapefruit juice.

4.6 Fertility, pregnancy and lactation

The data concerning teratogenicity and effects on postnatal development and behavior following benzodiazepine treatment are inconsistent. There is evidence from some early studies with other members of the benzodiazepine class that 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 labor have been reported to exhibit either the floppy infant syndrome or neonatal withdrawal symptoms. If triazolam is used during pregnancy, or if the patient becomes pregnant while taking triazolam, the patient should be apprised of the potential hazard to the foetus. Triazolam should not be used by nursing mothers.

4.7 Effects on ability to drive and use machines

Triazolam can have a major influence on the ability to drive and operate machines. Patients should be advised not to drive or operate machinery during treatment until it has been established that they are not affected by daytime drowsiness or dizziness. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also section 4.4).

4.8 Undesirable effects

Table 1: Adverse Reactions

Frequency of adverse reactions observed from placebo-controlled clinical trials and post-marketing experience frequency 'Not known.

Very Common (≥1/10)		**Common** (≥1/100 to <1/10)		**Uncommon** (≥1/1000 to <1/100)		**Rare** (≥ 1/10000 to <1/1000)		**Very rare** (<1/ 10000)		**Not Known**	
Immune system disorders											
									Anaphylactic shock, Anaphylactoid reaction, Angioedema, Allergic oedema, Hypersensitivity (see section 4.4)		
Psychiatric Disorders											
			Confusional state, Insomnia*						Aggression, Hallucination, Somnambulism, Anterograde amnesia, Restlessness, Agitation, Irritability, Delusion, Rages, Nightmares, Psychoses, Inappropriate behaviour (see section 4.4), Drug abuse, Drug dependence		

Nervous System Disorders											
	Somnolence, Dizziness, Ataxia, Headache		Memory impairment						Syncope, Sedation, Depressed level of consciousness, Speech disorder, Disturbance in attention, Dysgeusia		
Eye Disorders											
			Visual impairment								
Respiratory, thoracic and mediastinal disorders											
									In patients with compromised respiratory function: Respiratory depression		
Skin and subcutaneous tissue disorders											
					Rash						
Musculoskeletal and connective tissue disorders											
					Myasthenia						
Reproductive system and breast disorders											
									Change in libido		
General disorders and administration site conditions											
									Drug withdrawal syndrome		
Injury, poisoning and procedural complications											
									Fall		

* *these adverse reactions also occurred in post-marketing experience.*

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Symptoms of overdose with triazolam are extensions of its pharmacological action and include drowsiness, slurred speech, motor in coordination, coma, and respiratory depression. Serious sequelae are rare unless other drugs and/or ethanol are concomitantly ingested. In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken. 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.

Following overdose with any medicinal product, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives, ATC code: NO5CD05

Triazolam is a short-acting benzodiazepine with anticonvulsant anxiolytic, sedative, muscle relaxant and amnesic properties. It is used as a hypnotic in the short-term management of insomnia.

5.2 Pharmacokinetic properties

Triazolam is rapidly and nearly completely absorbed from the gastro-intestinal tract; peak plasma concentrations being achieved within 2 hours of administration by mouth.

Triazolam has a short plasma elimination half-life ranging from 1.5 to 5.5 hours. It is reported to be about 89% bound to plasma proteins. Triazolam undergoes hydroxylation in the liver and is excreted in the urine mainly in the form of its conjugated metabolites with only small amounts appearing unchanged.

5.3 Preclinical safety data

Carcinogenesis
No evidence of carcinogenic potential was observed in rats or mice during 24-month studies with triazolam at doses greater than or equal to 800 times the maximum human daily dose of 0.5 mg.

Mutagenesis
Triazolam was not mutagenic in the in vitro Ames bacterial reverse mutation assay, and no DNA damage was observed in an in vitro alkaline elution assay in Chinese hamster lung fibroblast cells.

Impairment of Fertility
In a one generation reproduction study, rats were administered triazolam in the diet at doses up to 5 mg/kg/day (greater than or equal to 100 times the maximum daily human dose). Female rats were dosed for 14 days before cohabitation, during gestation, and until 21 days post-parturition, and males were dosed for 60 days before cohabitation. There were no effects on mating or fertility at any dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Microcrystalline cellulose
Colloidal anhydrous silica
Docusate sodium
Sodium benzoate (E211)
Magnesium stearate
Erythrosine (E127 aluminium lake)
Indigo carmine (E132 aluminium lake).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 25˚C. Keep the blister in the outer carton. Store in the original package.

6.5 Nature and contents of container

PVC/AL foil blister strips: pack sizes: 7, 10 and 30 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland Unlimited Company
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8 MARKETING AUTHORISATION NUMBER

PA0822/129/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 November 1984

Date of last renewal: 13 November 2009

10 DATE OF REVISION OF THE TEXT

December 2024