Proprietary name:	ZOLTAB 5 ; ZOLTAB 10
Dosage form:	Tablets
Active Ingredient:	Zolpidem (as tartrate)
Strength per dosage unit:	5 mg or 10 mg of zolpidem per tablet

1.3.1.1 PROFESSIONAL INFORMATION (FINAL)

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ZOLTAB 5 Film-coated Tablets

ZOLTAB 10 Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOLTAB 5: Each film-coated tablet contains 5 mg of zolpidem (as tartrate).

ZOLTAB 10: Each film-coated tablet contains 10 mg of zolpidem (as tartrate).

Excipient(s) with known effect:

ZOLTAB 5 contains 42,30 mg of lactose monohydrate.

ZOLTAB 10 contains 84,60 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ZOLTAB 5: White to off-white round biconvex film coated tablets, plain on both sides.

ZOLTAB 10: White to off-white capsule shaped film coated tablets having a break line on one side and plain on other sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZOLTAB is indicated for the short-term treatment of insomnia. **ZOLTAB** is a short-acting hypnotic, is only indicated when the disorder is severe, debilitating or is causing severe distress for the patient.

4.2 Posology and method of administration

Posology:

Treatment should be as short as possible. The duration of treatment ranges from a few days to two weeks, with a maximum of four weeks (includes the tapering off period).

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.

The recommended daily dose for adults is 10 mg to be taken immediately before bedtime. The lowest effective daily dose of **ZOLTAB** should be used and must not exceed 10 mg.

Special populations:

Elderly patients:

Elderly or debilitated patients may be especially sensitive to the effects of **ZOLTAB** therefore a 5 mg dose is recommended in these patients. The total dose should not exceed 10 mg in these patients.

Patients with hepatic impairment:

In hepatic impairment patients, the recommended dosage of **ZOLTAB**
is 5 mg with particular caution being exercised in elderly patients.

Paediatric patients:

Safety and effectiveness of **ZOLTAB** in paediatric patients under the age of 18 years have not been established. **ZOLTAB** should not be prescribed in this population (see *section 4.3*).

Method of administration:

ZOLTAB is for once-daily oral administration.

4.3 Contraindications

- Hypersensitivity to zolpidem or to any of the excipients listed in section 6.1.
- Obstructive sleep apnoea.
- Myasthenia gravis.
- Severe hepatic insufficiency (see section 4.4).
- Acute and/or severe respiratory depression.
- Children under the age of 18.
- Safety in Pregnancy and lactation has not been established (see section 4.6).

4.4 Special warnings and precautions for use

The cause of insomnia should be identified wherever possible and the underlying factors treated before **ZOLTAB** is prescribed. The failure of insomnia to remit after a 7 – 14 day course of treatment may indicate the presence of a primary psychiatric or physical disorder, and the patient should be carefully re-evaluated at regular intervals.

Severe hepatic insufficiency:

ZOLTAB is contraindicated in patients with severe hepatic insufficiency as it may precipitate encephalopathy (see *section 4.3*).

Respiratory insufficiency:

As hypnotics have the capacity to depress respiratory drive, precautions should be observed if **ZOLTAB** is prescribed to patients with compromised respiratory function.

Risks from concomitant use with opioids:

Concomitant use of **ZOLTAB** and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related medicines such as zolpidem with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe **ZOLTAB** concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2). The patients should be followed closely for signs and symptoms of respiratory depression and sedation.

Paediatric patients:

ZOLTAB is contraindicated in patients under the age of 18 years due to increased occurrence of adverse effects including dizziness, headache and hallucinations.

Elderly patients:

See section 4.2 for dose recommendations.

Psychomotor impairment:

ZOLTAB has CNS-depressant effects. The risk of next-day psychomotor impairment, including impaired driving ability, is increased if:

- **ZOLTAB** is taken within less than 8 hours before performing activities that require mental alertness (see *section 4.7*);
- a dose higher than the recommended dose is taken;
- **ZOLTAB** is co-administered with other CNS depressants or with other medicines that increase the blood levels of zolpidem, or with alcohol or illicit medicines (see *section 4.5*).

History of medicine or alcohol abuse:

ZOLTAB should not be used in patients with a history of medicine or alcohol abuse.

Psychotic illness:

ZOLTAB is not recommended for the primary treatment of psychotic illness.

Suicidality and depression:

Increased incidence of suicide and suicide attempt in patients with or without depression, treated with benzodiazepines and other hypnotics, including **ZOLTAB** were observed. **ZOLTAB** should not be used as the primary treatment depressive syndromes.

ZOLTAB should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present therefore the least amount of **ZOLTAB** that is feasible should be supplied to these patients to avoid the possibility of intentional overdose by the patient. Pre-existing depression may be unmasked during use of **ZOLTAB**. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

Duration of treatment:

The duration of treatment should be as short as possible and should not exceed 4 weeks, including the tapering off process. Extensions beyond these periods should not take place without 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.

Tolerance:

Some loss of efficacy to the hypnotic effects of short-acting benzodiazepines and benzodiazepine-like medicines like zolpidem as in **ZOLTAB** may develop after repeated use for a few weeks.

Rebound insomnia:

A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine or benzodiazepine-like medicine recur in an enhanced form, may occur on withdrawal of **ZOLTAB** treatment.

It may be accompanied by other reactions including mood changes, anxiety and restlessness. The syndrome is more likely to develop if **ZOLTAB** is discontinued abruptly, and therefore treatment with **ZOLTAB** should be withdrawn gradually.

It is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur when the medicine is discontinued.

In the case of benzodiazepines and benzodiazepine-like medicines with a short duration of action, such as **ZOLTAB**, withdrawal phenomena can become manifest within the dosage interval.

Dependence:

Use of **ZOLTAB** may lead to the development of abuse and/or physical and psychological dependence. The risk of dependence increases with dose and duration of treatment, it is also greater in patients with a history of psychiatric disorders and/or alcohol, substance or medicine abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety and tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

ZOLTAB have produced withdrawal signs and symptoms following abrupt discontinuation. These symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors and convulsions. The following adverse events have been reported fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness and abdominal discomfort.
Patients with a history of psychiatric disorders or addiction to, or abuse of, medicines or alcohol are at increased risk of habituation and dependence. Patients with a history of psychiatric disorders should be under careful surveillance when receiving **ZOLTAB** or any other hypnotic.

Amnesia:

ZOLTAB 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 8 hours (see *section 4.8*).

Other psychiatric and "paradoxical" reactions:

Other psychiatric and paradoxical reactions like restlessness, exacerbated insomnia, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, psychosis, abnormal behaviour and other adverse behavioural effects are known to occur when using benzodiazepines or benzodiazepine-like medicines. Should this occur, the use of **ZOLTAB** should be discontinued. These reactions are more likely to occur in the elderly.

Somnambulism and associated behaviours:

Sleep walking and other associated behaviours such as "sleep driving", preparing and eating food, making phone calls or having sex, with amnesia for the event, have been reported in patients who had taken **ZOLTAB** and were not fully awake. The use of alcohol and other CNS-depressants with **ZOLTAB** appears to increase the risk of such behaviour, as does the use of **ZOLTAB** at doses exceeding the maximum recommended dose. Discontinuation of **ZOLTAB** should be strongly considered for patients who report such behaviours.

Severe injuries:

Due to its pharmacological properties, **ZOLTAB** can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries.

Patients with Long QT syndrome:

ZOLTAB may lead to reduction of the hERG (human ether-a-go-go-related gene) related potassium currents, under experimental conditions using very high concentration and pluripotent stem cells. The potential consequence in patients with congenital long QT syndrome is unknown. As a precaution, the benefit/risk ratio of **ZOLTAB** treatment in patients with known congenital long QT syndrome should be carefully considered.

Excipients:

Lactose: Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take **ZOLTAB**.

4.5 Interaction with other medicines and other forms of interaction

Alcohol:

Concomitant intake with alcohol is not recommended. The sedative effects may be enhanced when **ZOLTAB** is used in combination with alcohol. This affects the ability to drive or use machines.

CNS depressants:

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant medicines, narcotic analgesics, antiepileptic medicines, anaesthetics and sedative antihistamines. Therefore, concomitant use of **ZOLTAB** with these medicines may increase drowsiness and following day psychomotor impairment, including impaired driving ability (see *sections 4.4 and 4.7*).

Cases of visual hallucinations were reported in patients taking **ZOLTAB** with antidepressants including bupropion, desipramine, fluoxetine, sertraline and venlafaxine.

Co-administration of fluvoxamine may increase blood levels of zolpidem as in **ZOLTAB**, concomitant use is not recommended.

In the case of narcotic analgesics enhancement of euphoria may also occur leading to an increase in psychological dependence.

Opioids:

The concomitant use of sedative medicines such as benzodiazepines or related medicines such as **ZOLTAB** with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see *section 4.4*).

CYP450 inhibitors and inducers:

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines and benzodiazepine-like medicines such as **ZOLTAB**.

ZOLTAB is metabolised via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2.

The pharmacodynamic effect of **ZOLTAB** is decreased when it is administered with a CYP3A4 inducer such as rifampicin and St. John's Wort.

Co-administration of St. John's Wort may decrease blood levels of **ZOLTAB**, concurrent use is not recommended.

However when **ZOLTAB** was administered with itraconazole (a CYP3A4 inhibitor) its pharmacokinetics and pharmacodynamics were not significantly modified. The clinical relevance of these results is unknown.

Co-administration of **ZOLTAB** with ketoconazole (200 mg twice daily), a potent CYP3A4 inhibitor, prolonged **ZOLTAB** elimination half-life, increased total AUC, and decreased apparent oral clearance when compared to **ZOLTAB** plus placebo). The total AUC for **ZOLTAB**, when co-administered with ketoconazole, increased by a factor of 1.83 when compared to **ZOLTAB** alone. A routine dosage adjustment of zolpidem is not considered necessary, but patients, should be advised that use of **ZOLTAB** with ketoconazole may enhance the sedative effects.

Fluvoxamine is a strong inhibitor of CYP1A2 and a moderate to weak inhibitor of CYP2C9 and CYP3A4. Co-administration of fluvoxamine may increase blood levels of **ZOLTAB**, concurrent use is not recommended.

Co-administration of ciprofloxacin may increase blood levels of **ZOLTAB**, concurrent use is not recommended.

Other medicines:

When **ZOLTAB** was administered with warfarin, digoxin, ranitidine or cimetidine, no significant pharmacokinetic interactions were observed.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential:

If **ZOLTAB** is prescribed to a woman of childbearing potential, she should be warned to contact her medical doctor about stopping the **ZOLTAB** if she intends to become or suspects that she is pregnant.

Pregnancy:

The use of **ZOLTAB** is not recommended during pregnancy. **ZOLTAB** crosses the placenta.

Administration of **ZOLTAB** during the late phase of pregnancy, or during labour has been associated with effects on the neonate, such as hypothermia, hypotonia, feeding difficulties (which may result in poor weight gain), and respiratory depression, sometimes severe, due to the pharmacological action of the medicine.

Infants born to mothers who took sedative/hypnotic medicines as in **ZOLTAB** chronically during the latter stages of pregnancy may develop physical dependence and may be at risk of developing withdrawal symptoms in the postnatal period.

Lactation:

Small quantities of zolpidem as in **ZOLTAB** appear in breast milk. The use of **ZOLTAB** in nursing mothers is therefore contra-indicated.

4.7 Effects on ability to drive and use machines

ZOLTAB has major influence on the ability to drive and use machines.

Vehicle drivers and machine operators should be warned that there may be a possible risk of adverse reactions including drowsiness, prolonged reaction time, dizziness and vertigo, sleepiness, blurred/double vision, reduced alertness and impaired driving the morning after therapy.

If insufficient sleep duration occurs, the likelihood of impaired alertness may increase. In order to minimise this risk a full night of sleep (7 – 8 hours) is recommended.

The co-administration of **ZOLTAB** with alcohol and other CNS depressants increases the risk of such effects. Patients should be warned not to use alcohol or other psychoactive substances when taking **ZOLTAB**.

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: *Frequent, less frequent, frequency unknown*.

Infections and infestations:

Frequent: upper respiratory tract infection, lower respiratory tract infection.

Psychiatric disorders:

Frequent: hallucination, agitation, nightmare.

Less frequent: confusional state, irritability

Frequency unknown: restlessness, aggression, anger, delusion, abnormal behaviour, somnambulism (see *section 4.4*), dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation); euphoric mood, libido disorder, depression, and psychosis. Most of these psychiatric undesirable effects are related to paradoxical reactions.

Nervous system disorders:

Frequent: somnolence, headache, dizziness, exacerbated insomnia, cognitive disorders such as anterograde amnesia (amnesic effects may be associated with inappropriate behaviour).

Less frequent: paraesthesia, tremor.

Frequency unknown: disturbance in attention, speech disorder, depressed level of consciousness.

General disorders and administrative site conditions:

Frequent: fatigue

Frequency unknown: gait disturbances, medicine tolerance and fall.

Eye disorders:

Less frequent: diplopia, vision blurred and visual impairment.

Metabolism and nutrition disorders:

Less frequent: appetite disorder.

Respiratory, thoracic and mediastinal disorders

Frequency unknown: respiratory depression (see section 4.4).

Gastrointestinal disorders:

Frequent: diarrhoea, nausea, vomiting and abdominal pain.

Hepatobiliary disorders:

Frequency unknown liver enzymes elevated, hepatocellular, cholestatic or mixed liver injury (see sections 4.2, 4.3 and 4.4).

Skin and subcutaneous tissue disorders:

Frequency unknown: rash, pruritus, angioneurotic oedema, hyperhidrosis and urticaria.

Musculoskeletal, connective tissue and bone disorders:

Frequent: back pain.

Less frequent: arthralgia; myalgia, muscle spasms, neck pain.

Frequency unknown: muscular weakness.

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. Healthcare professionals 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 Alternatively all adverse events can be reported to Alkem Laboratories vial the e-mail: pharmacist.rsa@Alkem.com.

4.9 Overdose

In cases of overdose, involving **ZOLTAB** alone or with other CNS-depressant medicines (including alcohol), impairment of consciousness ranging from somnolence to coma, and more severe symptomatology, including fatal outcomes have been reported.

Management:

General symptomatic and supportive measures should be used. Sedating medicines should be withheld even if excitation occurs.

Use of flumazenil may be considered where serious symptoms are observed. However, flumazenil administration may contribute to appearance of neurological symptoms (convulsions).

In the management of overdose with any medicine, it should be borne in mind that multiple medicines may have been taken.

ZOLTAB is not dialysable.

5.1 Pharmacodynamic properties

Category and Class: A 2.2 Sedatives, hypnotics

Pharmacotherapeutic group: Hypnotics and Sedatives Benzodiazepine related medicines GABA-A receptor modulator selective for omega-1 receptor subtype hypnotic medicine.

ATC code: N05CF 02

Zolpidem is an imidazopyridine, with sedative and hypnotic effects. These effects are related to a specific agonist action at central receptors belonging to GABA-omega benzodiazepine-1 and benzodiazepine-2 macromolecular receptor complex, modulating, the opening of the chloride ion channel. Zolpidem preferentially binds the omega-1 subtype.

5.2 Pharmacokinetic properties

Absorption:

After oral administration, bioavailability is 70 % following oral administration and reaching peak plasma concentration within 0.5 and 3 hours.

Distribution:

At therapeutic dose levels, the pharmacokinetics are linear. Protein binding amounts to 92 %. The distribution volume in adults is 0.54 ± 0.02 L/kg and decreases to 0.34 ± 0.05 L/kg in the very elderly.

Elimination:

Zolpidem is metabolised via several hepatic cytochrome P450 enzymes. The elimination half-life is about 2 hours and duration of action of up to 6 hours. First pass metabolism by the liver amounts to approximately 35 %. All metabolites are pharmacologically inactive and are eliminated in the urine (56 %) and in the faeces (37 %).

Renal insufficiency:

In patients with renal insufficiency, whether dialysed or not, there is a moderate reduction in clearance. The other pharmacokinetic parameters are unaffected.

Hepatic impairment:

Plasma concentrations in patients with hepatic impairment are increased. Clearance is reduced and the elimination half-life prolonged (about 10 hours).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and coating solution (hypromellose, macrogol and titanium dioxide).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light and moisture.

Keep sealed blister in outer container until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Aluminium/ PVC blister strips containing 14 tablets. The blister strips are packed in an outer carton.

White HDPE bottles and caps containing 400 tablets each.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Alkem Laboratories (Pty) Ltd.

R21 Corporate Park

121 Sovereign Drive, Block A, Office 202

Irene Ext.30, Centurion, 0157

8 REGISTRATION NUMBER(S)

ZOLTAB 5: To be allocated

ZOLTAB 10: To be allocated

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

To be allocated

10 DATE OF REVISION OF THE TEXT

To be allocated