SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zopiclone 7.5mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Zopiclone 7.5mg tablets contain 7.5mg of Zopiclone per tablet.

Excipient with known effect: lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White ouderless, round, biconvex film coated tablets with a diameter of 6.8 – 7.2mm and a thickness of 3.5 - 4.0mm. The tablets are embossed with ‘ZOC 7.5@ on one side and a division line on both sides (snap-tab).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults
Short term treatment of insomnia, 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

Posology

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

The duration of treatment should be limited to 4 weeks, including any tapering off.

Adults: The recommended dose is one 7.5mg tablet shortly before retiring.

Elderly: A lower dose of 3.75mg should be employed to start treatment in the elderly. Depending upon effectiveness and acceptability, the dosage subsequently may be increased if clinically necessary to 7.5mg/day.

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 nightly is recommended. The standard dose of 7.5mg may be used with caution in some cases, depending upon 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 3.75mg zopiclone is recommended initially. The dosage subsequently may be increased to 7.5mg.

Treatment duration

Transient insomnia 2 - 5 days.

Short term insomnia 2 - 3 weeks.

A single course of treatment should not continue for longer than 4 weeks including any tapering off. Extension beyond the maximum treatment period should not take place without re-evaluation of the patient's status.

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

Method of administration
For oral use only.

Each tablet should be swallowed whole without sucking, chewing or breaking.

4.3 Contraindications

Zopiclone is contraindicated in patients with:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1;

- myasthenia gravis;
- severe respiratory insufficiency / respiratory failure;
- severe sleep apnoea syndrome;
- severe hepatic insufficiency.

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

4.4 Special warnings and precautions for use

Specific patient groups

Use in hepatic insufficiency:
A reduced dosage is recommended, see Posology. 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:
Clinical experience to date with zopiclone suggests that the risk of dependence is minimal when the duration of treatment is limited to not more than 4 weeks.
Use of benzodiazepines and benzodiazepine-like agents (even at therapeutic doses) may lead to the development of physical and psychological dependence on these products. The risk of dependence increases with:
- Dose and duration of treatment
- Use with alcohol or other psychotropics
- It is also greater in patients with a history of alcohol and/or drug abuse
- Those who have marked personality disorders.

The decision to use a hypnotic in such patients should be taken only with this clearly in mind.

If physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (see section 4.4). These may consist of headaches, muscle pain, extreme anxiety, 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. Rare cases of abuse have been reported.

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 of the dose before discontinuation (see section 4.8).

Depression:
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). Any underlying cause of the insomnia should also be addressed before symptomatic treatment to avoid under treating potentially serious effects of depression.

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 overdosage 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.

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.

Somnambulism and associated behaviour:
Sleep walking and other associated behaviours such as “sleep driving”, sleep eating, with amnesia for the event, have been reported in patients who have taken zopiclone and were not fully awake. 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. Discontinuation of zopiclone should be strongly considered for patients who report such behaviours.

Rebound insomnia:
This is 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 posology 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.

Risks from concomitant use of opioids and benzodiazepines
Concomitant use of benzodiazepines, including zopiclone, and opioids 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
Sleep walking and other associated behaviours such as “sleep driving”, preparing and eating food, or making phone calls, with amnesia for the event, have been reported in patients who have taken zopiclone and were not fully awake. 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. Discontinuation of zopiclone should be strongly considered for patients who report such behaviours (see section 4.5).

Excipients:
Zopiclone tablets contain 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

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.

In combination with CNS depressants an enhancement of the central depressive effect may occur. The therapeutic effect of co-administration antipsychotics (neuroleptics),

hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines should therefore be carefully weighed. Concomitant use of benzodiazepines or benzodiazepine-like agents with narcotic analgesics may enhance their euphoric effect and may lead 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 the presence of erythromycin which indicates that erythromycin can inhibit the metabolism of drugs metabolised by CYP3A4. 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 Pharmacokinetic properties), 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, 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

Insufficient data are available on zopiclone to assess its safety during human pregnancy and lactation.

Fertility
If the product is prescribed to a woman of child bearing potential, she should be advised to contact her physician about stopping the product if she intends to become pregnant, or suspects that she is pregnant.

Pregnancy
Experience of the use of zopiclone during pregnancy in humans is limited although there have been no adverse findings in animals. Use in pregnancy is therefore not recommended.

Moreover, if zopiclone is used during the last three months of pregnancy or during labour, due to the pharmacological action of the product, effects on the neonate, such as hypothermia and respiratory depression can be expected.

Infants born to mothers who took benzodiazepines or benzodiazepine-like agents chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

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

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: drowsiness, restlessness, delusion, anger, depressed mood, abnormal behaviour (possibly associated with amnesia) and somnambulism (see section 4.4: somnambulism and associated behaviour), dependence (see section 4.4), withdrawal 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 the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard 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. Overdosage 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 an 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. Haemodialysis is of no value due to the large volume and distribution of zopiclone. Flumazenil may be a useful antidote.

5.1 Pharmacodynamic properties

ATC code: N05C F01.
Pharmacological properties are: anxiolysis, sedation, hypnosis, anticonvulsion and muscle relaxation.

Zopiclone is a hypnotic agent belonging to the cyclopyrrolone class of psychotherapeutic agents.
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. Maximum plasma concentrations are achieved after 1½ - 2 hours and are approximately 30 and 60ng/ml after administration of 3.75mg and 7.5mg respectively. Absorption is the same in men and women and is not affected by simultaneous ingestion of food or repetition of doses.

Distribution
Zopiclone is rapidly distributed from the vascular compartment. The plasma protein binding is at least 45% and is not saturable. There is very little risk of drug interactions due to protein binding. The volume of distribution is 91.8 - 104.6 litres.

The decrease in plasma level does not depend on the dose between 3.75mg and 15mg.

The elimination half-life is approximately 5 hours at the recommended doses.

No accumulation occurs after repeated administration and individual differences appear slight.

Less than 1.0% of the dose ingested by the mother is eliminated in breast milk.

Biotransformation
The most important metabolites are the N-oxide derivative (pharmacologically active in animals) and the N-desmethyl metabolite (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-life times are approximately 4.5 hours and 1.5 hours respectively. No significant accumulation of the compound is seen following repeat dosing (15mg) for 14 days. In animals, no enzyme induction has been observed even at high doses.

Elimination
The low renal clearance of unchanged zopiclone (on average 8.4ml/min compared to the plasma clearance 232ml/min) shows that zopiclone is cleared chiefly by metabolism. Zopiclone is eliminated in the urine (approximately 80%) in the form of unconjugated metabolites (N-oxide and N-desmethyl derivatives) and in the faeces (approximately16%).

Special Patient Groups

Elderly
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.
Renal impairment
In renal insufficiency, no accumulation of zopiclone or its metabolites have been detected after prolonged administration. Zopiclone crosses the dialysing membrane.

Hepatic impairment
In patients with cirrhosis of the liver, the slow demethylating process causes the plasma clearance of zopiclone to be delayed by approximately 40%. For this reason the dosage should be adjusted for these patients.

5.3. Pre-clinical Safety Data

Carcinogenicity
From studies performed in rats and mice it can be concluded that for patients receiving long-term medication with Zopiclone no carcinogenic potential exists.

Mutagenicity

Both *in vitro* and *in vivo* studies failed to show mutagenicity produced by Zopiclone.

Fertility
In animal studies Zopiclone caused a decrease in fertility in rats. Zopiclone did not affect fertility in rabbits.

Teratogenicity
Zopiclone did not show any teratogenic or embryotoxic effect in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

The following ingredients are used in Zopiclone Tablets: lactose monohydrate, calcium hydrogen phosphate, maize starch, carmellose sodium, magnesium stearate, titanium dioxide and methylhydroxypropylcellulose.

6.2. Incompatibilities

Not applicable.

6.3 Shelf life

Shelf-life

Blister

3 years.

The expiry date is printed on the outer package and on the strips. Do not use after this date. The first two digit numbers represent the month and the last two digit numbers represent the year.

Glass jar

24 months.

The expiry date is printed on the outer package and on the glass jar. Do not use after this date. The first two digit numbers represent the month and the last two digit numbers represent the year.

Shelf-life after dilution/reconstitution

Not applicable.

Shelf-life after first opening

Not applicable.

6.4. Special Precautions for Storage

Store below 25°C in a dry place and protected from light

6.5 Nature and contents of container

Blister: PVC/PVDC/Al (250 µm/40g/m^2/20µm) Enclosed within a cardboard carton containing 1, 3 or 6 strips of 10 tablets, or 1, 2 or 4 strips of 14 tablets. Each box contains a Patient Information Leaflet.

Blister: PVC/PVDC/Al (250 µm/60g/m^2/20µm)

Pack Sizes: 10, 14, 28, 30, 56, 60

Glass jar: Amber coloured glass type III with child resistant cap, containing 28, 30, 56 or 60 tablets, enclosed within a cardboard carton also containing a Patient Information Leaflet.

6.6 Special precautions for disposal and other handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Actavis UK Limited

(Trading style: Actavis)

Whiddon Valley

BARNSTAPLE

N Devon EX32 8NS

8. MARKETING AUTHORISATION NUMBER(S)

PL 0142/0434

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

06/02/2018