

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Edluar 5 mg sublingual tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 5 mg zolpidem tartrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual tablet.

White, round, flat-faced, bevel-edged tablet approximately 7.5 mm in diameter with V debossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short term treatment of insomnia in adults.

Hypnotic/ sedative drugs are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Duration of treatment

Treatment should be as short as possible. Generally the duration of treatment varies from a few days to two weeks with a maximum, including the tapering off process, of four weeks. The tapering off process should be tailored to the individual.

As with all hypnotics, long-term use is not recommended and a course of treatment should not exceed four weeks. In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status.

Posology

Adults

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.

The total dose of Zolpidem should not exceed 10 mg in any patient.

Elderly (over 65 years) or debilitated patients

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

Hepatic impairment

Patients with hepatic insufficiency do not clear the drug as rapidly as patients with normal hepatic function; therefore 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. Severe hepatic insufficiency is a contraindication.

See section 5.2.

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 evidence from placebo-controlled clinical trials is presented in section 5.1

Method of administration

For sublingual use.

Zolpidem acts rapidly and therefore should be taken just before going to bed, or in bed. The tablet should be put under the tongue and should be kept there until dissolved. Edluar should not be taken with or immediately after a meal (see section 5.2).

4.3 Contraindications

Hypersensitivity to zolpidem tartrate or to any of the excipients listed in section 6.1.

Severe hepatic insufficiency.

Sleep apnoea syndrome.

Myasthenia gravis.

Acute and/or severe respiratory insufficiency.

4.4 Special warnings and precautions for use

General

The cause of insomnia should be identified wherever possible. The underlying factors should be 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, which should be evaluated.

General information relating to effects seen following administration of benzodiazepines or 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 benzodiazapine-like agents may develop after repeated use for a few weeks.

Dependence

Use of benzodiazepines or benzodiazapine-like agents may lead to the development of physical and psychic dependence of these products. The risk of dependence increases with dose and duration of treatment and is also greater in patients with a history of drug dependence, alcohol, substance or drug abuse.

These patients should be under careful surveillance when receiving hypnotics. Dependence may also occur at therapeutic doses, and/or for subjects who do not show an individualised risk factor. 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, irritability and insomnia. 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 benzodiazepines or benzodiazepine like agent recur in an enhanced form, may occur on withdrawal of hypnotic agent. 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 if 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 more 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 (see section 4.2), and should not exceed 4 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 patient 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).

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

Amnesia

Benzodiazepines or benzodiazapine-like agents may induce anterograde amnesia. The condition usually occurs 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

When using benzodiazepines or benzodiazapine-like agents, reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, increased insomnia and other adverse behavioural effects are known to occur. Should this occur, use of the product should be discontinued. These reactions are more likely to occur in the elderly.

Somnambulism and associated behaviours

Sleep walking and other associated behaviours such as “sleep driving”, preparing and eating food, making phone calls or having sex, with amnesia for the event, have been reported in patients who had taken zolpidem and were not fully awake. The use of alcohol and other CNS-depressants with zolpidem appears to increase the risk of such behaviours, as does the use of zolpidem at doses exceeding the maximum recommended dose. Discontinuation of zolpidem should be strongly considered for patients who report such behaviours (see section 4.5 and section 4.8).

Specific patient groups

Elderly or debilitated patients should receive a lower dose: see recommended dosage (section 4.2).

Due to the myorelaxant and sedative effect there is a risk of falls and consequent injury particularly for elderly patients when they get up at night.

Although dose adjustment is not necessary, caution should be exercised in patients with renal insufficiency (see section 5.2).

Caution should be observed when prescribing zolpidem to patients with chronic respiratory insufficiency since benzodiazepines have been shown to impair respiratory drive. It should also be taken into consideration that anxiety or agitation have been described as signs of deterioration respiratory insufficiency.

Benzodiazepines and benzodiazapine-like agents are not indicated for the treatment of patients with severe hepatic insufficiency as they may precipitate encephalopathy.

Use in patients with psychotic illness: benzodiazepines and benzodiazapine-like agents are not recommended for the primary treatment.

Depression

Benzodiazepine and benzodiazepine-like agents should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients). 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 the drug that is feasible should be supplied to these patients. Pre-existing depression may be unmasked during use of zolpidem. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

Use in patients with a history of drug or alcohol abuse: benzodiazepines and benzodiazepine-like agents should be used with extreme caution in patients with a history of alcohol or drug abuse. These patients should be under careful surveillance when receiving zolpidem since they are at risk of habituation and psychological dependence.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be observed when other psychoactive drugs are used.

Zolpidem should not be taken in combination 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.

Combination with CNS depressants

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives/muscle relaxants, antidepressant agents, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines. Therefore, concomitant use of zolpidem with these drugs may increase drowsiness and next-day psychomotor impairment, including impaired driving ability (see section 4.4 and section 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.

Therefore, caution should be exercised when Zolpidem is used in combination with other CNS depressants (see sections 4.8 and 5.1)

In the case of narcotic analgesics enhancement of euphoria may also occur leading to an increase in psychological dependence.

No clinical significant pharmacokinetic or pharmacodynamic interactions with selective serotonin reuptake inhibitors (fluoxetine and sertraline) have been described.

CYP450 inhibitors and inducers

Zolpidem is metabolised by some enzymes of the cytochrome P450-family. The main enzyme is CYP3A4, but CYP1A2 is involved as well

Rifampicin induces the metabolism of zolpidem, resulting in approximately 60% reduction in peak plasma concentrations and possibly decreased efficacy. Similar effects might be expected also with other strong inducers of cytochrome P450-enzymes.

Compounds that inhibit hepatic enzymes (particularly CYP3A4) may increase plasma concentrations and enhance the activity of zolpidem. Co- administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

However, when zolpidem is administered with ketokonazol (200 mg twice daily) a potent CYP3A4 inhibitor, the AUC increases with 83%. It is not necessary to adjust the dose of zolpidem by routine but the patient should be informed that use of zolpidem together with ketokonazol may increase the sedative effect.

Others: when zolpidem tartrate was administered with haloperidol, chlorpromazin, itraconazol, digoxin, or ranitidine, no significant pharmacokinetic interactions were observed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are insufficient data to permit an assessment of the safety of zolpidem during pregnancy and lactation. Although animal studies have shown no teratogenic or embryotoxic effects, safety in pregnancy has not been established in humans. Therefore zolpidem should not be used during pregnancy especially in the first trimester.

If zolpidem is prescribed to a woman of childbearing potential, she should be encouraged to contact her physician regarding discontinuance of the product if she intends to become or suspect that she is pregnant.

If, for compelling medical reason, zolpidem 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.

Infants born to mothers who took benzodiazepines or benzodiazepine-like agents chronically during the latter stages of pregnancy may develop withdrawal symptoms in the postnatal period as a result of physical dependence.

Breastfeeding

Zolpidem passes into breast milk in small amounts. Zolpidem should therefore not be used by breast-feeding mothers since effects on the infant are not studied.

Fertility

Oral administration of zolpidem doses of 4, 20, and 100 mg base/kg or 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 20 mg base/kg/day (approximately 24 times the MRHD on a mg/m² basis).

4.7 Effects on ability to drive and use machines

Edluar 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 and driving, using machinery and working at heights.

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

Furthermore, the co-administration of zolpidem 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.

4.8 Undesirable effects

These effects seem to be related with individual sensitivity and to appear more often within the hour following the drug intake if the patient does not go to bed or does not sleep immediately (see section 4.2).

The adverse drug reactions are stated in the table below using the following convention:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from 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.

SOC	<i>Frequency</i>			
	<i>Common</i>	<i>Uncommon</i>	<i>Rare</i>	<i>Not known</i>
Immune system disorders				Angioneurotic disorders
Psychiatric disorders	Hallucination, agitation, nightmare, numbed emotions, confusion	Irritability	Decreased libido	Restlessness, aggression, delusion, anger, psychosis, abnormal behaviour, sleep walking (see section 4.4), dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation), depression
Nervous System Disorders	Somnolence, headache, dizziness, increased insomnia, anterograde amnesia: (amnesic effects may be associated with inappropriate behaviour) drowsiness during the following day, reduced alertness	Ataxia		Depressed level of consciousness
Eye disorders	Double vision			
Ear and labyrinth disorders	Vertigo			
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain			
Hepatobiliary disorders				Elevated liver enzymes
Skin and Subcutaneous tissue disorders	Skin reactions			Rash, pruritus, urticaria, hyperhidrosis
Musculoskeletal and connective tissue and bone disorders		Muscle weakness		
General Disorders	Fatigue		Paradoxical reactions	Gait disturbance, drug tolerance, fall (predominantly in elderly)

				patients and when zolpidem was not taken in accordance with prescribing recommendation)
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These phenomena occur predominantly at the start of the therapy or in elderly patients and usually disappear with repeated administration.

Amnesia
Anterograde amnesia may occur during therapeutic dosages, the risk increasing at higher dosages. In order to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 8 hours. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

Depression
Pre-existing depression may become manifest during use of benzodiazepines or benzodiazepine-like agents (see section 4.4).

Psychiatric and “paradoxical” reactions
Reactions like restlessness, agitation, irritability, aggressiveness, delusions, rage, nightmares, increased insomnia, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects may occur when using benzodiazepines and benzodiazepine-like agents. Such reactions are more likely to occur in the elderly (see section 4.4).

Dependence
Use (even at therapeutic dosages) may lead to physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4).

Psychic dependence may occur. Abuse has been reported in polydrug abusers.

Reporting of suspected adverse reactions
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

In reports of overdose with zolpidem alone or with other CNS-depressant agents (including alcohol), impairment of consciousness has ranged from somnolence to coma and fatal outcomes have been reported

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

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 in intensive care units should be considered. Sedating medicinal products should be withheld even if excitation occurs.

Use of flumazenil may be considered when serious symptoms are observed. Flumazenil administration may contribute to the appearance of 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, haemodialysis and forced diuresis are not

effective measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and Sedatives, Benzodiazepine related drugs

ATC Code: N05CF02

Zolpidem, an imidazopyridine, is a benzodiazepine-like hypnotic agent. 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 agonist action at central receptors belonging to the “GABA_A- ω ” (BZ₁ & BZ₂) macromolecular receptor” complex, modulating the opening of the chloride ion channel. Zolpidem acts primarily upon ω_1 (BZ₁) receptor subtypes.

Zolpidem has been shown to be effective for the short-term treatment of insomnia characterized by difficulties with sleep initiation. The randomized trials only showed convincing evidence of efficacy of 10mg zolpidem. In a randomized double-blind trial in 462 non-elderly healthy volunteers with transient insomnia, zolpidem 10mg decreased the mean time to fall asleep by 10 minutes compared to placebo, while for 5mg zolpidem this was 3 minutes. In a randomized double-blind trial in 114 non-elderly patients with chronic insomnia, zolpidem 10mg decreased the mean time to fall asleep by 30 minutes compared to placebo, while for 5mg zolpidem this was 15 minutes. In some patients, a lower dose of 5mg could be effective.

Overall, zolpidem sublingual tablets at the 10 mg dose shortened latency to persistent sleep by approximately ten-minutes, relative to standard tablets containing 10 mg.

Zolpidem also promotes sleep maintenance. There were no differences in sleep maintenance efficacy parameters (wake after sleep onset and total duration of sleep) between sublingual and standard oral tablets.

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 Attention Deficit Hyperactivity Disorder (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 section 4.2).

5.2 Pharmacokinetic properties

Absorption

Zolpidem has both a rapid absorption and onset of hypnotic effect. Bioavailability is 70% following oral administration. It demonstrates linear kinetics in the therapeutic dose range. The therapeutic plasma level is between 80 and 200 ng/ml. With Edluar sublingual tablet peak plasma concentrations are reached between 0.25 and 3.5 hours after administration. Median time to C_{max} was similar compared to a conventional tablet formulation. However, early plasma concentrations at 5-15 minutes were higher with Edluar.

The mean AUC and C_{max} were decreased by 12% and 34%, respectively, while median t_{max} was prolonged from 1.0 to 1.75 hours when Edluar was administered after a high fat meal. The half-life remained unchanged (see section 4.2).

Distribution

The distribution volume in adults is 0.54 l/kg and decreases to 0.34 l/kg in the elderly.

Protein binding amounts to 92%. First pass metabolism by the liver amounts to approximately 35%. Repeated administration has been shown not to modify protein binding, indicating a lack of competition between zolpidem and its metabolites for binding sites.

Elimination

The elimination half-life is short. Mean zolpidem elimination half-life after administration of Edluar was 2.85 hours (5 mg) and 2.65 hours (10 mg). Zolpidem duration of action is up to 6 hours.

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

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

Special populations

In patients with renal insufficiency, including patients on dialysis a moderate reduction in clearance is observed. The other pharmacokinetic parameters remain unaffected.

In elderly patients and in patients with hepatic insufficiency, the bio-availability of zolpidem is increased. Clearance is reduced and the elimination half-life is prolonged (approximately 10 hours).

In patients with liver cirrhosis a 5-fold increase in AUC and a 3-fold increase in half-life were observed.

5.3 Preclinical safety data

Preclinical effects were only observed at dosages well above the maximum human exposure levels and are therefore of little significance for clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Silicified microcrystalline cellulose (mixture of microcrystalline cellulose and silica colloidal anhydrous)
Silica colloidal anhydrous
Croscarmellose sodium
Saccharin sodium
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10, 14, 20, 28, 30, 60, 100 and 150 sublingual tablets in aluminium/aluminium blisters.

Not all packs sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Meda Health Sales Ireland Limited
Unit 34/35, Block A,
Dunboyne Business Park
Dunboyne
Co. Meath
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1332/040/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: 24th September 2012

10 DATE OF REVISION OF THE TEXT

March 2015