SCHEDULING STATUS:

Schedule 5

PROPRIETARY NAME (and dosage form):

HALCION 0,125 mg (Tablets)

HALCION 0,25 mg (Tablets)

COMPOSITION:

Each tablet contains 0,125 mg or 0,25 mg triazolam.

HALCION tablets contain the following inactive ingredients: corn starch, colloidal silicon dioxide, docusate sodium with sodium benzoate, lactose, magnesium stearate, microcrystalline cellulose and FD and C Blue 2 aluminium lake or lavender aluminium lake as colourant.

PHARMACOLOGICAL CLASSIFICATION:

A 2.2 Sedatives, hypnotics

PHARMACOLOGICAL ACTION:

Triazolam is a short-acting benzodiazepine type hypnotic agent which significantly affects REM or stage III and IV sleep. Latency to stage REM I increases significantly.

Triazolam is rapidly and nearly completely absorbed. Peak plasma concentrations are achieved within one hour of administration by mouth. Triazolam has a short elimination half life ranging 2-4 hours.

INDICATIONS:

HALCION is indicated for the transient and short-term treatment of insomnia. HALCION is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

CONTRA-INDICATIONS:

HALCION is contra-indicated in patients with known hypersensitivity to benzodiazepines.
It is contra-indicated in mental depression (unless there is a marked component of anxiety in their illness), pre-existing central nervous system depression or coma and psychiatric patients with suicidal tendencies. (See SIDE-EFFECTS AND SPECIAL PRECAUTIONS).
HALCION should not be used for long-term treatment of insomnia.

The co-administration with ketoconazole , itraconazole and nefazodone is contra-indicated (See INTERACTIONS). HALCION should not be co-administered with ritonavir. (See INTERACTIONS).
HALCION should not be given during labour because it crosses the placenta and can cause the floppy-infant syndrome characterised by central respiratory depression, hypothermia and poor sucking. HALCION should not be used by breast-feeding mothers because metabolites are excreted in the milk.
The safety and efficacy in patients under the age of 18 years have not been established.

WARNINGS:

Patients should be cautioned against hazardous occupations requiring mental alertness such as operating machinery or driving a motor vehicle, the day after a night time dose of HALCION, until it is established that they do not exhibit daytime drowsiness or dizziness.

When HALCION is used at recommended doses for short-term treatment, the dependence potential is low. However, the risk of dependence with benzodiazepines increases with higher doses and long-term use and is further increased in patients with a history of alcoholism and drug abuse. Once physical dependence has developed after long periods of ordinary therapeutic doses or multiple daily doses of HALCION, abrupt termination will be accompanied by withdrawal symptoms which may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur : derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. Patients with a history of seizures should not be abruptly withdrawn from HALCION.

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 HALCION. These and other complex sleep behaviour-related events may occur with sedative-hypnotics, including HALCION, alone at therapeutic doses. The use of alcohol and other CNS depressants with sedative-hypnotics appears to increase the risk of such behaviours, as does the use of sedative-hypnotics at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of HALCION should be strongly considered for patients who report such events.

Severe anaphylactic and anaphylactoid reactions, including rare fatal cases of anaphylaxis, have been reported in patients receiving HALCION. 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 HALCION. (See SIDE EFFECTS AND SPECIAL PRECAUTIONS).

INTERACTIONS:

If HALCION is to be combined with other medicines having known hypnotic properties or central nervous system depressant effects, consideration should be given to potential additive effects.

HALCION plasma concentrations may approximately double when cimetidine is co-administered. The co-administration of HALCION and cimetidine results in a reduction of HALCION clearance without a change in elimination half-life in most subjects. The elimination half-life may be prolonged in some subjects, but does not result in drug accumulation on once-daily dosing.

HALCION plasma concentrations may double when erythromycin is co-administered. The co-administration of HALCION and erythromycin or clarithromycin results in a reduction of HALCION clearance without an increase in elimination half-life.

Caution and consideration of dose reduction is recommended when HALCION is co-administered with troleandomycin.

Interactions with medicines involve antibacterial agents, antimycobacterial agents, gastro-intestinal agents and oral contraceptives.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450IIIA4) may increase concentration of HALCION and enhance its activity. Varying degrees of interaction and possible interaction with HALCION for a number of medicines was reported. Based on the degree of interaction and type of data available the following recommendations are made:

- The co-administration with ketoconazole , itraconazole and nefazodone is contra-indicated (See CONTRA-INDICATIONS).
- Co-administration with other azole-type antifungals is not recommended.
- Caution is recommended when HALCION is co-administered with isoniazid, fluvoxamine, paroxetine, diltiazem, verapamil, sertraline.
- Interactions involving HIV protease inhibitors (e.g. ritonavir) and HALCION are complex and time-dependent. Low doses of ritonavir resulted in a large impairment of HALCION clearance, prolonged its elimination half-life and enhanced clinical effects. This interaction will require discontinuation of HALCION.

PREGNANCY AND LACTATION:

HALCION is contra-indicated in pregnant women and women at risk of pregnancy. There is insufficient clinical data at this stage.

DOSAGE AND DIRECTIONS FOR USE:

It is important to individualise the dosage of HALCION tablets for maximum beneficial effect and to help avoid significant adverse effects. The recommended dose for adults is 0,25 mg before retiring. A dose of 0,5 mg should be reserved for those patients who do not respond adequately to a lower dose.

A dose of 0,125 mg may be found to be sufficient for selected, geriatric and/or debilitated patients. Therapy should be initiated at 0,125 mg in this group until individual response is determined and can then be increased to 0,25 mg if necessary. The lowest effective dose should be used.

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 recommended treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

In accordance with good medical practice, it is recommended that therapy be initiated at the lowest effective dose. Severe sedation and impaired co-ordination are indicative of drug intolerance or overdosage. (See KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT).

The table below contains adverse events categorized as follows utilizing the incidence rates: Very common ≥ 1/10 (≥ 10%); Common ≥ 1/100 and < 1/10 (≥ 1% and < 10%); Uncommon ≥ 1/1000 and < 1/100 (≥ 0,1% and < 1%), Rare ≥ 1/10 000 and < 1/1000 (≥ 0,01% and < 0,1%); Very rare < 1/10 000 (< 0,01%).

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Blood and lymphatic system disorders	*Rare*	Blood disorders
Psychiatric disorders	*Common*	Depression
	Rare	Confusional states, memory impairment, aggressiveness, hallucinations, somnambulism, euphoria, agitation
Nervous system disorders	*Very common*	Drowsiness, grogginess, headache
	Common	Dizziness, impaired coordination, light-headedness
	Uncommon	Syncope, taste alteration, slurred speech, dysarthria
	Rare	Transient insomnia after drug discontinuance, amnesia, ataxia, tremor

Eye disorders	*Common*	Visual disturbances, blurred vision
Cardiac disorders	*Common*	Palpitations
Vascular disorders	*Rare*	Hypotension
Gastrointestinal disorders	*Uncommon*	Epigastric discomfort
	Rare	Excessive salivation, diarrhoea
Hepato-biliary disorders	*Rare*	Jaundice
Skin and subcutaneous tissue disorders	*Rare*	Hypersensitivity reactions (pruritis, skin rash)
Musculoskeletal and connective tissue disorders	*Rare*	Paresis
Renal and urinary disorders	*Uncommon*	Incontinence
	Rare	Urinary retention
Reproductive system and breast disorders	*Rare*	Changes in libido
Injury, poisoning and procedural complications	*Rare*	Falling

Post-marketing surveillance:

Immune system disorder: Hypersensitivity reactions including angioneurotic oedema, anaphylactoid reaction, allergic oedema and anaphylactic shock have been reported. See WARNINGS.

Precautions:

It is recommended that HALCION not be taken for sleep of less than 7-8 hours, since amnestic episodes have been reported.

In elderly and/or debilitated patients, it is recommended that treatment with HALCION be initiated at 0,125 mg to decrease the possibility of development of over-sedation, dizziness or impaired co-ordination. In other adults the recommended dose is 0,25 mg.

A transient syndrome, whereby the symptoms that led to treatment with HALCION recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since the risk of withdrawal

phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually (see WARNINGS).

The duration of treatment should be as short as possible (see DOSAGE AND DIRECTIONS FOR USE), but should not exceed 4 weeks, including tapering-off process. Extension beyond these periods should not take place without re-evaluation of the situation. 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 be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms, should they occur while the product is being discontinued.

HALCION is not recommended for the primary treatment of psychotic illness. HALCION should not be used alone to treat depression or anxiety with depression (suicide may be precipitated in such patients). It should be used with extreme caution in patients with a history of alcohol or drug abuse.

Clinical trials in depressed patients have not shown exacerbation of depression by HALCION; however, caution should be exercised if the patient is in a depressed state or reveals evidence of a latent depression since these conditions may be intensified by hypnotic agents. Although benzodiazepines are not depressogenic, they may be associated with mental depression which may or may not be associated with ideas of suicide or suicidal attempts. This occurs in a rare or unpredictable fashion. The prescription size must be limited in patients with signs and/or symptoms of a depressive disorder or suicidal tendencies, also in addiction prone individuals and for patients who are not under medical supervision (see WARNINGS).

Caution must also be exercised in pulmonary insufficiency. In patients with compromised respiratory function, respiratory depression and apnoea have been reported infrequently.

Caution is required in patients with organic brain changes, particularly arteriosclerosis.

HALCION is mainly excreted after metabolism by the liver; therefore caution is required in patients with impaired liver and kidney function.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms of overdose with HALCION are extensions of its pharmacological action and include drowsiness, slurred speech, motor-inco-ordination, coma and respiratory depressions. 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.

IDENTIFICATION:

HALCION 0,125 mg: Lavender elliptical, flat, bevelled tablet with "Upjohn 10" on the one side.

HALCION 0,25 mg: Powder blue elliptical tablet, scored on the one side and "Upjohn 17" impressed on the other side.

PRESENTATION:

HALCION 0,125 mg tablets are available in blister packs of 10, 30 and 100 tablets.

HALCION 0,25 mg tablets are available in blister packs of 10, 30 and 100 tablets and in glass bottles of 500 tablets.

STORAGE INSTRUCTIONS:

Store at room temperature (15 - 30 ^{o}C).

Protect from moisture and light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

HALCION 0,125 mg tablets: T/2.2/99

HALCION 0,25 mg tablets: J/2.2/320

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton

2196

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

23 July 2010

BOTSWANA: S1

Halcion 0.125mg Reg no. B9312030

Halcion 0.25mg Reg no. B9312035

NAMIBIA: S3

Halcion 0.125mg Reg no.90/2.2/001316

Halcion 0.25mg Reg no.90/2.2/001317