SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zolpidem 10 mg film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg zolpidem tartrate. Excipient with known effect:

Lactose monohydrate 99 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Zolpidem film-coated tablets are White, oval shaped, biconvex, film-coated tablets with “ZOLPIDEM” and “10 mg” embossing and other side break line. Length 10 mm, width 7.5 mm and thickness 3.1-3.5 mm.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term treatment of insomnia in adults in situations where the insomnia is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Prior to starting treatment with zolpidem, a discussion should be held with patients to put in place a strategy for ending treatment with zolpidem in order to

minimise the risk of dependence, addiction and drug withdrawal syndrome (see section 4.4).

Treatment should be given for the shortest possible duration.

Posology

The treatment should be as short as possible and should not last more than 4 weeks, including the tapering period. 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). Zolpidem effect sets in rapidly and must therefore be taken immediately before bedtime.

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. **Special populations**

Paediatric population
Safety and efficacy in children and adolescents under 18 years of age have not been established. The available data are described in section 5.1.

Elderly and debilitated patients
Elderly or debilitated patients may be especially sensitive to the effects of zolpidem therefore a 5 mg dose is recommended.

Hepatic impairment
As clearance and metabolism of zolpidem is reduced in hepatic impairment (see section 5.2), 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 is contraindicated in patients with severe hepatic impairment (see section 4.3).

Method of administration
For oral administration only.

4.3 Contraindications

Zolpidem is contraindicated in patients with:

- Myasthenia gravis.
- Obstructive sleep apnea.
- Severe hepatic insufficiency
- Acute and / or severe respiratory insufficiency.
- Complex sleep behaviour after taking zolpidem in the anamnesis (see section 4.4)
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Zolpidem must not be administered to children and adolescents under 18 years of age (see sections 4.2 and 5.1).

4.4 Special warnings and precautions for use

Warnings

Respiratory insufficiency:
As hypnotics have the capacity to depress respiratory drive, precautions should be observed if zolpidem is used in patients with compromised respiratory function (see section 4.8).

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 (see section 4.8)."

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.

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

Drug dependence, tolerance and potential for abuse

Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for treatment with Zolpidem should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment with Zolpidem.

Tolerance

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

Dependence

Use of benzodiazepines or benzodiazepine-like agents may lead to the development of abuse and/or physical or psychological dependence upon these products.
The risk of dependence increases with dose and duration of treatment and is also

greater in patients with a history of alcohol or drug abuse.

Drug withdrawal syndrome

Prior to starting treatment with zolpidem, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with zolpidem should also be put in place with the patient before starting treatment (there may be exceptions to this in specific clinical situations such as symptom management in end of life palliative care.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.

The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person's preferences, changes to their circumstances and the response to dose reductions.

If physical dependence is developed, a sudden discontinuation of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety or tension, restlessness, confusion, irritability or insomnia. In severe cases the following symptoms may occur: derealization and depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Suggest a slow stepwise rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed.

If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Rebound effect

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 minimizing anxiety over such symptoms should they occur when the medicinal product is being discontinued.

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. As the risk of

withdrawal symptoms/rebound phenomena are most likely to develop after abrupt discontinuation of treatment, it is recommended to decrease the dose gradually.

Duration of treatment
The duration of treatment should be as short as possible (se section 4.2), but should not exceed four weeks including the tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.
It may be useful to inform the patients, when treatment is started, that it will be of limited duration.

Next-day psychomotor impairment
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 (see section 4.7);
- 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 (see section 4.5).

Amnesia**:**

Sedatives/hypnotics 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).

Psychiatric and "paradoxical" reactions
Reactions like restlessness, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, psychosis, sleep walking, abnormal behavior, exacerbated insomnia and other adverse behavioral 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.

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.

Despite the fact that relevant clinical, pharmacokinetic, and pharmacodynamic interactions with SSRI have not been demonstrated, Zolpidem should be

administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present. Due to the possibility of intentional overdose by the patient, the lowest amount of medicinal product that is feasible should be supplied to these patients. Unacknowledged existing depression may be exacerbated by the use of benzodiazepines and benzodiazepine like agents.
Benzodiazepines and benzodiazepine-like agents should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).
As insomnia may be a symptom of depression, the patient should be re-evaluated if the insomnia persists.

Somnambulism and associated behaviors
It has been reported complex sleeping pattern including sleep walking and other associated behaviors 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. This behaviour may occur after the first dose or subsequent doses of zolpidem.
Discontinue treatment immediately if a patient experience complex sleep behaviour, due to the risk to the patient and others (see sections 4.3 and 4.8).

The use of alcohol and other CNS-depressants with zolpidem appears to increase the risk of such behaviors, as does the use of zolpidem at doses exceeding the maximum recommended dose.

Risk from concomitant use of 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 (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).

It should also be taken into account that anxiety and arousal have been described as signs of uncompensated respiratory insufficiency.

Patients with long QT-syndrome
As a precautionary measure, the benefit / risk profile for the treatment with zolpidem in patients with known congenital long QT syndrome should be carefully considered.

Specific patient groups

- Elderly or debilitated patients should receive a lower dose: see recommended dosage (section 4.2). Due to the muscle relaxant effects there is a risk of falls and consequently of hip fractures particularly for elderly patients when they get up at night.
- Although dose adjustments are not necessary in patients with renal insufficiency, caution should be exercised (see section 5.2).
- Benzodiazepines and benzodiazepine-like agents should be used with extreme caution in patients with a history of alcohol and drug abuse. These patients should be under careful surveillance when receiving Zolpidem since they are at risk of habituation and psychological dependence.
- Liver insufficiency: See recommendations under "Posology and method of administration" (section 4.2).

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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.

CNS depressants:

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics, hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, an aesthetics and sedative antihistamines.

Therefore, concomitant use of zolpidem 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 with antidepressants including bupropion, desipramine, fluoxetine, sertraline and venlafaxine.

Co-administration of fluvoxamine may increase blood levels of zolpidem, concurrent use is not recommended.

No clinically significant pharmacokinetic or pharmacodynamic interactions with SSRI ant depressive agents have been observed (fluoxetine and sertraline) (see section 4.4).

For centrally acting analgesics (opioids), increased 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 (see section 4.4).

CYP450 inhibitors and inducers:

Substances which inhibit cytochrome P450 may enhance the activity of certain hypnotics like zolpidem. Zolpidem is metabolized via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2.

Rifampicin induces the metabolism of zolpidem resulting in a reduction of approx. 60% in plasma concentration and possibly reduced effect. Similar effect can also be expected for other substances with strong inducing effect on cytochrome P450 enzymes.

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.

Substances that inhibit liver enzymes (especially CYP3A4) may increase plasma concentrations and enhance the activity of zolpidem. Concomitant use of ciprofloxacin may increase zolpidem levels in the blood and is not recommended.

Ketoconazole inhibits the metabolism of zolpidem by CYP3A4 in the liver, thereby increasing the effect of zolpidem. 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.

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. Itraconazole and fluconazole do not affect the metabolism of zolpidem in the liver, so these drugs should be preferred.

Combination of Zolpidem and muscle relaxants can increase the muscle relaxing effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of zolpidem is not recommended during pregnancy. There are insufficient data to assess the safety of Zolpidem during pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Zolpidem 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.

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.

Administration of zolpidem during the late phase of pregnancy or during labor 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.

Breast-feeding

Small quantities of zolpidem appear in breast milk. The use of zolpidem in nursing mothers is therefore not recommended as the impact of the child has not been studied. There are insufficient data to assess the safety of Zolpidem during lactation.

4.7 Effects on ability to drive and use machines

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 **is** 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 minimize 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 behaviors such as 'sleep-driving' have occurred with zolpidem alone at therapeutic doses. Furthermore, the co-administration of zolpidem with alcohol and other CNS depressants increases the risk of such behaviors (see sections 4.4 and 4.5). Patients should be warned not to use alcohol or other psychoactive substances when taking zolpidem.

4.8 Undesirable effects

The adverse drug reactions are stated in the table below using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

There is evidence for a dose connection for reactions associated with use of zolpidem, especially certain CNS-reactions. Theoretically they should be less if zolpidem is taken immediately before bedtime. They occur most frequently in elderly patients.

	Frequency				
System Organ Class	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Respiratory, thoracic and mediastinal disorders				Respiratory depression	
Immune system disorders					Angioneurotic oedema

Psychiatric disorders	Hallucination Agitation Nightmare Depression (see section 4.4) Emotional indifference	Confusion Irritability Restlessness Aggression Somnambulism (See section 4.4 "Somnambulism and Associated Behaviour") Complex sleep behaviours (see section 4.4). Euphoric mood	Libido disorder		Anger Abnormal behavior Withdrawal symptoms (see section 4.4) The majority of the psychiatric side effects are related to paradoxical reactions. Delusion Psychosis *Drug dependence* (see section 4.4)
Nervous system disorders	Somnolence Headache Dizziness Increased insomnia Cognitive disorders such as anterograde amnesia (amnestic effects may be associated with inappropriate behavior) Drowsiness during the following day	Paranesthesia Tremor Disturbance in attention Speech disorder Ataxia	Depressed level of consciousness		
Eye disorders		Diplopia Vision blurred	Visual impairment		

Ear and labyrinth disorders	Vertigo				
Infections and infestations	Upper and lower respiratory tract infection				
Gastrointestinal disorders	Diarrhea Nausea Vomiting Abdominal pain				
Hepatobiliary disorders		Liver enzymes elevated	Hepatocellular cholestatic or mixed liver injury (see sections 4.2, 4.3 and 4.4)		
Skin and subcutaneous tissue disorders	Skin reactions	Rash Pruritus, Hyperhidrosis	Urticaria		
Musculoskeletal and connective tissue disorders	Back pain	Arthralgia Myalgia Muscle spasms Neck pain Muscular weakness			
Metabolism and nutrition disorders		Appetite disorder			
General disorders and administration site conditions	Fatigue		Gait disturbance, fall (predominantly in elderly patients and when zolpidem was not taken in accordance with prescribing recommendation) (see section 4.4).		Drug tolerance

Withdrawal syndrome:
Withdrawal syndrome has been reported upon discontinuation of Zolpidem (see section 4.4). Withdrawal symptoms vary and may include rebound insomnia, muscle pain, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations, panic attacks, muscle aches/cramps, gastrointestinal disturbances 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. In very rare cases, seizures may occur.

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 via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms
In cases of overdose involving zolpidem alone or with other CNS depressant agents (including alcohol), impairment of consciousness ranging from somnolence to light coma and fatal outcomes have been reported.

Individuals have fully recovered from zolpidem overdoses up to 400 mg, 40 times the recommended dose.

Management:
General symptomatic and supportive measures should be used. Immediate gastric lavage should be used where appropriate. Intravenous fluids should be administered as needed. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption.
Monitoring of respiratory and cardiovascular functions should be considered.
Sedating drugs should be withheld even if excitation occurs.
Use of flumazenil may be considered when serious symptoms are observed.
Administration of flumazenil can cause neurological symptoms (convulsions). In the treatment of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Due to the high distribution volume and protein binding of zolpidem, hemodialysis and forced diuresis are not effective measures.

Haemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialyzable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and Sedatives, Benzodiazepine related drugs, ATC code: N05C F02 (GABA-A receptor modulator selective for omega-1 receptor subtype hypnotic agent).

Zolpidem is an imidazopyridine, which binds selectively to omega-1 receptors which constitute the alpha unit in the GABA-A receptor complex. Whereas benzodiazepines non-selectively binds to all three omega- subtype receptors, zolpidem binds preferentially to the alpha-1 subunit.

The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem.

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.

The preservation of deep sleep (stages 3 and 4 - slow-wave sleep) may be explained by the selective omega-1 binding by zolpidem.

In experimental studies it was shown that it has sedative effects at lower dosages than those required to exert anticonvulsant, myorelaxant, or anxiolytic effects. These effects are related to a specific antagonist action at the central receptors belonging to the "GABA-omega (BZ1 & BZ2) macromolecular receptor" complex, modulating the opening of the chloride ion channel.

The effects of zolpidem 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.

Paediatric population

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 ADHD failed to demonstrate efficacy of zolpidem 0.25 mg/kg/day (with a 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%), and hallucinations (7.4% versus 0%) (see sections 4.2 and 4.3).

5.2 Pharmacokinetic properties

Absorption
Bioavailability is approximately 70% following oral administration. Peak plasma concentration is reached at between 0.5 and 3 hours after administration.

Distribution
In the therapeutic dose range, zolpidem demonstrates linear pharmacokinetics. Protein binding amounts to approximately 92 %. The plasma elimination half-life is approximately 2.4 hours (0.7 – 3.5 hours). The distribution volume in adults is 0.54 ± 0.02 L/kg.

Elimination
All metabolites of zolpidem are pharmacologically inactive (liver metabolism) and are mainly eliminated in the urine (56 %) and faces (37 %). It has no inducing effect on liver enzymes.

Older people
In elderly a reduced clearance has been observed. The maximum concentration is increased by approximately 50% without any significant increase in the half-life (approx. 3 hours). The volume of distribution decreases to 0.34 ± 0.05 L/kg in the very elderly.

Renal impairment
In patients with renal insufficiency, whether dialyzed or not, there is a moderate reduction in clearance.

Hepatic impairment
In patients with liver insufficiency bioavailability of zolpidem is increased. Clearance is decreased and elimination half-life is increased (approx. 10 hours).

5.3 Preclinical safety data

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate

Cellulose, microcrystalline

Hypromellose

Sodium starch glycolate

Magnesium stearate

Film-coating

Titanium dioxide (E 171)

Macrogol 400

Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Cartons of 7 tablets in Alu-PVC/PVDC blister.
Cartons of 10, 20, 28, 30 or 100 tablets containing Alu-PVC/PVDC blisters of 7 or 10 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Novumgen Limited
20-22 Wenlock Road, London,
N1 7GU, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 55863/0103

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/05/2024

10 DATE OF REVISION OF THE TEXT

04/02/2026