Approved Package Insert

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

ZOPICLONE 7,5 mg AUSTELL Tablets

COMPOSITION

Each film coated tablet contains Zopiclone 7,5 mg

Excipients:

Calcium hydrogen phosphate dihydrate, lactose monohydrate, magnesium stearate, maize starch and sodium starch glycollate.

Film coating: hydroxypropylmethylcellulose, propylene glycol, talc and titanium Dioxide.

Contains sugar (lactose).

PHARMACOLOGICAL CLASSIFICATION

A 2.2 Sedatives, hypnotics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Zopiclone is a cyclopyrrolone hypnotic agent. It has sedative, anxiolytic, muscle relaxant, hypnotic and anticonvulsant properties. These effects are related to a specific agonist action at central receptors belonging to the gamma-aminobutyric acid (GABA) macromolecular complex in the brain, modulating the opening of the chloride ion channel.

Pharmacokinetic properties

Absorption:

Zopiclone is rapidly absorbed. Peak concentrations (30 to 60 ng/ml after doses of 3,75 mg and 7,5 mg) are reached within 1,5 to 2 hours. Absorption is not affected by co-administration with food.

Distribution:

Plasma protein binding is weak (approximately 45 %) and non-saturable. Zopiclone is distributed into breast-milk, its concentration being approximately 50 % that of plasma concentrations.

Metabolism:

After repeated administration there is no accumulation of zopiclone and its metabolites. Inter-individual variations appear to be low.

Zopiclone is extensively metabolized in humans to two major metabolites, N-oxide zopiclone (pharmacologically active in animals) and N-desmethyl zopiclone (pharmacologically inactive in animals). An *in vitro* study indicates that cytochrome P450 (CYPO 34A is the major isoenzyme involvement in the metabolism of zopiclone to both metabolites, and that CYP2C8 is also involved with N-desmethyl zopiclone formation.

Excretion:

At recommended doses, the elimination half-life of the zopiclone is approximately 5 hours. Approximately 80 % of Zopiclone is eliminated renally, mainly in the form of free metabolites (N-oxide and N-demethyl derivatives). Faecal elimination is approximately 16 %.

Pharmacokinetics in special populations:

In renal insufficiency, no accumulation of Zopiclone or its metabolites has been detected after prolonged administration. Zopiclone is removed by haemodialysis.

In cirrhotic patients, the plasma clearance of zopiclone is reduced by approximately 40 % in relation to the decrease of the demethylation process. Therefore, dosage will have to be modified in these patients.

In elderly patients, not withstanding a slight decrease in hepatic metabolism and lengthening of elimination half life to approximately 7 hours, various studies have not shown plasma accumulation of the medicine substance on repeated dosing.

INDICATIONS

ZOPICLONE 7,5 mg AUSTELL is indicated for the short –term treatment of insomnia in adults when the disorder is severe, disabling or subjecting the individual to extreme stress.

CONTRAINDICATIONS

ZOPICLONE 7,5 mg AUSTELL is contraindicated in patients with:

Hypersensitivity to zopiclone or any of the excipients of **ZOPICLONE 7,5 mg AUSTELL.**

Respiratory failure

Severe sleep apnoea syndrome

Severe hepatic insufficiency

Myasthenia gravis

ZOPICLONE 7,5 mg AUSTELL should not be used in children under the age of 18 years. Safety in pregnancy and lactation has not been established (see PREGNANCY AND LACTATION).

WARNINGS AND SPECIAL PRECAUTIONS

This medicine may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other central nervous system depressants. Patients should be warned against driving motor vehicles or operating machinery or performing potentially hazardous tasks where loss of concentration may lead to accidents.

ZOPICLONE 7,5 mg AUSTELL should be used with extreme caution in patients with a history of drug or alcohol abuse.

Dependence – There is a potential for abuse and the development of physical and psychological dependence, especially with prolonged use and high doses. The risk of dependence is also greater in patients with a history of alcohol or drug abuse. Once physical dependence has developed, abrupt termination of therapy will result in a withdrawal syndrome presenting with headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalization, hyperacusis (abnormal acute hearing), numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound Insomnia and withdrawal phenomena

The risk of such phenomena is greater after abrupt discontinuation of **ZOPICLONE 7,5 mg AUSTELL,** especially after prolonged treatment. It is, therefore, recommended to decrease the dosage gradually and to advise patient accordingly (see also SIDE EFFECTS).

Effects on ability to drive and use machines

ZOPICLONE 7,5 mg AUSTELL may adversely affect the ability to drive or use machines. The risk increases by concomitant intake of alcohol.

Some loss of efficacy of **ZOPICLONE 7,5 mg AUSTELL** may develop after repeated use. To minimise the risk of anterograde amnesia and mental confusion, **ZOPICLONE 7,5 mg AUSTELL** should be taken only when the patient's schedule will allow for a full night's sleep (7 to 8 hours). **ZOPICLONE 7,5 mg AUSTELL** should not be used alone to treat depression or anxiety with depression, as suicide may be precipitated in these patients. **ZOPICLONE 7,5 mg AUSTELL** is not recommended for primary treatment of psychotic illness.

Excipients of

Contains lactose. Patients with rare hereditary conditions of galactose intolerance e.g. galactosemia, Lapp lactase deficiency, or glucose-galactose malabsorption should not take ZOPICLONE 7,5 mg AUSTELL. Contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS ZOPICLONE 7,5 mg AUSTELL

- **Alcohol:** Concomitant use may enhance the sedative effect of **ZOPICLONE 7,5 mg AUSTELL**.
- **Central nervous System (CNS) depressant medicines:** Concurrent use with ZOPICLONE 7,5 mg AUSTELL may produce additive CNS depressant effects.
- **Hepatic enzyme inhibitors including erthromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and cimetidine:** Inhibitors of cytochrome P450 enzymes may increase the effects of **ZOPICLONE 7,5 mg AUSTELL.** A dose reduction for **ZOPICLONE 7,5 mg AUSTELL** may be required when it is co-administered with CYP34 inhibitors.

- **Hepatic enzyme inducers such as rifampicin, carbamazepine, phenobarbital, and phenytoin and St. John's wort:** CYP3A4 inducers may decrease the plasma concentrations of **ZOPICLONE 7,5 mg AUSTELL**. Therefore, a dose increase for **ZOPICLONE 7,5 mg AUSTELL** may be required when it is co-administered with CYP3A4 inducers.

PREGNANCY AND LACTATION

Insufficient data are available on **ZOPICLONE 7,5 mg AUSTELL** to assess its safety during human pregnancy and lactation. If **ZOPICLONE 7,5 mg AUSTELL** is used during the last three months of pregnancy or during labour, due to pharmacological action of the product, effects on the neonate, such as hypothermia, hypotonia, and respiratory depression can be expected.

The use of **ZOPICLONE 7,5 mg AUSTELL** during pregnancy is not recommended. (See CONTRAINDICATIONS)

If **ZOPICLONE 7,5 mg AUSTELL** is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of the product if she intends to become or suspects that she is pregnant.

Although the concentration of **ZOPICLONE 7,5 mg AUSTELL** in the breast milk is very low, **ZOPICLONE 7,5 mg AUSTELL** should not be used by breastfeeding mothers. (See CONTRAINDICATIONS)

DOSAGE AND DIRECTIONS FOR USE

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

Adults: 7,5 mg orally, shortly before retiring. This dose should not be exceeded.

Elderly Patients and patients with impaired hepatic function or chronic respiratory insufficiency:

The lower dose of 3,75 mg **ZOPICLONE 7,5 mg AUSTELL** should be used initially in these patients, and if necessary, the dose may be increased to 7,5 mg.

Renal insufficiency: patients with impaired renal function should start treatment with 3,75 mg, although accumulation of **ZOPICLONE 7,5 mg AUSTELL** or its metabolites has not been seen during treatment of insomnia in patients with renal insufficiency.

ZOPICLONE 7,5 mg AUSTELL therapy should be for as short a time 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. Use for any longer periods requires re-evaluation of the patient.

SIDE EFFECTS

Psychiatric disorders

Less frequent: residual somnolence, anterograde amnesia (especially when sleep is interrupted, or when tablet is taken too early before retiring), (see WARNINGS AND SPECIAL PRECAUTIONS), nightmares, irritability, confusion, hallucinations, aggressiveness and inappropriate behaviour possibly associated with amnesia. Drowsiness and inco-ordination on waking.

Nervous system disorders

Less frequent: Dizziness, headache.

Gastrointestinal disorders

Frequent: Bitter taste in the mouth

Less frequent: Dyspepsia, nausea, dry mouth

Skin and subcutaneous tissue disorders

Less frequent: Pruritus, rash (may be a sign of hypersensitivity)

Rebound effects: Discontinuation of treatment of **ZOPICLONE 7,5 mg AUSTELL** may result in a transient syndrome of anxiety, restlessness and mood changes, as well as an enhancement of symptoms that led to the treatment with **ZOPICLONE 7,5 mg AUSTELL.** (See DIRECTIONS FOR USE).

KNOWN SYMPTOMS OF OVER DOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms of overdose:

(See **SIDE EFFECTS**)

Overdose is usually manifested by varying degrees of central nervous system depression according to the quantity ingested. In mild cases, symptoms include drowsiness, confusion, lethargy; in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression and coma Overdose may be life-threatening especially when combined with other CNS depressants (including alcohol). Other risk factors such as the presence of concomitant illness and the debilitated state of the patient may contribute to the severity of the symptoms and can result in fatal outcome.

Treatment of overdose:

Symptomatic and supportive treatment in an adequate clinical environment is recommended, with special attention being paid to respiratory and cardiovascular functions.

Gastric lavage is only useful when performed soon after ingestion. Haemodialysis is of no value due to the large volume of distribution of **ZOPICLONE 7,5 mg AUSTELL**. Flumazenil may be a useful antidote.

IDENTIFICATION

White coloured, circular, biconvex film coated tablets with a score line on one side.

PRESENTATION

Clear PVC/PVDC blister strips of 30 tablets. The blister strips are packed in an outer carton.

STORAGE INSTRUCTIONS

Store at or below 25 ºC. Protect from light.

KEEP OUT OF THE REACH OF CHILDREN

Blisters should not be removed from the outer carton until required for use.

REGISTRATION NUMBER

A39/2.2/0022

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals Pty (Ltd)

1 Sherborne Road

Parktown

Johannesburg, 2193

South Africa

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