Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zolpidem Tartrate 5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg zolpidem tartrate.

Excipient with known effect: Each film-coated tablet contains 42.30 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

For oral use.
Zolpidem tartrate acts rapidly and therefore should be taken immediately before retiring, or in bed.
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 10mg to be taken immediately at bedtime. The lowest effective daily dose of zolpidem tartrate should be used and must not exceed 10mg.
The duration of treatment should usually vary from a few days to two weeks with a maximum of four weeks including tapering off where clinically appropriate.
Treatment should be as short as possible. 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 (see section 4.4).

Special Populations

Paediatric population
Zolpidem tartrate 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 in section 5.1.

Elderly
Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate, therefore a 5mg dose is recommended. The zolpidem tartrate dose should not exceed 10mg in this population.

Hepatic impairment
Severe hepatic impairment
Zolpidem tartrate is contraindicated in patients with severe hepatic impairment as it may contribute to encephalopathy (see section 4.3).
Mild to moderate hepatic impairment

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

4.3 Contraindications

Zolpidem tartrate is contraindicated in patients:

- With hypersensitivity to zolpidem tartrate or any of the inactive ingredients listed in section 6.1
- With severe hepatic insufficiency
- With acute and/or severe respiratory insufficiency
- Known to have previously experienced complex sleep behaviours after taking zolpidem tartrate, see section 4.4

4.4 Special warnings and precautions for use

Zolpidem tartrate should be used with caution in patients with sleep apnoea syndrome, and myasthenia gravis.

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

- **Risk from concomitant use of opioids**Concomitant use of zolpidem tartrate 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 tartrate with opioids should be reserved for patients for whom alternative treatment options are not possible.If a decision is made to prescribe zolpidem tartrate 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. In this respect, it is strongly recommended to inform patients and others in their environment to be aware of these symptoms (see section 4.5).

- **Hepatic Insufficiency**Mild to moderate hepatic impairment/insufficiency – see dose recommendations (see sections 4.2, 4.3 and 4.8).

- **Dependence**

Use of zolpidem tartrate 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 tartrate 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.
Precautions:
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.

4.4.1 Specific patient groups

- **Elderly**See section 4.2 dose recommendations. Due to the myorelaxant effect, there is a risk of falls and consequent injury, particularly for elderly patients when they get up at night.

- **Psychotic illness**Hypnotics such as zolpidem tartrate are not recommended for the primary treatment of psychotic illness.

- **Paediatric patients**Safety and effectiveness of zolpidem tartrate have not been established in patients below the age of 18 years. In an 8-week study in paediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem tartrate versus placebo and included dizziness (23.5% vs 1.5%), headache (12.5% vs 9.2%), and hallucinations (7.4% vs 0%). (See section 4.2 Posology and method of administration).

- **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.

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

- Zolpidem tartrate is taken less than 8 hours before performing activities that require mental alertness (see section 4.7).
- 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 (see section 4.5).Zolpidem tartrate should be taken in a single intake immediately at bedtime and not be re-administered during the same night.

- **Amnesia**Sedative/hypnotic agents such as zolpidem tartrate may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product. In order to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 8 hours (see section 4.8).

- **Depression and suicidality**Some epidemiological studies show an increased incidence of completed suicide and suicide attempt in patients with or without depression, treated with hypnotics such as zolpidem tartrate. A causal relationship has not been established. Although no clinically significant pharmacokinetic and pharmacodynamic interactions with SSRIs have been demonstrated (see section 4.5 Interactions with other medicinal products and other forms of interactions), 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 zolpidem tartrate that is feasible should be supplied to these patients to avoid the possibility of intentional overdosage by the patient. Pre-existing depression may be unmasked during use of zolpidem tartrate. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

4.4.2 General Information

- **Tolerance**

Some loss of efficacy of the hypnotic effects of sedative/hypnotic agents like zolpidem tartrate may develop after repeated use for a few weeks.

- **Rebound insomnia**A transient syndrome whereby the symptoms that led to treatment with sedative/hypnotic agents 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. 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. 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.In the case of sedative/hypnotic agents with a short duration of action, withdrawal phenomena can manifest within the dosage interval.

- **Severe injuries**Due to its pharmacological properties, zolpidem tartrate can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries, see section 4.8.

- **Patients with long QT syndrome**An *in vitro* cardiac electrophysiological study showed that under experimental conditions using very high concentration and pluripotent stem cells zolpidem tartrate may reduce the hERG

related potassium currents. The potential consequence in patients with congenital long QT syndrome is unknown. As a precaution, the benefit/risk ratio of zolpidem tartrate treatment in patients with known congenital long QT syndrome should be carefully considered.

- **Other psychiatric and "paradoxical" reactions**Other psychiatric and "paradoxical" reactions like restlessness, insomnia, exacerbated agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, abnormal behaviour and other adverse behavioural effects are known to occur when using sedative/hypnotic agents like zolpidem tartrate. Should this occur, use of the product should be discontinued. These reactions are more likely to occur in the elderly.

- **Somnambulism and associated behaviours**Complex sleep behaviours, including sleep walking and other associated behaviours such as "sleep driving", preparing and eating food, making phone calls or having sex, with amnesia of the event, have been reported in patients who had taken zolpidem tartrate and were not fully awake. These events may occur following the first or any subsequent use of zolpidem tartrate. Discontinue treatment immediately if a patient experiences a complex sleep behaviour, due to the risk to the patient and others (see section 4.3). The use of alcohol and other CNS-depressants with zolpidem tartrate appears to increase the risk of such behaviours, as does the use of zolpidem tartrate at doses exceeding the maximum recommended dose.

- **Intolerance**Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

- **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 tartrate. However, a causal relationship has not been established.

4.5 Interaction with other medicinal products and other forms of interactions

- **Alcohol**Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product 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 agents, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines. Therefore, concomitant use of zolpidem tartrate with these drugs may increase drowsiness and next-day psychomotor impairment, including impaired driving ability (see sections 4.4 and 4.7). Also, isolated cases of visual hallucinations were reported in patients taking zolpidem tartrate with antidepressants including bupropion, desipramine, fluoxetine, sertraline and venlafaxine.Co-administration of fluvoxamine may increase blood levels of zolpidem tartrate, 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 tartrate 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 cytochrome P450 may enhance the activity of some hypnotics like zolpidem tartrate.Zolpidem tartrate is metabolised via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2. The pharmacodynamic effect of zolpidem tartrate 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 zolpidem tartrate, concurrent use is not recommended. However, when zolpidem tartrate 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 tartrate with ketoconazole (200mg twice daily), a potent CYP3A4 inhibitor, prolonged zolpidem tartrate elimination half-life, increased total AUC, and decreased apparent oral clearance when compared to zolpidem tartrate plus placebo. The total AUC for zolpidem tartrate was increased modestly when co-administered with ketoconazole, it increased by a factor of 1.83 when compared to zolpidem tartrate alone. A routine dosage adjustment of zolpidem tartrate is not considered necessary, but patients should be advised that use of zolpidem tartrate with ketoconazole may enhance the sedative effects. Co-administration of ciprofloxacin may increase blood levels of zolpidem tartrate, concurrent use is not recommended.

- **Other drugs**When zolpidem tartrate was administered with warfarin, digoxin, ranitidine, no significant pharmacokinetic interactions were observed.

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of zolpidem tartrate is not recommended during pregnancy.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
Zolpidem tartrate crosses the placenta.
A large amount of data on pregnant women (more than 1000 pregnancy outcomes) collected from cohort studies has not demonstrated evidence of the occurrence of malformations following exposure to benzodiazepines or benzodiazepine-like substances during the first trimester of pregnancy. However, certain case-control studies reported an increased incidence of cleft lip and palate associated with use of benzodiazepines during pregnancy.
Cases of reduced foetal movement and foetal heart rate variability have been described after administration of benzodiazepines or benzodiazepine-like substances during the second and/or third trimester of pregnancy. Administration of zolpidem tartrate during the late phase of pregnancy or during labour has been associated with effects on the neonate, such as hypothermia, hypotonia, feeding difficulties ('floppy infant syndrome'), and respiratory depression, due to the pharmacological action of the product. Cases of severe neonatal respiratory depression have been reported.
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 risk of developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.
If zolpidem tartrate 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.
Lactation
Small quantities of zolpidem tartrate appear in breast milk. The use of zolpidem tartrate in nursing mothers is therefore not recommended

4.7 Effects on ability to drive and use machines

Zolpidem tartrate 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 (see section 4.8). In order to minimise this risk, a resting period of at least 8 hours is recommended between taking zolpidem tartrate and driving, using machinery and working at heights.

Driving ability impairment and behaviours such as 'sleep-driving' have occurred when zolpidem tartrate is used alone at therapeutic doses.

Furthermore, co-administration of zolpidem tartrate with alcohol and other CNS depressants increases the risk of such behaviours (see section 4.4 and 4.5). Patients should be warned not to use alcohol or other psychoactive substances when taking zolpidem tartrate.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:
Very common ≥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 tartrate use, particularly for certain CNS events. As recommended in section 4.2, they should in theory be less if zolpidem tartrate is taken immediately before retiring, or in bed. They occur most frequently in elderly patients.
Nervous system disorders
Common: somnolence, headache, dizziness, exacerbated insomnia, cognitive disorders such as memory disorders (memory impairment, amnesia, anterograde amnesia).
Uncommon: paraesthesia, tremor, disturbance in attention, speech disorder

Rare: depressed level of consciousness

Psychiatric disorders
Common: hallucination, agitation, nightmare, depression (see section 4.4).
Uncommon: confusional state, irritability, restlessness, aggression, somnambulism (see section 4.4), euphoric mood, complex sleep behaviours (see sections 4.4 and 4.3)
Rare: libido disorder
Very rare: delusion, dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation)
Not known: anger, abnormal behaviour
Most of these psychiatric undesirable effects are related to paradoxical reactions.

General disorders and administration site conditions
Common: fatigue
Rare: gait disturbance, fall (predominantly in elderly patients and when zolpidem tartrate was not taken in accordance with prescribing recommendation) (see section 4.4).
Not known: drug tolerance

Eye disorders
Uncommon: diplopia, vision blurred
Rare: visual impairment

Respiratory, thoracic and mediastinal disorders
Very rare: respiratory depression (see section 4.4)

Gastrointestinal disorders
Common: diarrhoea, nausea, vomiting, abdominal pain

Musculoskeletal and connective tissue disorders
Common: back pain
Uncommon:arthralgia, myalgia, muscle spasms, neck pain, muscular weakness

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

Skin and subcutaneous tissue disorders
Uncommon: rash, pruritus, hyperhidrosis
Rare: urticaria

Hepatobiliary disorders
Uncommon:liver enzymes elevated
Rare: hepatocellular, cholestatic or mixed liver injury (see section 4.2, section 4.3 and section 4.4)

Immune system disorders
Not known: angioneurotic oedema

Metabolism and nutrition disorders
Uncommon:appetite disorder

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via: HPRA Pharmacovigilance, website: www.hpra.ie

4.9 Overdose

Signs and Symptoms:
In cases of overdose, involving zolpidem tartrate alone or with other CNS-depressant agents (including alcohol), impairment of consciousness up 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. Special attention should be paid to respiratory and cardiovascular functions in intensive care. Sedating drugs should be withheld even if excitation occurs. Use of flumazenil may be considered where serious symptoms are observed. However, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

Zolpidem tartrate is not dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

(GABA-A receptor agonist selective for omega-1-type sub-unit hypnotic agent).
Zolpidem tartrate 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 tartrate preferentially binds the omega-1 subtype. The clinical relevance is not known. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem tartrate. These effects are reversed by the benzodiazepine antagonist flumazenil.
In animals: The selective binding of zolpidem tartrate 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 human: The preservation of deep sleep (stages 3 and 4-slow-wave sleep) may be explained by the selective omega-1 binding by zolpidem tartrate. All identified effects of zolpidem tartrate are reversed by the benzodiazepine antagonist flumazenil.
Preliminary single dose studies did not reveal respiratory depressant effects in normal subjects or in mild or moderate COPD.
The randomised trials only showed convincing evidence of efficacy of 10mg zolpidem tartrate.
In a randomised double-blind trial in 462 non-elderly healthy volunteers with transient insomnia, zolpidem tartrate 10mg decreased the mean time to fall asleep by 10 minutes compared to placebo, while for 5mg zolpidem tartrate this was 3 minutes.
In a randomised double-blind trial in 114 non-elderly patients with chronic insomnia, zolpidem tartrate 10mg decreased the mean time to fall asleep by 30 minutes compared to placebo, while for 5mg zolpidem tartrate this was 15 minutes.
In some patients, a lower dose of 5mg could be effective.
Paediatric population
Safety and efficacy of zolpidem tartrate has not been established in children aged less than 18 years. A randomised 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 tartrate 0.25mg/kg/day (with a maximum of 10mg/day) as compared to placebo.
Psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem tartrate versus placebo and included dizziness (23.5% versus 1.5%), headache (12.5% versus 9.2%), and hallucinations (7.4% versus 0%) (see sections 4.2 and 4.3).

5.2 Pharmacokinetic properties

Zolpidem tartrate 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 (± 0.2 h) 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 tartrate 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 tartrate 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.

5.3 Preclinical safety data

No data of therapeutic relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose PH101
Sodium starch glycolate (Type A)
Hypromellose (HPMC E5)
Magnesium stearate

Film-coating:
Hypromellose (HPMC E3)
Macrogol (PEG-400)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/-PVC blisters containing 28 tablets.
HDPE tablets containers with child-resistant polypropylene cap containing 400 tablets. Not all packs sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Lexon Pharmaceuticals (Ireland) Limited
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8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation : 19th May 2017
Date of last Renewal: 14th March 2022

10 DATE OF REVISION OF THE TEXT

July 2021