SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zopiclone 3.75mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Zopiclone 3.75 mg.

Excipients with known effect:

Lactose, 15.75mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off white, round, biconvex, film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short term treatment of insomnia in adults, including difficulties in falling asleep, nocturnal awakening and early awakening, transient, situational or chronic insomnia, and insomnia secondary to psychiatric disturbances, in situations where the insomnia is debilitating or is causing severe distress for the patient. Long term continuous use is not recommended. A course of treatment should employ the lowest effective dose.

4.2 Posology and method of administration

Use the lowest effective dose. Zopiclone should be taken in a single intake and not be re-administered during the same night.

Adults

The recommended dose is 7.5mg zopiclone by the oral route shortly before retiring.

Elderly patients

A lower dose of 3.75mg zopiclone should be employed to start treatment in the elderly. Depending on effectiveness and acceptability, the dosage subsequently may be increased if clinically necessary.

Paediatric population

Zopiclone should not be used in children and adolescents less than 18 years.
The safety and efficacy of zopiclone in children and adolescents aged less than 18 years have not been established.

Patients with hepatic insufficiency

As elimination of zopiclone may be reduced in patients with hepatic dysfunction, a lower dose of 3.75mg zopiclone nightly is recommended. The standard dose of 7.5mg zopiclone may be used with caution in some cases, depending on effectiveness and acceptability.

Patients with Renal insufficiency

Accumulation of zopiclone or its metabolites has not been seen during treatment of insomnia in patients with renal insufficiency. However, it is recommended that patients with impaired renal function should start treatment with 3.75mg.

Chronic respiratory insufficiency

In patients with chronic respiratory insufficiency, a starting dose of 3.75 mg zopiclone is recommended initially. The dosage subsequently may be increased to 7.5 mg.

As with all hypnotics, long term use of zopiclone is not recommended.

Treatment should be as short as possible and should not exceed four weeks including the period of tapering off. 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 increase with the duration of treatment (see section 4.4)

The product should be taken just before retiring for the night.

Method of administration

For oral use only.

Each tablet should be swallowed without sucking or chewing.

4.3 Contraindications

Zopiclone is contraindicated in patients:

- With myasthenia gravis
- With respiratory failure
- With severe sleep apnoea syndrome
- With severe hepatic insufficiency
- With hypersensitivity to zopiclone or to any of the excipients listed in section 6.1.
- Who have previously experienced complex sleep behaviours after taking zopiclone, see section 4.4.

As with all hypnotics Zopiclone should not be used in children.

4.4 Special warnings and precautions for use

The cause of insomnia should be identified wherever possible and the underlying factors treated before a hypnotic is prescribed.

Specific patient groups

Use in hepatic insufficiency

A reduced dosage is recommended (see section 4.2). Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy (see section 4.3).

Use in renal insufficiency

A reduced dosage is recommended, see Posology.

Use in respiratory insufficiency

As hypnotics have the capacity to depress respiratory drive, precautions should be observed if zopiclone is prescribed to patients with compromised respiratory function (see section 4.8). A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Use in paediatric population

Zopiclone should not be used in children and adolescents less than 18 years.
The safety and efficacy of zopiclone in children and adolescents aged less than 18 years have not been established.

Use in Elderly patients

Elderly should be given a reduced dose (see section 4.2).

Risk of dependence

Use of zopiclone may lead to the development of abuse and/or physical and psychological dependence.

The risk of dependence increases with dose and duration of treatment. Cases of dependence have been reported more frequently in patients treated with Zopiclone for longer than 4 weeks. The risk of abuse and dependence is also greater in patients with a history of psychiatric disorders and/or alcohol, substance or drug abuse. Zopiclone should be used with extreme caution in patients with current or a history of alcohol, substance or drug abuse or dependence.

If physical dependence is developed, a sudden discontinuation of treatment will be accompanied by withdrawal symptoms (See Section 4.8).

Withdrawal

The termination of treatment with Zopiclone is unlikely to be associated with withdrawal effects when duration of treatment is limited to 4 weeks. Patients may benefit from tapering off the dose before discontinuation (see section 4.8.).

Suicidal ideation/suicide attempt/suicide and *Depression*
Some epidemiological studies show an increased incidence of suicidal ideation, suicide attempt and suicide in patients with or without depression, and treated with benzodiazepines and other hypnotics, including zopiclone. However, a causal relationship has not been established.

As with other hypnotics, zopiclone does not constitute a treatment for depression and may even mask its symptoms (suicide may be precipitated in such patients).
Zopiclone should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present therefore the least amount of Zopiclone that is feasible should be supplied to these patients to avoid the possibility of intentional overdose by the patient. Pre-existing depression may be unmasked during use of Zopiclone. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.
Any underlying cause of the insomnia should also be addressed before symptomatic treatment to avoid under treating potentially serious effects of depression.

Tolerance

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

However, with Zopiclone there is an absence of any marked tolerance during treatment periods of up to 4 weeks.

Rebound insomnia

A transient syndrome where the symptoms which led to treatment with a benzodiazepine or benzodiazepine-like agent recur in an enhanced form on discontinuation of therapy. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since the risk of withdrawal/rebound phenomena may be increased after prolonged treatment, or abrupt discontinuation of therapy, it is, therefore, recommended to decrease the dosage gradually and to advise the patient accordingly.

A course of treatment should employ the lowest effective dose for the minimum length of time necessary for effective treatment. See see section 4.2 for guidance on possible treatment regimen. A course of treatment should not continue for longer than 4 weeks including any tapering off (see section 4.8).

Amnesia

Amnesia is rare, but anterograde amnesia may occur, especially when sleep is interrupted or when retiring to bed is delayed after taking the tablet.

Therefore, patients should ensure that they take the tablet when certain of retiring for the night and they are able to have a full night's sleep (uninterrupted sleep of about 7 to 8 hours).

Psychomotor impairment

Like other sedative/hypnotic drugs, zopiclone has CNS-depressant effects. The risk of psychomotor impairment, including impaired driving ability, is increased if: zopiclone is taken within 12 hours of performing activities that require mental alertness, a dose higher than the recommended dose is taken, or zopiclone is co-administered with other CNS depressants, alcohol or with other drugs that increase the blood levels of zopiclone (see section 4.5).
Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle following administration of zopiclone and in particular during the 12 hours following that administration.

Risk from concomitant use with opioids:

Concomitant use of opioids with benzodiazepines or other sedative-hypnotic drug, including zopiclone may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe zopiclone concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation (see section 4.5).

Other psychiatric and paradoxical reactions

Other psychiatric and paradoxical reactions have been reported (see section 4.8), like restlessness, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, inappropriate behaviour and other adverse behavioural effects are known to occur when using sedative/hypnotic agents like zopiclone. Should this occur, use of zopiclone should be discontinued. These reactions are more likely to occur in the elderly.

Somnambulism and associated behaviours

Complex sleep behaviour, 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 zopiclone and were not fully awake. These events may occur following the first or any subsequent use of zopiclone. Discontinue treatment immediately if a patient experiences a complex sleep behaviour, due to the risk to the patient and others (see section 4.3). The use of alcohol and other CNS-depressants with zopiclone appears to increase the risk of such behaviours, as does the use of zopiclone at doses exceeding the maximum recommended dose..

Excipients
Zopiclone tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the

total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Association not recommended: The sedative effect of zopiclone may be enhanced when used in combination with alcohol, concomitant use is therefore not recommended. In particular this could affect the patient's ability to drive or use machines.

Associations to be taken into account:
In combination with CNS depressants an enhancement of the central depressive effect may occur. The therapeutic benefit of co-administration with antipsychotics (neuroleptics), hypnotics anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines should therefore be carefully weighed. In the case of narcotic analgesic, enhancement of euphoria may also occur leading to an increase in psychic dependence. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines and benzodiazepine-like agents.

The effect of erythromycin on the pharmacokinetics of zopiclone has been studied in 10 healthy subjects. The AUC of zopiclone is increased by 80% in presence of erythromycin which indicates that erythromycin can inhibit the metabolism of drugs metabolised by CYP 3A4. As a consequence, the hypnotic effect of zopiclone may be enhanced.

Since zopiclone is metabolised by the cytochrome P450 (CYP) 3A4 isoenzyme (see section 5.2), plasma levels of zopiclone may be increased when co-administered with CYP3A4 inhibitors such as erythromycin, clarithromycin, ketoconazole, itraconazole and ritonavir. A dose reduction for zopiclone may be required when it is co-administered with CYP3A4 inhibitors. Conversely, plasma levels of zopiclone may be decreased when co-administered with CYP3A4 inducers such as rifampicin, carbamazepine, phenobarbital, phenytoin and St. John's wort. A dose increase for zopiclone may be required when it is co-administered with CYP3A4 inducers.

Opioids:

The concomitant use of benzodiazepines and other sedative-hypnotic drugs, including zopiclone, and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see section 4.4)

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of zopiclone is not recommended during pregnancy.

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

Zopiclone 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 fetal movement and fetal heart rate variability have been described after administration of benzodiazepines or benzodiazepine-like substances during the second and/or third trimester of pregnancy.

Administration of benzodiazepines or benzodiazepine-like substances, including zopiclone, during the late phase of pregnancy or during labour have 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/hypnotics 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.

If zopiclone 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.

Breast-feeding
Zopiclone is excreted in breast milk, although the concentration of zopiclone in the breast milk is low, use in nursing mothers must be avoided.

4.7 Effects on ability to drive and use machines

Because of its pharmacological properties and its effect on central nervous system, Zopiclone may adversely affect the ability to drive or to use machines. The risk of psychomotor impairment, including impaired driving ability, is increased if:

- Zopiclone is taken within 12 hours of performing activities that require mental alertness,
- a dose higher than the recommended dose is taken, or
- zopiclone is co-administered with other CNS depressants, alcohol, or with other drugs that increase the blood levels of zopiclone.

Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle following administration of zopiclone and in particular during the 12 hours following that administration.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

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).

Immune system disorders
Very rare: angiooedema, anaphylactic reaction

Psychiatric disorders
Uncommon: nightmare, agitation
Rare: confusional state, libido disorder, irritability, aggression, hallucination
Not known: restlessness, delusion, anger, , abnormal behaviour (possibly associated with amnesia)

and complex sleep behaviours including somnambulism (see Section 4.4, dependencewithdrawal syndrome (see below)

Nervous system disorders
Common: dysgeusia (Bitter taste), somnolence (residual)
Uncommon: dizziness, headache
Rare: anterograde amnesia
Not known: ataxia, paraesthesia, cognitive disorders such as memory impairment, disturbance in attention, speech disorder

Eye disorders
Not known: diplopia

Respiratory, thoracic and mediastinal disorders

Rare: dyspnoea (see section 4.4)

Not known: respiratory depression (see section 4.4)

Gastrointestinal disorders
Common: dry mouth
Uncommon: nausea, vomiting

Not known: dyspepsia

Hepatobiliary disorders
Very rare: transaminases increased and/or blood alkaline phosphatase increased (mild to moderate)

Skin and subcutaneous tissue disorders
Rare: urticaria or rash, pruritus

Musculoskeletal and connective tissue disorders
Not known: muscular weakness.

General disorders and administration site conditions
Uncommon: fatigue
Not known: light headedness, incoordination

Injury, poisoning and procedural complications
Rare: fall (predominantly in elderly patients)

Withdrawal syndrome has been reported upon discontinuation of zopiclone (See section 4.4). Withdrawal symptoms vary and may include rebound insomnia, muscle pain, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, 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 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 Yellow Card Scheme at: www.mhra.gov.uk/ yellow card or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Fatal dose not known.

Symptoms

Overdose is usually manifested by varying degrees of central nervous system depression ranging from drowsiness to coma according to the quantity ingested. In mild cases, symptoms include drowsiness, confusion, and lethargy; in more severe cases, symptoms may include ataxia, hypotonia, hypotension, methaemoglobinaemia, respiratory depression, and coma. Overdose should not be life threatening unless combined with other CNS depressants, including alcohol. Other risk factors, such as the presence of concomitant illness and the debilitated state of the patient, may contribute to the severity of symptoms and very rarely can result in fatal outcome.

Management

Symptomatic and supportive treatment in adequate clinical environment is recommended, attention should be paid to respiratory and cardiovascular functions.

Consider activated charcoal if an adult has ingested more than 150 mg or a child more than 1.5 mg/kg within one hour. Alternatively, consider gastric lavage in adults within one hour of a potentially life-threatening overdose. If CNS depression is severe consider the use of flumazenil. It has a short half-life (about an hour). NOT TO BE USED IN MIXED OVERDOSE OR AS A "DIAGNOSTIC" TEST. Management should include general symptomatic and supportive measures including a clear airway and monitoring cardiac and vital signs until stable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives; Benzodiazepine related drugs, ATC Code: N05C F01

Mechanism of action

Zopiclone is a hypnotic agent and a member of the cyclopyrrolone group of compounds . It rapidly initiates and sustains sleep without reduction of total REM sleep and with preservation of slow wave sleep. Negligible residual effects are seen the following morning. Its pharmacological properties include hypnotic, sedative, anxiolytic, anticonvulsant and muscle-relaxant actions. These are related to its high affinity and specific agonist action at central receptors belonging to the 'GABA' macromolecular receptor complex modulating the opening of the chloride ion channel. However, it has been shown that zopiclone and other cyclopyrrolones act on a different site to those of benzodiazepines including different conformational changes in the receptor complex.

5.2 Pharmacokinetic properties

Absorption: Zopiclone is absorbed rapidly. Peak concentrations are reached within 1.5 - 2 hours and they are approximately 30 ng/ml and 60 ng/ml after administration of 3.75mg and 7.5mg respectively. Absorption is not modified by gender, food or repetition of doses.

Distribution: The product is rapidly distributed from the vascular compartment. Plasma protein binding is weak (approximately 45%) and non saturable. There is very little risk of drug interactions due to protein binding. The volume of distribution is 91.8 - 104.6 litres.

At doses between 3.75 - 15mg, plasma clearance does not depend on dose. The elimination half life is approximately 5 hours. After repeated administration, there is no accumulation, and inter-individual variations appear to be very small.

Metabolism : Zopiclone is exensively metabolised in humans to two major metabolites, N-oxide zopiclone (pharmacologically active in animals) and N- desmethyl zopiclone (pharmacologically inactive in animals). An in-vitro study indicates that cytochrome P450 (CYP) 3A4 is the major isoenzyme involved in the metabolism of zopiclone to both metabolites, and that CYP2C8 is also involved with N-desmethyl zopiclone formation. Their apparent half-lives (evaluated from the urinary data) are approximately 4.5 hours and 1.5 hours respectively. No significant accumulation is seen on repeated dosing (15mg) for 14 days. In animals, no enzyme induction has been observed even at high doses.

Excretion : The low renal clearance value of unchanged zopiclone (mean 8.4ml/min) compared with the plasma clearance (232ml/min) indicates that zopiclone clearance is mainly metabolic. The product is eliminated by the urinary route (approximately 80%) in the form of free metabolites (n-oxide and n-desmethyl derivatives) and in the faeces (approximately 16%).

Special patient groups:

In elderly patients, notwithstanding a slight decrease in hepatic metabolism and lengthening of elimination half-life to approximately 7 hours, various studies have shown no plasma accumulation of drug substance on repeated dosing.

In renal insufficiency, no accumulation of zopiclone or of its metabolites has been detected after prolonged administration. Zopiclone crosses dialysis membranes. In cirrhotic patients, the plasma clearance of zopiclone is clearly reduced by the slowing of the desmethylation process: dosage will therefore have to be modified in these patients.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate

Starch pregelatinised
Hydroxy propyl cellulose
Lactose monohydrate
Maize starch
Magnesium stearate
Opadry white 03B28796, which contains:
Hypromellose
Titanium dioxide
Macrogol 400

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C.

Keep the blister in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

Clear PVC/aluminium foil blisters containing 10, 28, 30 film-coated tablets

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

RIA Generics Ltd

36 Ingleby Way, Wallington, Surrey,

SM6 9LR, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 36282/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE

AUTHORISATION

02/06/2017

10 DATE OF REVISION OF THE TEXT

29/09/2021