Summary of product characteristic (SmPC)

Name of the medicinal Product

Zolpidem Tablets BP 10 mg

1. Qualitative and Quantitative Composition

Each film coated tablet contains 10 mg of Zolpidem Tartrate BP

For full list of Excipients, see section 6.1

2. **Pharmaceutical Form**

Oral Tablet

Yellow colored, round shaped, biconvex, breakline on one side and plain on other side of Film coated tablet.

The breakline is only to facilitate breaking of ease of swallowing and not to divide into equal doses

3. Clinical Particulars

1. 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.

2. Posology and Method of Administration

Distribution Category: POM

Method of administration: Orally. It should be taken with a glass of water or another suitable liquid. It is taken with or without meal or as directed by physician.

The recommended daily dose for adults is 10 mg should be taken the single intake immediately at bedtime. Do not take another dose during the same night.

The duration of treatment should be started with low doses for short duration as possible, it must not exceed recommend daily doses, treatment usually vary from a few days to two weeks with a maximum of four weeks including tapering off where clinically appropriate.

It should not exceed four weeks including the period of tapering off. In certain cases extension beyond the maximum treatment period may be necessary; if so, 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: Safety and efficacy was not established for pediatrics, therefore it should not be recommended for children and adolescents below 18 years of age or patients

with psychotic illness.

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

Hepatic impairment: clearance and metabolism of zolpidem is reduced in hepatic impairment, treatment should be started with low doses (5 mg) in these patients with particular caution being exercised in elderly patients.

Adults (under 65 years): dosage may be increased to 10 mg only where the clinical response is inadequate and the drug is well tolerated. It must not be used in patients with severe hepatic impairment as it may contribute to encephalopathy.

3. Contraindications

It is contraindicated in patients with a hypersensitivity to active substance or any of the excipients. Contra-indications obstructive sleep apneal, severe hepatic insufficiency, acute or severe respiratory depression, marked neuromuscular respiratory weakness including unstable myasthenia gravis, psychotic illness.

4. Special Warnings and Special Precautions for Use

Warning: Co-administration with other CNS depressants, drug-induced complex sleep-related behaviors, driving or operating machinery, ethanol ingestion.

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: sedative/hypnotic drugs, zolpilin has CNS-depressant effects. The risk of next-day psychomotor impairment, including impaired driving ability, is increased if: zolpidem tartrate is taken within less than 8 hours before performing activities that require mental alertness, a dose higher than the recommended dose is taken, zolpidem tartrate is co-administered with other CNS depressants or with other drugs that increase the blood levels of zolpidem tartrate, or with alcohol or illicit drugs.

Zolpilin 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 zolpilin is prescribed to patients with compromised respiratory function.

Hepatic insufficiency: clearance and metabolism of zolpidem is reduced in hepatic impairment, treatment should be started with low doses in these patients with particular caution being exercised in elderly patients.

Elderly: The treatment should be started with low doses.

Risk from concomitant use of opioids: Patients should avoid the concomitant use with of opioids drugs: 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 zolpilin with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe zolpilin 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 zolpilin 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 wit 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 tartrate should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present therefore the least amount of zolpilin 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 Zolpilin-10. 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 zolpilin 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. 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.

If physical dependence is developed, a sudden discontinuation of treatment will be accompanied by withdrawal symptoms. These 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 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 zolpilin may induce anterograde amnesia. The condition occurs most often several hours after ingesting the medicines. In order to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 8 hours.

Patients more likely (Elder)feel any other psychiatric and “paradoxical” reactions: like restlessness, exacerbated insomnia, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, psychosis, abnormal behaviour and other adverse behavioral effects are known to occur when using benzodiazepines or benzodiazepine-like agents. Use of the medicine should be stopped.

Somnambulism and associated behaviors: 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, may report in patients who had taken zolpilin and were not fully awake.

Patients should avoid the use of alcohol and other CNS-depressants with zolpilin appears to increase the risk of such behaviours, as does the use of zolpilin at doses exceeding the maximum recommended dose.

If patients may report such behaviors (i.e. sleep driving) stopped to taking of zolpilin should be strongly considered. Patient should caution to avoid driving and other hazardous activities while under drug’s influence.

Patients may cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries.

Pregnancy: It crosses the placenta. It should not be recommended to used during pregnancy.

Lactation: It passes into the maternal milk in small amounts. Therefore, it should not be recommended to used in mothers who breastfeed unless clearly necessary.

This product contains lactose excipients with known effect: Patients with galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

5. Interaction with other medicinal products and other forms of interaction

It is not recommended concomitant intake with alcohol. **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 with these drugs may increase drowsiness and next-day psychomotor impairment, including impaired driving ability also, isolated cases of visual hallucinations, antidepressants including bupropion, desipramine, fluoxetine, sertraline and venlafaxine. **Fluvoxamine:** zolpidem tartrate concurrent use with fluvoxamine 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 with opioids increases the risk of sedation, respiratory depression, and coma because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited. **CYP450 inhibitors and inducers:** Ciprofloxacin, benzodiazepines and benzodiazepine-like agents. Several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2. **CYP3A4:** as rifampicin and St. John's Wort, concurrent use is not recommended. Itraconazole (a CYP3A4 inhibitor). **Other drugs:** Antihistamines

6. Pregnancy and Lactation

Pregnancy: It crosses the placenta. It should not be recommended to used during pregnancy.

Lactation: It passes into the maternal milk in small amounts. Therefore, it should not be recommended to used in mothers who breastfeed unless clearly necessary.

7. Effects on ability to Drive and use Machines

The ability to perform tasks that demand an increased concentration such as driving or operating machinery will also be affected. If patients may report such behaviors (i.e. sleep driving) stopped to taking of zolpilin-10 should be strongly considered. Patient should caution to avoid driving and other hazardous activities while under drug's influence. Patients should be counselled about the effects on driving.

8. Undesirable effect

Immune System Disorder: angioneurotic oedema.

Psychiatric disorders: hallucination, agitation, nightmare, depression, confusional state, irritability, restlessness, aggression, somnambulism, euphoric mood, libido disorder delusion, physical or psychological drug dependence, drug tolerance, anger, psychosis, abnormal behavior, most of these psychiatric undesirable effects are related to paradoxical reactions.

Nervous system disorders: somnolence, headache, dizziness, exacerbated insomnia, cognitive disorders such as anterograde amnesia with (inappropriate behaviour), paraesthesia, tremor, disturbance in attention, speech disorder, depressed level of consciousness.

Eye disorders: diplopia, vision blurred, visual.

Impairment Respiratory, thoracic and mediastinal disorders: respiratory depression.

Gastro-intestinal disorders: diarrhoea, nausea, vomiting, abdominal pain.

Hepatobiliary disorders: liver enzymes elevated: hepatocellular, cholestatic or mixed liver injury.

Metabolism and nutrition disorders: appetite disorder.

Skin and subcutaneous tissue disorders: rash, pruritus, hyperhidrosis, urticaria.

Musculoskeletal and connective tissue disorders: back pain, myalgia, muscle spasms, muscular weakness.

Infections and infestations: upper respiratory tract infection, lower respiratory tract infection.

General disorders and administration site conditions*:* fatigue.

9. Overdose

Signs and symptoms:

In cases of overdose involving zolpidem tartrate alone or with other CNS-depressant agents (including alcohol),impairment of consciousness ranging from somnolence to coma, and more severe symptomatology, including serious outcomes may occurred.

Management:

In the management of overdose general symptomatic and supportive measures should be used. It is not dialyzable, dialysis in patients with renal failure receiving therapeutic doses of zolpidem there may no reduction in levels of zolpidem. 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. Patients should be kept under close observation, flumazenil has elimination half-life of about 40-80 minutes. Further doses of flumazenil may be necessary. However, it may contribute to the appearance of neurological symptoms (convulsions).

4. Pharmacological Properties

5.1 Pharmacodynamics Properties

It is an imidazopyridine which preferentially binding to gammaaminobutyric acid receptors (also known as the benzodiazepine-1 subtype) which corresponds to GABA-A receptors containing the alpha-1 sub-unit, whereas benzodiazepines non-selectively bind both omega-1 and omega-2 subtypes and depresses CNS. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects proved by zolpidem tartrate. These effects are reversed by the benzodiazepine antagonist flumazenil.

5.2 Pharmacokinetic Properties

Absorption: It 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.

Distribution: 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. Protein binding amounts to 92.5% ± 0.1%. Repeated administration shown not to modify protein binding between zolpidem tartrate and its metabolites for binding sites.

Biotransformation: It is metabolized by the liver (approx.35%) via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2. Since CYP3A4 plays an important role in metabolism, possible interactions with drugs that are substrates or inducers of CYP3A4 should be considered.

Elimination: All metabolites are pharmacologically inactive and are eliminated in the urine (56%) and in the faeces (37%). The elimination half-life is short, with a mean of 2.4 hours (± 0.2 h) and a duration of action of up to 6 hours. It is non-dialyzable. In patients with hepatic insufficiency, Plasma concentrations in elderly 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.

5.3 Preclinical Safety Data

There are no pre-clinical data of any relevance to the prescriber, which are additional to those already included in other sections.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose (Plain) BP
Microcrystalline Cellulose (PH 102) BP
Lactose (Lactose Monohydrate) BP
Sodium Starch Glycolate (Type-A) BP
Hypromellose (HPMC 5 CPS) BP
Magnesium Stearate BP
Colour Iron Oxide Yellow Spraycel SC-SP-2645 IHS
Purified Water IP/BP

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Do not store above 30°C. Protect from light.

6.5 Nature and Contents of Container

10 tablets are packed in Alu- PVC blister pack; Such 3 blisters are packed in printed carton with packing insert.

6.6 Special precaution for disposal and other handling

Any unused medicinal product or waste material should br disposed of in accordance with local requirements.

KEEP OUT OF THE REACH OF CHILDREN

7. Marketing Authorization Holder And Manufacturing Site Addresses

7.1 Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

7.2 Name and Address of manufacturing site(s)

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

8. Marketing Authorization Number

TAN 22 HM 0284

9. Date of First <Registration> / Renewal of The <Registration>

19th July, 2022

10. Date of Revision of the Text