Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Edluar 10 mg sublingual tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 10 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 X 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. and should not exceed 4 weeks including the tapering off process.

Extension beyond the maximum treatment period should not be carried out without reviewing the patient's status, as the risk of abuse and dependence increases with treatment duration (see section 4.4).

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 (*See section 5.2.*); 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 4.3).

Renal impairment
A dose adjustment is not necessary for patients with renal impairment.

Chronic respiratory insufficiency
In patients with chronic respiratory insufficiency a lower dose is recommended (see section 4.4 under 'Specific patient groups')

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.

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.
Obstructive sleep apnoea.
Myasthenia gravis.
Acute and/or severe respiratory insufficiency.
Complex sleep behaviour after having taken zolpidem in the medical history (see section 4.4).

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, and the patient should be carefully re-evaluated at regular intervals.
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.

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 patient's status.

It may be useful to inform the patient when treatment is started that it will be of limited duration and explain exactly how the dose is gradually decreased when treatment is stopped.

Warnings
Respiratory insufficiency
Caution should be observed when prescribing zolpidem to patients with chronic respiratory insufficiency since benzodiazepines have been shown to impair respiratory function (see section 4.8).

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 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 caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Precautions

Psychosis
Hypnotics such as zolpidem are not recommended for the primary treatment of psychoses.

Amnesia
Benzodiazepines or benzodiazepine-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).

Depression
Benzodiazepine and benzodiazepine-like agents such as zolpidem should not be used without appropriate treatment of the 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.

Suicidal thoughts/suicide attempts/suicide and depression
Several epidemiological studies show an increased incidence of suicidal thoughts, suicide attempts and suicide in patients with or without depression, treated with benzodiazepines or other hypnotics including zolpidem. However, a causal relationship could not be shown.

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 dependence.

Next-day psychomotor impairment
As with other sedatives/hypnotics, zolpidem has CNS depressant effects. 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.

Psychiatric and 'paradoxical' reactions

When using benzodiazepines or benzodiazepine-like agents, reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, increased insomnia, delirium 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

Complex sleep behaviour has been reported, including 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. This behaviour may occur after the first dose or subsequent doses of zolpidem. 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. Treatment with zolpidem should be discontinued immediately if the patient experience a complex sleep behaviour (see section 4.5 and section 4.8), due to the risks for the patient and others.

Tolerance

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

Dependence

Use of zolpidem can lead to abuse and/or physical or 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 previous psychiatric illness and/or alcohol or substance abuse. Zolpidem should be used with the utmost caution in patients with existing or previous 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, delirium 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.

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).

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).

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

Patients with long QT syndrome

As a safety precaution, the risk-benefit ratio for treatment with zolpidem should be weighed carefully for patients with known, congenital long QT syndrome.

As an in vitro cardiac electrophysiological study has shown that zolpidem has the potential to cause QT prolongation possible consequences in patients with long QT syndrome cannot be excluded.

Excipients

This medicinal product 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

Caution should be observed when other psychoactive drugs are used.

Co-administration of muscle relaxants may potentiate the muscle-relaxant effect and the risk of falls, especially in elderly patients and at higher dosage (see section 4.4).

Alcohol
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.

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

Zolpidem is metabolised by some enzymes of the cytochrome P450-family. The main enzyme is CYP3A4, but CYP1A2 is involved as well. Substances which inhibit cytochrome P450 may increase the plasma concentration and enhance the effect of zolpidem.

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-enzymessuch as carbamazepine, phenytoin and St John's Wort; concomitant use is not recommended.

A pharmacokinetic reaction between St. John's Wort and zolpidem has been observed. Mean C_{max} and AUC were reduced (33.7 and 30.0% lower, respectively) for zolpidem when administered concomitantly with St. John's Wort compared to when zolpidem was administered alone. Co-administration of St. John's Wort may reduce levels of zolpidem in the blood. Concomitant use is not recommended.

Interaction with grapefruit juice (inhibitor of cytochrome P450-enzymes) may occur.

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.

Co-administration of zolpidem and ketoconazole (200 mg twice daily), a potent CYP3A4 inhibitor, prolonged the elimination half-life of zolpidem, increased the total AUC and reduced the apparent oral clearance when compared with zolpidem and placebo. The total AUC during concomitant administration with ketoconazole increases with 83% when compared to zolpidem alone.

It is not necessary to adjust the dose of zolpidem by routine but the patient should be informed that use of zolpidem together with ketoconazole may increase the sedative effect.

However, when zolpidem was administered concomitantly with itraconazole (a CYP3A4 inhibitor), its pharmacokinetics and pharmacodynamics were not significantly modified. The clinical relevance of these results is unknown.

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

Use of zolpidem is not recommended during pregnancy.

Studies in animals do not indicate direct or harmful effects with respect to reproductive toxicity.

Zolpidem crosses the placenta.

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 suspects that she is pregnant.

A large amount of data on pregnant women (more than 1,000 pregnancies) gathered from cohort studies showed no signs of an increase in the incidence of malformations following exposure to benzodiazepines or benzodiazepine-like substances during the first trimester of pregnancy. However, in some case-control studies an increase in the incidence of cleft lip and palate was observed with the use of benzodiazepines during pregnancy.

Cases of reduced fetal movement and fetal heart rate variability have been described after administration of benzodiazepines during the second and/or third trimester of pregnancy.

Administration of zolpidem during the late phase of pregnancy, or during labour, has been associated with effects on the neonate, such as hypothermia, hypotonia (floppy infant syndrome), feeding difficulties and respiratory depression, due to the pharmacological action of the product. Cases of severe neonatal respiratory depression have been reported.

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. Appropriate post-natal monitoring of the newborn is recommended.

Breastfeeding

Zolpidem passes into breast milk in small amounts. Zolpidem should therefore not be used by breast-feeding mothers.

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/m^2 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/m^2 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.

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 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 frequently in elderly patients.

SOC	***Frequency***				
	Common	***Uncommon***	***Rare***	***Very rare***	***Not known***
Infections and infestations	Upper and lower respiratory tract infections				
Immune system disorders					Angioneurotic oedema
Metabolism and nutrition disorders		Loss of appetite			
Psychiatric disorders	Hallucination, agitation, nightmare, numbed emotions, depression (see section 4.4)	Confusion, irritability, restlessness, aggression, somnambulism (see section 4.4 'Somnambulism and associated behaviours'), complex sleep behaviour (e.g. sleep walking	Libido disorder		Delusion, anger, psychosis, abnormal behaviour, dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation), delirium (see

		(see section 4.4)), euphoric mood			section 4.4)). The majority of the psychiatric side effects are related to paradoxical reactions.
Nervous System Disorders	Somnolence, headache, dizziness, increased insomnia, cognitive disorders such as anterograde amnesia: (amnestic effects may be associated with inappropriate behaviour) drowsiness during the following day	Ataxia, paraesthesia, tremor, reduced alertness, speech disorder	Depressed level of consciousness		
Eye disorders	Double vision	Blurred vision	Visual impairment		
Ear and labyrinth disorders	Vertigo				
Respiratory, thoracic and mediastinal disorders				Respiratory depression (see section 4.4)	
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain				
Hepatobiliary disorders		Elevated liver enzymes	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 and bone disorders	Back pain	Muscle weakness, arthralgia, myalgia, muscle spasm, neck pain			
General Disorders and administration site conditions	Fatigue		Paradoxical reactions, gait disturbance, falls (predominantly in elderly patients and when zolpidem was not taken in accordance with prescribing recommendation) (see section 4.4)		Drug tolerance

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 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

Symptoms

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.

Treatment

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). Monitoring of respiratory or cardiovascular functions should be considered.

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 is an imidazopyridine, which bonds selectively to omega-1 receptors containing the alpha-1 sub-unit of the GABA-A receptor complex.

Benzodiazepines bind non-selectively to all three omega receptors, but zolpidem binds preferentially to the omega-1 receptor. Modulation of the chloride anion channel via this receptor leads to zolpidem's specific sedative effects. Zolpidem's selective bonding to omega-1 receptors may explain the virtual absence of muscle relaxation and anti-convulsant effects in animals at hypnotic doses of Zolpidem. This effect normally occurs with benzodiazepines which are not selective for omega-1 receptors. Maintaining a deep sleep (stages 3 and 4 – slow-wave sleep) in humans may also be explained by zolpidem's selective omega-1 binding.

Experimental studies have indicated it has sedative effects at lower doses than those necessary to provide anticonvulsant, muscle relaxation or anxiolytic effects. These effects can be counteracted by flumazenil, a benzodiazepine antagonist.

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 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 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).

As zolpidem's plasma concentration in the elderly and for patients with hepatic insufficiency is higher than normal, the dose may need to be adjusted for these patient groups (see sections 4.2 and 4.3).

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

Mylan IRE Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER

PA2010/050/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: 24th September 2012
Date of last renewal: 14th June 2017

10 DATE OF REVISION OF THE TEXT

December 2023