

**ZIDLE
(Zolpidem Tartrate)**

Tablet

10 mg

COMPOSITION –

Each film-coated tablet contains:
Zolpidem Tartrate U.S.P. 10mg

THERAPEUTIC INDICATIONS

Zolpidem is indicated for the short-term treatment of insomnia in adults in situations where the insomnia is debilitating or is causing severe distress for the patient

DOSAGE AND ADMINISTRATION

Posology

The treatment should be taken in a single intake and not be re-administered during the same night.

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

As with all hypnotics, long-term use is not recommended. Treatment should be as short as possible and should not exceed four weeks including the period of tapering off. Extension beyond the maximum treatment period should not take place without re-evaluation of the patient's status, since the risk of abuse and dependence increases with the duration of treatment.

Special populations

Paediatric population

Zolpidem is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented.

Elderly

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem therefore a 5 mg dose is recommended. These recommended doses should not be exceeded.

Hepatic impairment

As clearance and metabolism of zolpidem is reduced in hepatic impairment, dosage should begin at 5 mg in these patients with particular caution being exercised in elderly patients. In adults (under 65 years) dosage may be increased to 10 mg only where the clinical response is inadequate and the drug is well tolerated.

Zolpidem must not be used in patients with severe hepatic impairment as it may contribute to encephalopathy.

Method of administration

Oral administration.

CONTRAINDICATIONS

- Zolpidem tartrate is contraindicated in patients with a hypersensitivity to zolpidem tartrate or any of the excipients.
- Obstructive sleep apnoea.
- Myasthenia gravis.
- Severe hepatic insufficiency.
- Acute and/or severe respiratory depression.

In the absence of data, zolpidem should not be prescribed for children or patients with psychotic illness.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The cause of insomnia should be identified wherever possible and the underlying factors treated before a hypnotic 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.

Next-day psychomotor impairment

Like other sedative/hypnotic drugs, zolpidem has CNS-depressant effects. The risk of next-day psychomotor impairment, including impaired driving ability, is increased if:

- zolpidem is taken within less than 8 hours before performing activities that require mental alertness
- a dose higher than the recommended dose is taken;
- zolpidem is co-administered with other CNS depressants or with other drugs that increase the blood levels of zolpidem, or with alcohol or illicit drugs.

Zolpidem should be taken in a single intake immediately at bedtime and not be re-administered during the same night.

Specific patient groups

Respiratory insufficiency:

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

Hepatic insufficiency:

Posology and method of administration

Elderly:

Posology and method of administration

Risks from concomitant use with opioids:

Concomitant use of zolpidem 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 drugs 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 zolpidem concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms

Use in patients with a history of drug or alcohol abuse:

Extreme caution should be exercised when prescribing for patients with a history of drug or alcohol abuse. These patients should be under careful surveillance when receiving zolpidem tartrate or any other hypnotic, since they are at risk of habituation and psychological dependence.

Psychotic illness:

Hypnotics such as zolpidem are not recommended for the primary treatment of psychotic illness.

Suicidal ideation/suicide attempt/suicide and depression:

Some epidemiological studies suggest an increased incidence of suicidal ideation, suicide attempt and suicide in patients with or without depression, and treated with benzodiazepines and other hypnotics, including zolpidem. However, a causal relationship has not been established. As with other sedative/hypnotic drugs, zolpidem should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present therefore the least amount of zolpidem 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 zolpidem. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

General information relating to effects seen following administration of benzodiazepines and other hypnotic agents which should be taken into account by the prescribing physician are described below.

Tolerance:

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

Dependence:

Use of zolpidem may lead to the development of abuse and/or physical and psychological dependence. The risk of dependence increases with dose and duration of treatment. Cases of dependence have been reported more frequently in patients treated with zolpidem for longer than 4 weeks. The risk of abuse and dependence is also greater in patients with a history of psychiatric disorders and/or alcohol, substance or drug abuse. Zolpidem should be used with extreme caution in patients with current or a history of alcohol, substance or drug abuse or dependence.

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.

Rebound insomnia:

A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine or benzodiazepine-like agent recur in an enhanced form, may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

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 medicinal product is discontinued. Since the risk of withdrawal phenomena or rebound has been shown to be greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually where clinically appropriate.

There are indications that, in the case of benzodiazepines and benzodiazepine-like agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

Amnesia:

Benzodiazepines or benzodiazepine-like agents such as zolpidem 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.

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 agents. Should this occur, use of the product 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 zolpidem and were not fully awake. The use of alcohol and other CNS-depressants with zolpidem appears to increase the risk of such behaviour, as does the use of zolpidem at doses exceeding the maximum recommended dose. Discontinuation of zolpidem should be strongly considered for patients who report such behaviour (for example, sleep driving), due to the risk to the patient and others.

Severe injuries:

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

Important information about the ingredients of Zolpidem tartrate

Zolpidem tartrate contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose galactose malabsorption should not take this medicine.

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

DRUG INTERACTIONS

Not recommended:

Concomitant intake with alcohol:

The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Take into account:

Combination 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, antiepileptic drugs, anaesthetics and sedative antihistamines. Therefore, concomitant use of zolpidem with these drugs may increase drowsiness and next-day psychomotor impairment, including impaired driving ability. Also, isolated cases of visual hallucinations were reported in patients taking zolpidem with antidepressants including bupropion, desipramine, fluoxetine, sertraline and venlafaxine.

Co-administration of fluvoxamine may increase blood levels of zolpidem, concurrent 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 drugs such as zolpidem 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.

CYP450 inhibitors and inducers:

Co-administration of ciprofloxacin may increase blood levels of zolpidem; concurrent use is not recommended.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines and benzodiazepine-like agents.

Zolpidem is metabolised via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2. The pharmacodynamic effect of zolpidem is decreased when it is administered with a CYP3A4 inducer such as rifampicin and St. John's Wort. St. John's Wort has been shown to have a pharmacokinetic interaction with zolpidem. Mean C_{max} and AUC were decreased (33.7 and 30.0% lower, respectively) for zolpidem administered with St. John's Wort compared to zolpidem administered alone. Co-administration of St. John's Wort may decrease blood levels of zolpidem, concurrent use is not recommended.

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

Since CYP3A4 plays an important role in zolpidem metabolism, possible interactions with drugs that are substrates or inducers of CYP3A4 should be considered.

Other drugs:

When zolpidem was administered with ranitidine, no significant pharmacokinetic interactions were observed.

EFFECT ON ABILITY TO DRIVE

Zolpidem has major influence on the ability to drive and use machines. Vehicle drivers and machine operators should be warned that, as with other hypnotics, there may be a possible risk of drowsiness, prolonged reaction time, dizziness, sleepiness, blurred/double vision and reduced alertness and impaired driving the morning after therapy. In order to minimise this risk a resting period of at least 8 hours is recommended between taking zolpidem and driving, using machinery and working at heights.

Driving ability impairment and behaviours such as 'sleep-driving' have occurred with zolpidem alone at therapeutic doses.

Furthermore, co-administration of zolpidem with alcohol and other CNS depressants increases the risk of such behaviours. Patients should be warned not to use alcohol or other psychoactive substances when taking zolpidem.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

The use of zolpidem is not recommended during pregnancy.

Zolpidem crosses the placenta.

A large amount of data collected from cohort studies has not demonstrated evidence of the occurrence of malformations following exposure to benzodiazepines during the first trimester of pregnancy. However, in certain epidemiological case-control studies, an increased incidence of cleft lip and palate was observed with benzodiazepines.

Cases of reduced fetal movement and fetal heart rate variability have been described after administration of benzodiazepines during the second and/or third trimester of pregnancy.

Administration of zolpidem 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 product.

Moreover, infants born to mothers who took sedative/hypnotic agents chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

If zolpidem is prescribed to a woman of childbearing potential, she should be warned to contact her physician about stopping the product if she intends to become or suspects that she is pregnant.

Breast-feeding

Small quantities of zolpidem appear in breast milk. The use of zolpidem in nursing mothers is therefore not recommended.

ADVERSE DRUG REACTIONS

The following CIOMS frequency rating is used, when applicable:

Very common $\geq 10\%$

Common ≥ 1 and $< 10\%$

Uncommon ≥ 0.1 and $< 1\%$

Rare ≥ 0.01 and $< 0.1\%$

Very rare $< 0.01\%$

Not known: cannot be estimated based on available data.

There is evidence of a dose-relationship for adverse effects associated with zolpidem use, particularly for certain CNS and gastrointestinal events. As recommended in section 4.2, they should in theory be less if zolpidem is taken immediately before retiring, or in bed. They occur most frequently in elderly patients.

Immune system disorders

Not known: angioneurotic oedema

Psychiatric disorders

Common: hallucination, agitation, nightmare, depression

Uncommon: confusional state, irritability, restlessness, aggression, somnambulism, euphoric mood

Rare: libido disorder

Very rare: delusion, dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation)

Not known: anger, psychosis, abnormal behaviour

Most of these psychiatric undesirable effects are related to paradoxical reactions.

Nervous system disorders

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

Uncommon: paraesthesia, tremor, disturbance in attention, speech disorder

Rare: depressed level of consciousness

Eye disorders

Uncommon: diplopia, vision blurred

Very rare: visual impairment

Respiratory, thoracic and mediastinal disorders

Very rare: respiratory depression

Gastro-intestinal disorders

Common: diarrhoea, nausea, vomiting, abdominal pain

Hepatobiliary disorders

Uncommon: liver enzymes elevated

Rare: hepatocellular, cholestatic or mixed liver injury

Metabolism and nutrition disorders

Uncommon: appetite disorder

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritus, hyperhidrosis

Rare: urticaria

Musculoskeletal and connective tissue disorders

Common: back pain

Uncommon: myalgia, muscle spasms, muscular weakness

Infections and infestations

Common: upper respiratory tract infection, lower respiratory tract infection

General disorders and administration site conditions

Common: fatigue

Rare: gait disturbance, fall (predominantly in elderly patients and when zolpidem was not taken in accordance with prescribing recommendation)

Not known: drug tolerance

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 at pv@searlecompany.com

OVERDOSE

Signs and symptoms:

In cases of overdose, involving zolpidem alone or with other CNS-depressant agents (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. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Sedating drugs should be withheld even if excitation occurs.

Use of flumazenil may be considered where serious symptoms are observed. Flumazenil is reported to have an elimination half-life of about 40 – 80 minutes. Patients should be kept under close observation because of

this short duration of action; further doses of flumazenil may be necessary. However, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

Zolpidem is not dialyzable. The value of dialysis in the treatment of an overdose has not been determined. Dialysis in patients with renal failure receiving therapeutic doses of zolpidem has demonstrated no reduction in levels of zolpidem.

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

(GABA-A receptor agonist selective for omega-1-type sub-unit hypnotic agent).

Zolpidem is an imidazopyridine which selectively binds the omega-1 receptor subtype (also known as the benzodiazepine-1 subtype) which is the alpha unit of the GABA-A receptor complex. Whereas benzodiazepines non-selectively bind all three omega receptor subtypes, zolpidem preferentially binds the omega-1 subtype. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem. These effects are reversed by the benzodiazepine antagonist flumazenil.

The randomized trials only showed convincing evidence of efficacy of 10 mg zolpidem. In a randomized double-blind trial in 462 non-elderly healthy volunteers with transient insomnia, zolpidem 10 mg decreased the mean time to fall asleep by 10 minutes compared to placebo, while for 5 mg zolpidem this was 3 minutes.

In a randomized double-blind trial in 114 non-elderly patients with chronic insomnia, zolpidem 10 mg decreased the mean time to fall asleep by 30 minutes compared to placebo, while for 5 mg zolpidem this was 15 minutes.

In some patients, a lower dose of 5 mg could be effective.

In animals: The selective binding of zolpidem to omega-1 receptors may explain the virtual absence at hypnotic doses of myorelaxant and anti-convulsant effects in animals which are normally exhibited by benzodiazepines which are not selective for omega-1 sites.

In humans: The preservation of deep sleep (stages 3 and 4 - slow-wave sleep) may be explained by the selective omega-1 binding by zolpidem. All identified effects of zolpidem are reversed by the benzodiazepine antagonist flumazenil.

Paediatric populations

Safety and efficacy of zolpidem have not been established in children aged less than 18 years. A randomized placebo-controlled study in 201 children aged 6 – 17 years with insomnia associated with Attention Deficit Hyperactivity Disorder (ADHD) failed to demonstrate efficacy of zolpidem 0.25 mg/kg/day (with maximum of 10 mg/day) as compared to placebo. Psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% versus 1.5%), headache (12.5% versus 9.2%), hallucinations (7.4% versus 0%).

Pharmacokinetic properties

Zolpidem has both a rapid absorption and onset of hypnotic action. Bioavailability is 70% following oral administration and demonstrates linear kinetics in the therapeutic dose range. Peak plasma concentration is reached at between 0.5 and 3 hours.

The elimination half-life is short, with a mean of 2.4 hours (0.7-3.5) and a duration of action of up to 6 hours. Protein binding amounts to 92.5% ± 0.1%. First pass metabolism by the liver amounts to approximately 35%. Repeated administration has been shown not to modify protein binding indicating a lack of competition between zolpidem and its metabolites for binding sites.

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.

All metabolites are pharmacologically inactive and are eliminated in the urine (56%) and in the faeces (37%).

Zolpidem has been shown in trials to be non-dialysable.

Plasma concentrations in elderly subjects and those with hepatic impairment are increased. In patients with renal insufficiency, whether

dialysed or not, there is a moderate reduction in clearance. The other pharmacokinetic parameters are unaffected.

Zolpidem is metabolised via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2. Since CYP3A4 plays an important role in zolpidem metabolism, possible interactions with drugs that are substrates or inducers of CYP3A4 should be considered.

PRECLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

PRESENTATION

Zidle 10 mg Tablets are available in pack size of 2x10's

STORAGE INSTRUCTIONS

To be sold on prescription of a registered medical practitioner only.

- Protect from sunlight, moisture and heat.

- Store below 30°C.

- Keep all medicines out of the reach of children

REGISTRATION NUMBER

Zidle 10mg: 081844

Manufacturing License No.: 00058

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION – As per registrations letter

Product Complies U.S.P. Specs

Manufactured by:

Searle IV Solutions (Pvt.) Limited.

1.5 km, Manga Raiwind Road, Manga

Mandi, Distt. Lahore – Pakistan

Marketed by:

SEARLE

The Searle Company Limited,

First Floor, N.I.C.L. Building, Abbasi

Shaheed Road, Karachi –Pakistan

DATE OF PUBLICATION OF THE PACKAGE INSERT

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