Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zolpidem Tartrate 10 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Zolpidem Tartrate 10 mg Film-coated Tablets: Each film-coated tablet contains 10 mg zolpidem tartrate.
Excipient with known effect: Each film-coated tablet contains 84.60mg lactose monohydrate.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.
Zolpidem Tartrate 10 mg Film-coated Tablets: White to off-white, capsule shaped, film coated tablets having a break line on the one side and plain on the other side. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of 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 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. As with all hypnotics, long-term use is not recommended and a course of treatment should not exceed four weeks.

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 in section 5.1.

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

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.

Zolpidem must not be used in patients with severe hepatic impairment as it may contribute to encephalopathy (see section 4.3).

Method of administration
Oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Myasthenia gravis

- Obstructive sleep apnoea
- Severe hepatic insufficiency
- Acute and/or severe respiratory depression
- In the absence of data, zolpidem tartrate should not be prescribed for children or patients with psychotic illness.

4.4 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
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 recreational 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.

Specific patient groups
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.
Hepatic Insufficiency:
See section 4.2.
Elderly:
See section 4.2 dose recommendations.
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 their environment to be aware of these symptoms (see section 4.5).

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 tartrate are not recommended for the primary treatment of psychotic illness.
Depression:
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.
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 of the hypnotic effects of short-acting benzodiazepines and benzodiazepine-like agents like zolpidem tartrate may develop after repeated use for a few weeks.
Dependence:
Use of benzodiazepines or benzodiazepine-like agents like zolpidem tartrate may lead to the development of 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 or drug abuse.
These patients should be under careful surveillance when receiving hypnotics.

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:

Benzodiazepine or benzodiazepine-like 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, patient 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 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 of the event, have been reported in patients who had taken zolpidem tartrate and were not fully awake. The use of alcohol and other CNS-depressants with zolpidem tartrate appears to increase the risk of such behaviour, as does the use of zolpidem tartrate at doses exceeding the maximum recommended dose. Discontinuation of zolpidem tartrate should be strongly considered for patients who report such behaviour (for example, sleep driving), due to the risk to the patient and others (see Section 4.5: Interactions with other medicinal products and other forms of interaction; and Section 4.8: Undesirable effects).

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.

Excipient with known effect:

Zolpidem tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of 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 tartrate with these drugs may increase drowsiness and next-day psychomotor impairment, including impaired driving ability (see section 4.4 and section 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:
Co-administration of ciprofloxacin may increase blood levels of zolpidem tartrate, 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 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 rifampicin 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 Cmax 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 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, when co-administered with ketoconazole, 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.
Since CYP3A4 plays an important role in zolpidem tartrate metabolism, possible interactions with drugs that are substrates or inducers of CYP3A4 should be considered.
Other drugs:
When zolpidem tartrate was administered with ranitidine, no significant pharmacokinetic interactions were observed.

4.6 Fertility, pregnancy and lactation

Pregnancy:
For zolpidem tartrate, no or very limited amount of data on pregnant patients are available. Although animal studies have shown no teratogenic effect, safety in pregnancy has not been established. As with all drugs zolpidem tartrate should be avoided in pregnancy particularly during the first trimester.

If the product 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.

If, for compelling medical reasons, zolpidem tartrate is administered during the late phase of pregnancy, or during labour, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression can be expected due to the pharmacological action of the product. Cases of severe neonatal respiratory depression have been reported when zolpidem tartrate was used with other CNS depressants at the end of pregnancy.

Infants born to mothers who took benzodiazepines or benzodiazepine-like 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.

Lactation:
Zolpidem tartrate passes into breast milk in small amounts. Zolpidem tartrate should therefore not be used by breastfeeding mothers since the effects on the infant have not been studied.

Fertility
There is no information on the effects of zolpidem tartrate on fertility in humans. The effects on fertility parameters in animals did not produce a decline or impair fertility (see section 5.3).

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 and gastrointestinal 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.
Immune system disorders
Not known: angioneurotic oedema

Psychiatric disorders
Common: hallucination, agitation, nightmare
Uncommon: confusional state, irritability
Not known: restlessness, aggression, delusion, anger, psychosis, abnormal behaviour, somnambulism (see Section 4.4), dependence (withdrawal symptoms or rebound effects may occur after abrupt withdrawal of zolpidem), libido disorder, depression (see Section 4.4), euphoric mood.
Most of these psychiatric undesirable effects are related to paradoxical reactions.

Nervous system disorders
Common: somnolence, headache, dizziness, exacerbated insomnia, anterograde amnesia (amnestic effects may be associated with inappropriate behaviour)
Uncommon: paraesthesia, tremor.
Not known: depressed level of consciousness

Eye disorders
Uncommon: diplopia, , vision blurred
Very rare: visual impairment

Respiratory, thoracic and mediastinal disorders
Not known: respiratory depression (see section 4.4)

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

Hepatobiliary disorders
Not known: Liver enzymes elevated, hepatocellular, cholestatic or mixed liver injury (see section 4.2, 4.3 and 4.4)

Metabolism and nutrition disorders
Uncommon: appetite disorder

Skin and subcutaneous tissue disorders
Not known: rash, pruritus, urticaria, hyperhidrosis

Musculoskeletal and connective tissue disorders
Common: back pain
Uncommon: myalgia, muscle spasms
Not known: muscular weakness

Infections and infestations

Common: upper respiratory tract infection, lower respiratory tract infection

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

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
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
E-mail: medsafety@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 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 to 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 tartrate is not dialysable.
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 tartrate has demonstrated no reduction in levels of zolpidem tartrate.
In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and Sedatives, Benzodiazepine related drugs.
ATC code: N05CF02
Mechanism of action
Zolpidem tartrate is an imidazopyridine which preferentially binds the omega-1 receptor subtype (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. 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 anticonvulsant effects in animals which are normally exhibited by benzodiazepines which are not selective for omega-1 sites.
In human: zolpidem tartrate decreases sleep latency and the number of awakenings, and increases sleep duration and sleep quality. These effects are associated with a characteristic EEG profile, different from that of the benzodiazepines. In studies that measured the percentage of time spent in each sleep stage, zolpidem tartrate has generally been shown to preserve sleep stages. At the recommended dose, zolpidem tartrate has no influence on the paradoxical sleep duration (REM). 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.
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

Absorption
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.
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%. 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.
Metabolism
Zolpidem tartrate 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 tartrate metabolism, possible interactions with drugs that are substrates or inducers of CYP3A4 should be considered.
Elimination
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.
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.
Special population
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

Oral administration of zolpidem at doses of 4, 20 and 100 mg base/kg (approximately 5, 24 and 120 times the maximum recommended human dose (MRHD) on a mg/m2 basis) to rats prior to and during mating, and continuing in females through postpartum day 25, resulted in irregular estrus cycles and prolonged precoital intervals, but did not produce a decline in fertility. No effects on other fertility parameters were noted. The no-effect dose was approximately 24 times the MRHD on a mg/m2 basis. There was no impairment of fertility at any dose tested (see section 4.6).
Animal studies have revealed evidence of incomplete ossification and increased post-implantation fetal loss at doses >7 times the maximum human dose or higher; however, there was no evidence of a teratogenic effect (see section 4.6).
There are no other 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

Aluminum/-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

Key Pharmaceuticals Ltd
Galen House
83 High Street, Somersham
Cambridgeshire
PE28 3JB
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0343/005/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation : 19th May 2017

10 DATE OF REVISION OF THE TEXT

September 2019