

## Summary of Product Characteristics

### 1 NAME OF THE MEDICINAL PRODUCT

Zolnod 10mg film-coated tablets.

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains:  
10 mg zolpidem tartrate

Excipients with known effect: contains 54 mg lactose per film-coated tablet

For the full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Film-coated tablet.

White, oblong, biconvex, with a break score.

The tablet can be divided into equal halves.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic Indications

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

#### 4.2 Posology and method of administration

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.

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.

The product should be taken with fluid just before going to bed.

#### 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.

##### Older people

In elderly or debilitated patients who may be especially sensitive to the effects of zolpidem a dose of 5 mg is recommended. This dose should only be increased to 10 mg where the clinical response is inadequate and the drug is well tolerated. The total dose of zolpidem should not exceed 10 mg in any patient.

##### Patients with hepatic insufficiency

Patients with hepatic insufficiency who do not clear the drug as rapidly as normal individuals, a dose of 5 mg is

recommended. This dose should only be increased to 10 mg where the clinical response is inadequate and the drug is well tolerated.

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

#### 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.

### **4.3 Contraindications**

Severe hepatic insufficiency

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

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 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 physical and psychological 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 psychiatric disorders and/or alcohol or drug abuse. These patients should be monitored carefully when receiving benzodiazepines or benzodiazepine-like agents.

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 the 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 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 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.), but 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.).

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

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.).

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 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.).

Other psychiatric and "paradoxical" reactions

When using benzodiazepines or benzodiazepine-like agents, reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, somnambulism, inappropriate behaviour, 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.

Specific patient groups

- Elderly or debilitated patients  
Should receive a lower dose: see recommended dosage (section 4.2.).  
Due to the myorelaxant effect there is a risk of falls and consequently of hip fractures particularly for elderly patients when they get up at night.
- Patients with renal insufficiency (see section 5.2.).  
Although dose adjustment is not necessary, caution should be exercised.
- Patients with respiratory insufficiency  
Caution should be observed when prescribing zolpidem 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 decompensated respiratory insufficiency.
- Patients with severe hepatic insufficiency  
Benzodiazepines and benzodiazepine-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 benzodiazepine-like agents are not recommended for the primary treatment.
- Use in depression  
Despite the fact that relevant clinical, pharmacokinetic and pharmacodynamic interactions with SSRI have not been demonstrated (see section 4.5.), 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 drug that is feasible should be supplied to these patients.  
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).  
Pre-existing depression may be disclosed 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.

Zolnod contains 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 interaction

### Alcohol

Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

### 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.

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

### CYP450 inhibitors and inducers

Zolpidem is metabolised by some enzymes of the cytochrome P450-family. The main enzyme is CYP3A4 with partial contribution of CYP1A2.

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. However, when zolpidem is administered with itraconazole (CYP3A4 inhibitor), the pharmacokinetic and pharmacodynamic effects are not significantly different. The clinical relevance of these results is unknown.

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

Concomitant administration of zolpidem and ketoconazole, which is a potent CYP3A4 inhibitor, prolonged the half-life of zolpidem. The total exposure of zolpidem increased by 83% and the apparent oral clearance was decreased. It is not necessary to perform a routine dose adjustment, but the patient should be informed about the potential increase in the sedative effect when ketoconazole and zolpidem are used concomitantly. Dose reduction of zolpidem may be considered when treatment with ketoconazole is introduced.

There is clinical evidence that sertraline, a CYP3A4 inhibitor, may interact with zolpidem leading to increased drowsiness. Also, isolated cases of visual hallucinations have been reported.

When zolpidem was administered with warfarin, haloperidol, chlorpromazine, 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 the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects 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. Cases of severe neonatal respiratory depression have been reported when zolpidem 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 develop withdrawal symptoms in the postnatal period as a result of physical dependence.

#### Lactation

Zolpidem is excreted in breast milk in minimal amounts. Zolnod should therefore not be used during breast-feeding since effects on the infant are not studied.

### **4.7 Effects on ability to drive and use machines**

Zolnod 10 mg 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**

The following frequency data is the basis for the evaluation of undesirable effects:-

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 the available data).

There is evidence of a dose-relationship for adverse effects associated with zolpidem tartrate use, particularly for certain CNS and gastrointestinal events.

These undesirable effects occur most frequently in elderly patients.

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.)

#### Infections and infestations

*Common:* Upper respiratory tract infections, lower respiratory tract infections

#### Immune system disorders

Not known: Angioneurotic oedema

#### Psychiatric disorders

*Common:* Hallucination, agitation, nightmare

*Uncommon:* Confusional state, irritability

*Not known:* Restlessness, aggression, delusions, anger, psychosis, sleep walking (see section 4.4), inappropriate

behaviour and other adverse behavioural effects (such reactions are more likely to occur in the elderly, see section 4.4), dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation), libido disorder, depression (see section 4.4)

Most of these psychiatric undesirable effects are related to paradoxical reactions.

#### Nervous system disorders

*Common:* Somnolence, drowsiness during the following day, numbed emotions, reduced alertness, headache, dizziness, anterograde amnesia, which may be associated with inappropriate behaviour, ataxia, exacerbated insomnia.

*Not known:* Depressed level of consciousness

#### Eye disorders

*Uncommon:* Double vision

#### Respiratory, thoracic and mediastinal disorders

*Not known:* Respiratory depression (see section 4.4)

#### Ear and labyrinth disorders

*Common:* Vertigo, ataxia

#### Gastrointestinal disorders

*Common:* Gastrointestinal disturbances (diarrhoea, nausea, vomiting, abdominal pain)

#### Hepatobiliary disorders

*Not known:* Liver enzymes elevated

#### Skin and subcutaneous tissue disorders

*Uncommon:* rash, pruritus, urticaria, hyperhidrosis

#### Musculoskeletal, connective tissue and bone disorders

*Common:* Back pain

*Not known:* Muscle weakness

#### 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).

#### 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](http://www.hpra.ie); E-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

## **4.9 Overdose**

#### Signs and symptoms

In reports of overdose with zolpidem alone or with other CNS-depressant agents (including alcohol), impairment of consciousness has ranged from somnolence to light coma and more severe symptoms including fatal outcomes.

Individuals have fully recovered from overdoses up to 400 mg of zolpidem, 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. 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. Hemodialysis 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: 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-omega" (BZ1 & BZ2) macromolecular receptor" complex, modulating the opening of the chloride ion channel. Zolpidem acts primarily upon omega (BZ1) receptor subtypes. The clinical relevance of this is not known.

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 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 sections 4.2. and 4.3.).

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 sections 4.2 and 4.3).

### 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. Peak plasma concentration is reached at between 0.5 and 3 hours after administration.

Interindividual variability is high, (CV% of AUC is 60-70 % and for Cmax 40-50 %).

#### 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, with a mean of 2.4 hours and a duration of action 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.

Clearance is approximately 300 ml/min.

### Special populations

In patients with renal insufficiency, a moderate reduction in clearance is observed (independent of possible dialysis). The other pharmacokinetic parameters remain unaffected.

In elderly patients the bio-availability of zolpidem is increased.

Reduced clearance, approximately 100 ml/min, has been observed in elderly. The maximal plasma concentration is increased by approximately 80 % without a significant increase of the half life (around 3 hours) in a patient group aged 81-95 years.

## **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**

#### *Tablet core:*

Magnesium stearate  
Microcrystalline cellulose  
Lactose monohydrate  
Colloidal silicon dioxide  
Sodium starch glycollate (Type A)  
Succinic acid

#### *Tablet coating:*

Lactose monohydrate  
Macrogol 4000  
Hypromellose  
Titanium dioxide (colouring agent E171)

### **6.2 Incompatibilities**

Not applicable



### **6.3 Shelf life**

5 years.

### **6.4 Special precautions for storage**

Store in the original container to protect from light.

### **6.5 Nature and contents of container**

The film-coated tablets are packed in polyvinylchloride/aluminium blisters and inserted into a carton.

The packages contain 10, 20, 28, 30, 30x1, 50, 98, 100 film-coated tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

ROWEX LTD  
Bantry  
Co Cork

## **8 MARKETING AUTHORISATION NUMBER**

PA0711/039/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 8 March 2002

Date of last renewal: 6 February 2011

## **10 DATE OF REVISION OF THE TEXT**

April 2015