SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

HALCION® 0,125 tablets

HALCION® 0,25 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar (lactose).

Excipients with known effect

Each 0,125 or 0,25 mg tablet contains 72 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

HALCION 0,125

Lavender elliptical, flat, tablet with length 7,9 mm and width 5,6 mm, with bevelled edges and "Upjohn 10" on the one side.

HALCION 0,25

Powder blue elliptical tablet with length 7,9 mm and width 5,6 mm, scored on the one side and "Upjohn 17" impressed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

Posology

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.

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.

Special populations

Elderly

A dose of 0,125 mg may be found to be sufficient for selected, elderly 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.

Paediatric population

The safety and efficacy of HALCION in children under 18 years of age has not yet been established.

Method of administration

For oral use.

4.3 Contraindications

HALCION is contraindicated in patients with:

- known hypersensitivity to triazolam, benzodiazepines or any of the excipients of HALCION (listed in section 6.1)
- mental depression (unless there is a marked component of anxiety in their illness)

- pre-existing central nervous system depression or coma
- psychiatric patients with suicidal tendencies (see section 4.8)
- long-term treatment of insomnia
- co-administration with ketoconazole, itraconazole, nefazodone and ritonavir (see section 4.5)
- HALCION is contraindicated in pregnant women, women at risk of pregnancy and breastfeeding mothers (see section 4.6).
- 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 breastfeeding mothers because metabolites are excreted in the milk (see section 4.6).
- The safety and efficacy in patients under the age of 18 years have not been established.

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.

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

Caution must also be exercised in pulmonary insufficiency. 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 be initiated at 0,125 mg to decrease the possibility of development of over-sedation, dizziness or impaired coordination. In other adults the recommended dose is 0,25 mg (see section 4.2). Because HALCION can cause sedation (drowsiness, somnolence, dizziness, ataxia and/or incoordination) and CNS depression, patients, particularly the elderly, are at higher risk of falls.

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

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.

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 medicines. 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.

Three central nervous system (CNS) idiosyncratic symptom clusters, which may overlap, have been reported with HALCION: amnestic 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). Other factors may contribute to these idiosyncratic reactions e.g. concomitant intake of alcohol or other medicines, sleep deprivation, an abnormal premorbid state, etc.

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) and other complex sleep behaviour-related events may occur with HALCION alone at therapeutic doses. The use of alcohol and other CNS depressants with HALCION may increase the risk of such behaviours, as does the use of 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 HALCION (see section 4.8).

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.

The duration of treatment should be as short as possible (see section 4.2), 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 HALCION 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.

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

HALCION contains lactose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

HALCION produces an additive CNS depressant effect, including respiratory depression, when co-administered with opioids, alcohol or other CNS depressants (see section 4.4).

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 medicine 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.

Medicines that inhibit hepatic cytochrome P450 3A4 enzymes may increase the 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 contraindicated (see section 4.3).
- 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. Short-term low doses of ritonavir resulted in a large impairment of HALCION clearance (less than 4 % of the control values), prolonged its elimination half-life and enhanced its clinical effects. The co-administration of HALCION with HIV protease inhibitors is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

HALCION is contraindicated in pregnant women, women at risk of pregnancy and breastfeeding mothers (see section 4.3).

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

In accordance with good medical practice, it is recommended that therapy be initiated at the lowest effective dose. Severe sedation and impaired coordination are indicative of medicine intolerance or overdosage (see section 4.9).

Tabulated summary of adverse reactions

The table below contains adverse events categorised as follows utilising the incidence rates: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1000); very rare (< 1/10 000).

MedDRA System organ class	**Frequency**	**Undesirable effects**
Psychiatric	Common	Depression

MedDRA System organ class	**Frequency**	**Undesirable effects**
disorders	Rare	Confusional states, memory impairment, aggressiveness, hallucinations, somnambulism, euphoria, agitation
	Very common	Drowsiness, somnolence, headache
	Common	Dizziness, impaired coordination, light-headedness
	Uncommon	Syncope, taste alteration, slurred speech, dysarthria
	Rare	Transient insomnia after medicine 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	Rare	Paresis

MedDRA System organ class	**Frequency**	**Undesirable effects**
tissue disorders		
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 angioedema, anaphylactoid reaction, allergic oedema and anaphylactic shock have been reported (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms of overdose with HALCION are extensions of its pharmacological action and include drowsiness, slurred speech, motor-incoordination, coma and respiratory depression. 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. If Flumazenil is used, the patient must be monitored to ensure that the duration of the pharmacological action does not end before the HALCION effects are dissipated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.2 Sedatives, hypnotics

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

5.2 Pharmacokinetic properties

Triazolam is rapidly and nearly completely absorbed. Peak plasma concentrations are reached within 2 hours following oral administration. Triazolam has a short elimination half-life ranging 2 - 4 hours. Following recommended doses of triazolam, plasma levels in the range of 1 ng/mL 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 unmetabolised 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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn starch

Colloidal silicon dioxide

Docusate sodium with sodium benzoate

Lactose

Magnesium stearate

Microcrystalline cellulose

FD&C Blue No. 2 aluminium lake as colourant

Erythrosine sodium aluminium lake as colourant (HALCION 0,125)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

HALCION 0,125: 36 months

HALCION 0,25: 48 months

6.4 Special precautions for storage

Store at or below 25 ^{o}C.

Keep blister in the carton until required for use.

Protect from moisture and light.

6.5 Nature and contents of container

HALCION 0,125 tablets are available in transparent PVC/aluminium blister packs of 10, 30 and 100 tablets, packed into an outer carton.

HALCION 0,25 tablets are available in transparent PVC/aluminium blister packs of 10, 30 and 100 tablets, packed into an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

HALCION 0,125: T/2.2/99

HALCION 0,25: J/2.2/320

9. DATE OF FIRST AUTHORISATION

HALCION 0,125: 06 June 1988

HALCION 0,25: 23 November 1978

10. DATE OF REVISION OF THE TEXT

16 September 2021

Manufacturer:

Pfizer Italia S.r.l., Ascoli Piceno, Italy

or Sanico NV, Turnhout, Belgium

BOTSWANA: S1C

HALCION 0,125 - Reg. No.: B9312030

HALCION 0,25 - Reg. No.: B9312035

NAMIBIA: NS3

HALCION 0,125 - Reg. No.: 90/2.2/001316

HALCION 0,25 - Reg. No.: 90/2.2/001317