

**ZOPICLONE 7.5MG FILM-COATED TABLETS**

**PL 18909/0159**

**ZOPICLONE 3.75MG FILM-COATED TABLETS**

**PL 18909/0160**

**UKPAR**

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**ZOPICLONE 7.5MG FILM-COATED TABLETS  
PL 18909/0159**

**ZOPICLONE 3.75MG FILM-COATED TABLETS  
PL 18909/0160**

**LAY SUMMARY**

The MHRA today granted Arrow Generics Limited Marketing Authorisations (licences) for the medicinal products Zopiclone 7.5mg Film-coated tablets (PL 18909/0159) and Zopiclone 3.75mg Film-coated tablets (PL 18909/0160).

These are prescription-only medicines (POM) used for short term treatment of insomnia. Insomnia is a word used to describe several problems, including difficulty getting to sleep, broken sleep and early waking. Zopiclone should help you sleep, without making you feel drowsy the next day.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Zopiclone 7.5 and 3.75mg film-coated tablets outweigh the risks, hence Marketing Authorisations have been granted.

**ZOPICLONE 7.5MG FILM-COATED TABLETS  
PL 18909/0159**

**ZOPICLONE 3.75MG FILM-COATED TABLETS  
PL 18909/0160**

**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Zopiclone 7.5mg film-coated tablets (PL 18909/0159) and 3.75mg film-coated tablets (PL 18909/0160) to Arrow Generics Limited on 2<sup>nd</sup> February 2007. The products are prescription-only medicines.

These applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC, claiming essential similarity to Zimovane<sup>®</sup> 7.5 mg Tablets (PL 00012/0259 granted on 6 May 1993) of May and Baker Limited.

The products contain the active ingredient zopiclone and are indicated for the short-term treatment of insomnia.

Zopiclone is a hypnotic agent, and a member of the cyclopyrrolone group of compounds. It rapidly initiates and sustains sleep with reduction of total REM sleep and with preservation of slow wave sleep.

## PHARMACEUTICAL ASSESSMENT

### DRUG SUBSTANCE

#### Nomenclature

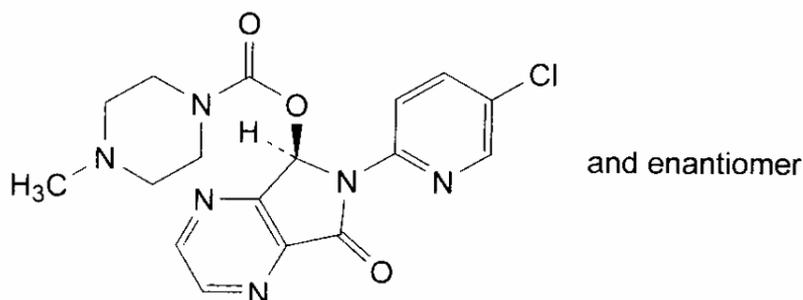
INN: Zopiclone

Chemical names: 6-(5-Chloropyrid-2-yl)-5-(4-methylpiperazin-1-yl)carbonyloxy-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine

CAS Number: 43200-80-2

#### Structure

C<sub>17</sub>H<sub>17</sub>ClN<sub>6</sub>O<sub>3</sub>



Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

All potential known impurities have been identified and characterised.

Active zopiclone is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

The current stability programme for zopiclone will continue at 25°C/60%RH storage condition and updated results will be submitted by the active substance manufacturer. The manufacturer is also committed to incorporate one new batch of Zopiclone annually to the stability programme at 25°C/60%RH storage condition.

## **DRUG PRODUCT**

### **Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely Calcium Hydrogen Phosphate, Sodium Starch Glycolate (Type A), Silicon Dioxide, Potato Starch, Magnesium Stearate, Water Purified, Opadry II 33G28707 White, Hypromellose, titanium dioxide E171, Lactose monohydrate, Macrogol, Glycerol Triacetate.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of silicon dioxide which complies with the USP and Opadry II 33G28707 White in House.

Satisfactory specifications and Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The application has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animal under the same conditions as that for human consumption.

### **Dissolution and Impurity profiles**

Dissolution and impurity profiles for both strengths of drug products were found to be similar to those of the reference products.

### **Manufacture**

A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

### **Finished product specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

### **Container Closure System**

Product is packaged in either blister strip composed of aluminium, PVDC and PVC or in polyethylene (PE) bottle with polypropylene closure (PP). Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with storage condition 'Do not store above 25 degree C', which is satisfactory.

**Conclusion**

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

## **PRECLINICAL ASSESSMENT**

These applications for generic products claim essential similarity to Zimovane tablets 7.5mg (PL 00012/0259), which has been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type.

## CLINICAL ASSESSMENT

### 1. INTRODUCTION

These national abridged applications claim essential similarity to Zimovane PL 00012/0259, May and Baker.

### 2. BACKGROUND

Zopiclone is a benzodiazepine hypnotic.

### 3. INDICATIONS

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.

### 4. DOSE & DOSE SCHEDULE

Long term continuous use is not recommended. A course of treatment should employ the lowest effective dose.

*Adults:* The recommended dose is 7.5 mg zopiclone shortly before retiring.

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

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

*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 3.75 mg.

#### 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.

#### Route of Administration

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

Satisfactory. Consistent with cross-reference product

### 5. TOXICOLOGY

No new data submitted.

**6. CLINICAL PHARMACOLOGY**

The applicant has submitted a single dose randomised cross-over study comparing bioavailability of test and reference product in 32 healthy volunteers with a one week washout period. Plasma levels of both amoxicillin and clavulanic acid were evaluated. Results were as follows:

	Test:reference	90% Confidence limits
$C_{max}$	92.47	86.46 – 98.90
$AUC_{0-t}$	95.81	92.45 – 99.29
$AUC_{0-inf}$	95.74	92.46 – 99.14

The geometric 90% confidence intervals for ratios of  $C_{max}$  and AUC fall within the guideline range 80 – 125%. Although the ratios do not bridge unity, this assessor considers this is clinically therapeutically appropriate for a sedative drug.

**7. EFFICACY**

No new data

**8. SAFETY**

No new data

**9. EXPERT REPORTS**

The applicant has submitted an expert report by an appropriately qualified physician.

**10. PATIENT INFORMATION LEAFLET (PIL)**

Satisfactory.

**11. LABELLING**

Satisfactory

**12. APPLICATION FORM (MAA)**

Medically satisfactory

**13. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

Satisfactory. Consistent with current cross-reference SPCs.

**14. DISCUSSION**

The applicant has demonstrated comparable bioavailability pharmacokinetics, which satisfy the guideline confidence intervals

**15. MEDICAL CONCLUSION**

Marketing Authorisation is recommended.

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The important quality characteristics of Zopiclone 7.5 and 3.75mg film-coated tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for applications of this type.

### **EFFICACY**

No new data were submitted and none are required for applications of this type.

The SPC, PIL and labelling are satisfactory and consistent with that for reference product.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Zopiclone is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is considered to be positive.

**ZOPICLONE 7.5MG FILM-COATED TABLETS  
PL 18909/0159****ZOPICLONE 3.75MG FILM-COATED TABLETS  
PL 18909/0160****STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the marketing authorisation applications on 13 <sup>th</sup> December 2004
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 12 <sup>th</sup> January 2005
3	Following assessment of the application the MHRA requested further information relating to the quality dossiers on 26 <sup>th</sup> October 2005 and 21 <sup>st</sup> of July 2006
4	The applicant responded to the MHRA's requests, providing further information on 21 <sup>st</sup> July 2006 and 21 <sup>st</sup> October 2006.
5	The applications were determined on 2 <sup>nd</sup> February 2007

**SUMMARY OF PRODUCT CHARACTERISTICS****1 NAME OF THE MEDICINAL PRODUCT**

Zopiclone 7.5 mg Film-coated Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains Zopiclone 7.5 mg

For excipients, see 6.1.

**3 PHARMACEUTICAL FORM**

Film-coated tablet.

White, oblong, film-coated tablet with Arrow logo on one side, "Z / 7.5" on the reverse.

Approximately 10 mm x 5 mm

**4 CLINICAL PARTICULARS****4.1 THERAPEUTIC INDICATIONS**

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.

**4.2 POSOLOGY AND METHOD OF ADMINISTRATION**

Long term continuous use is not recommended. A course of treatment should employ the lowest effective dose.

*Adults:* The recommended dose is 7.5 mg zopiclone shortly before retiring.

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

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

*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 3.75 mg.

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.

Route of Administration

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

**4.3 CONTRAINDICATIONS**

Hypersensitivity to the active substance or to any of the excipients. Patients with myasthenia gravis, respiratory failure, severe sleep apnoea syndrome and severe hepatic insufficiency. As with all hypnotics zopiclone should not be used in children.

**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

*Use in hepatic insufficiency:* A reduced dosage is recommended, see posology.

*Use in renal insufficiency:* A reduced dosage is recommended, see posology.

*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 upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol and or drug abuse, or 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 warnings and precautions). 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.

*Depression:* Zopiclone does not constitute a treatment for depression. 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* 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, decreasing the dosage in a stepwise fashion may be helpful.

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.

*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.

*Driving:* It has been reported that the risk of zopiclone adversely affecting driving ability is increased by the concomitant intake of alcohol. Therefore, it is recommended not to drive while taking zopiclone and alcohol concomitantly.

*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 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. Concomitant use of benzodiazepine or benzodiazepine-like agents with narcotic analgesics may enhance their euphoric effect and could 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 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.

#### 4.6 PREGNANCY AND LACTATION

*Use during pregnancy:* Experience of 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. 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.

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, hypnotic 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.

*Use during lactation:* Zopiclone is excreted in breast milk and use in nursing mothers must be avoided.

#### 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Although residual effects are rare and generally of minor significance patients should be advised not to drive or operate machinery the day after treatment until it is established that their performance is unimpaired.

The risk is increased by concomitant intake of alcohol (see section “4.4 Special warnings and special precautions for use”).

#### 4.8 UNDESIRABLE EFFECTS

A mild bitter or metallic after-taste is the most frequently reported adverse effect. Less commonly, mild gastrointestinal disturbances, including nausea and vomiting, dizziness, headache, drowsiness and dry mouth have occurred.

Psychological and behavioural disturbances, such as irritability, aggressiveness, confusion, depressed mood, anterograde amnesia, hallucinations and nightmares have been reported. Rarely these reactions may be severe and may be more likely to occur in the elderly. Rarely allergic and allied manifestations such as urticaria or rashes have been observed and, more rarely, light headedness and incoordination. Angiodema and/or anaphylactic reactions have been reported very rarely.

Mild to moderate increases in serum transaminases and/or alkaline phosphatase have been reported very rarely.

#### 4.9 OVERDOSE

*Overdose* is usually manifested by varying degrees of central nervous system depression ranging from drowsiness to coma according to the quantity ingested. Overdose should not be life-threatening unless combined with other CNS depressants (including alcohol). Symptomatic and supportive treatment in an adequate clinical environment is recommended, attention should be paid to respiratory and cardiovascular functions. Gastric lavage is only useful when performed soon after ingestion. Haemodialysis is of no value due to the large volume of distribution of zopiclone. Flumazenil may be a useful antidote.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 PHARMACODYNAMIC PROPERTIES

Benzodiazepine related drugs. ATC code: N05 CF01

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, anti convulsant 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 inducing 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 3.75 mg and 7.5 mg 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 bindings. The volume of distribution is 91.8-104.6 litres.

At doses between 3.75-15 mg, 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:* The main metabolites are the n-oxide derivative (pharmacologically active in animals) and the n-desmethyl metabolite (pharmacologically inactive in animals). 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 (15 mg) 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 8.4 ml/min) compared with the plasma clearance (232 ml/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 a 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**

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

Calcium Hydrogen Phosphate  
Potato Starch  
Silicon Dioxide  
Sodium Starch Glycollate  
Magnesium Stearate  
Coating:  
Opadry II 33G28707 White, which contains-  
Hypromellose  
Titanium Dioxide (E 171)  
Lactose monohydrate  
Macrogol  
Glycerol triacetate

### **6.2 INCOMPATIBILITIES**

Not applicable

### **6.3 SHELF LIFE**

2 years

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Do not store above 25°C.

### **6.5 NATURE AND CONTENTS OF CONTAINER**

PVC / PVdC / aluminium blister packs. Pack sizes 20, 28, 30, 50, 56, 60, 84, and 100 tablets.

High density polyethylene tablet containers with a polypropylene screw cap fitted with a pressure sensitive innerseal. Pack sizes 30, 1000 tablets.  
Not all pack sizes may be marketed.

### **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Arrow Generics Limited  
Unit 2, Eastman Way  
Stevenage  
Herts SG1 4SZ  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER(S)**

PL 18909/0159

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

02/02/2007

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

02/02/2007

**SUMMARY OF PRODUCT CHARACTERISTICS****1 NAME OF THE MEDICINAL PRODUCT**

Zopiclone 3.75 mg Film-coated Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains Zopiclone 3.75 mg

For excipients, see 6.1.

**3 PHARMACEUTICAL FORM**

Film-coated tablet.

Blue, round, film-coated tablet with Arrow logo on one side, "Z" on the reverse.

Approximately 6 mm diameter

**4 CLINICAL PARTICULARS****4.1 THERAPEUTIC INDICATIONS**

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.

**4.2 POSOLOGY AND METHOD OF ADMINISTRATION**

Long term continuous use is not recommended. A course of treatment should employ the lowest effective dose.

*Adults:* The recommended dose is 7.5 mg zopiclone shortly before retiring.

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

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

*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 3.75 mg.

**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.

**Route of Administration**

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

**4.3 CONTRAINDICATIONS**

Hypersensitivity to the active substance or to any of the excipients. Patients with myasthenia gravis, respiratory failure, severe sleep apnoea syndrome and severe hepatic insufficiency. As with all hypnotics zopiclone should not be

used in children.

#### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

*Use in hepatic insufficiency:* A reduced dosage is recommended, see posology.

*Use in renal insufficiency:* A reduced dosage is recommended, see posology.

*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 upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol and or drug abuse, or 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 warnings and precautions). 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.

*Depression:* Zopiclone does not constitute a treatment for depression. 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* 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, decreasing the dosage in a stepwise fashion may be helpful.

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.

*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.

*Driving:* It has been reported that the risk of zopiclone adversely affecting driving ability is increased by the concomitant intake of alcohol. Therefore, it is recommended not to drive while taking zopiclone and alcohol concomitantly.

*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 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. Concomitant use of benzodiazepine or benzodiazepine-like agents with narcotic analgesics may enhance their euphoric effect and could 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 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.

#### **4.6 PREGNANCY AND LACTATION**

*Use during pregnancy:* Experience of 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. 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.

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, hypnotic 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.

*Use during lactation:* Zopiclone is excreted in breast milk and use in nursing Mothers must be avoided.

#### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

Although residual effects are rare and generally of minor significance patients should be advised not to drive or operate machinery the day after treatment until it is established that their performance is unimpaired.

The risk is increased by concomitant intake of alcohol (see section "4.4 Special warnings and special precautions for use").

#### **4.8 UNDESIRABLE EFFECTS**

A mild bitter or metallic after-taste is the most frequently reported adverse effect. Less commonly, mild gastrointestinal disturbances, including nausea and vomiting, dizziness, headache, drowsiness and dry mouth have occurred.

Psychological and behavioural disturbances, such as irritability, aggressiveness, confusion, depressed mood, anterograde amnesia, hallucinations and nightmares have been reported. Rarely these reactions may be severe and may be more likely to occur in the elderly. Rarely allergic and allied manifestations such as urticaria or rashes have been observed and, more rarely, light headedness and incoordination. Angiodema and/or anaphylactic reactions have been reported very rarely.

Mild to moderate increases in serum transaminases and/or alkaline phosphatase have been reported very rarely.

#### 4.9 OVERDOSE

*Overdose* is usually manifested by varying degrees of central nervous system depression ranging from drowsiness to coma according to the quantity ingested. Overdose should not be life-threatening unless combined with other CNS depressants (including alcohol). Symptomatic and supportive treatment in an adequate clinical environment is recommended, attention should be paid to respiratory and cardiovascular functions. Gastric lavage is only useful when performed soon after ingestion. Haemodialysis is of no value due to the large volume of distribution of zopiclone. Flumazenil may be a useful antidote.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 PHARMACODYNAMIC PROPERTIES

Benzodiazepine related drugs. ATC code: N05 CF01

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, anti convulsant 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 inducing 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 3.75 mg and 7.5 mg 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 bindings. The volume of distribution is 91.8-104.6 litres.

At doses between 3.75-15 mg, 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:* The main metabolites are the n-oxide derivative (pharmacologically active in animals) and the n-desmethyl metabolite (pharmacologically inactive in animals). 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 (15 mg) 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 8.4 ml/min) compared with the plasma clearance (232 ml/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 a 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

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Calcium Hydrogen Phosphate  
Potato Starch  
Silicon Dioxide  
Sodium Starch Glycollate  
Magnesium Stearate  
Coating:  
Opadry II 85F20683 Blue, which contains-  
Polyvinyl alcohol  
Titanium Dioxide (E 171)  
Macrogol  
Talc  
Brilliant Blue FCF (E133)

### 6.2 INCOMPATIBILITIES

Not applicable

### 6.3 SHELF LIFE

2 years

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

### 6.5 NATURE AND CONTENTS OF CONTAINER

PVC / PVdC / aluminium blister packs. Pack sizes 20, 28, 30, 50, 56, 60, 84, 100 tablets.

High density polyethylene tablet containers with a polypropylene screw cap fitted with a pressure sensitive innerseal. Pack sizes 30, 1000 tablets.

Not all pack sizes may be marketed.

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**  
No special requirements.

**7 MARKETING AUTHORISATION HOLDER**  
Arrow Generics Limited  
Unit 2, Eastman Way  
Stevenage  
Herts SG1 4SZ  
United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**  
PL 18909/0160

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
02/02/2007

**10 DATE OF REVISION OF THE TEXT**  
02/02/2007

## PATIENT INFORMATION LEAFLET

**Zopiclone 3.75 & 7.5 mg Tablets**

Read this leaflet carefully before you start taking this medicine even if you have only collected a repeat prescription. This leaflet contains information about your medicine. This medicine has been prescribed for you personally and you should NOT pass it on to others. It may harm them, even if their symptoms are the same as yours. You may wish to keep this leaflet, as you may want to read it again. If you have further questions, please ask your doctor or your pharmacist.

## In this leaflet:

1. What Zopiclone Tablets are and what they are used for
2. Before you take Zopiclone Tablets
3. How to take Zopiclone Tablets
4. Possible side effects
5. How to store Zopiclone Tablets

The active substance in your medicine is zopiclone. The other ingredients are calcium hydrogen phosphate; sodium starch glycolate; silicon dioxide; potato starch; magnesium stearate. The 3.75 mg tablets are coated with Opadry II 85F20683 Blue which contains polyvinyl alcohol, titanium dioxide (E 171), macrogol, talc and Brilliant Blue FCF (E 133). The 7.5 mg tablets are coated with Opadry II 33G28707 White which contains hypromellose, titanium dioxide (E 171), lactose monohydrate, macrogol and glycerol triacetate.

**Marketing Authorisation Holder:** Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, UK

**Manufacturer:** Arrow Generics, Unit 4 Willsborough Cluster, Clonsbaugh Industrial Estate, Dublin 17, Ireland

**1. WHAT ZOPICLONE TABLETS ARE AND WHAT THEY ARE USED FOR**

Your medicine is available in two strengths of film-coated tablets containing 3.75 mg or 7.5 mg of zopiclone.

The 3.75 mg tablet is blue, round, film-coated and marked with 'Z' on one side and "Σ" on the reverse.

The 7.5 mg tablet is white, oblong, film-coated and marked with 'Z / 7.5' on one side and "Σ" on the reverse.

The tablets are available in blister packs (3.75mg and 7.5mg) of 20, 28, 30, 50, 56, 60, 84, 100 tablets and HDPE containers (7.5mg only) of 30 and 1000 tablets.

Zopiclone belongs to a group of medicines called hypnotics. Zopiclone is used for short term treatment of insomnia. Insomnia is a word used to describe several problems, including difficulty getting to sleep, broken sleep and early waking. Zopiclone should help you sleep, without making you feel drowsy the next day.

**2. BEFORE YOU TAKE ZOPICLONE TABLETS**

Do not take your medicine and tell your doctor if:-

- You have had an allergic reaction to zopiclone or any of the other ingredients (check by reading the list above).
- You have a condition that causes muscle weakness called myasthenia gravis.
- You have any breathing problems or a condition called sleep apnoea syndrome.
- You have any liver problems.
- You are pregnant, trying to become pregnant, or are breastfeeding.
- The tablets are to be given to a child.

Tell your doctor before you start taking your medicine if:-

- You have any liver or kidney problems.
- You have a personality disorder.
- You have been addicted to alcohol or any other drug.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Zopiclone 7.5 mg Tablets.

Tell your doctor if you are taking any of the following medicines:-

- Erythromycin, an antibiotic.
- Any other medicines that work on the brain or nervous system including medicines for mental illness (e.g. chlorpromazine, flupentixol, haloperidol, prochlorperazine); sedatives or medicines for anxiety (e.g. nitrazepam, diazepam, lorazepam); medicines for depression (e.g. amitriptyline, clomipramine, lofepramine); or medicines for epilepsy (e.g. carbamazepine, phenobarbital, phenytoin).
- Antihistamines with a sedative effect (e.g. chlorphenamine & chlorpheniramine, hydroxyzine, promethazine).
- Narcotic pain-killers (e.g. codeine, morphine, dihydrocodeine).
- Medicines that inhibit liver enzymes (if the other medicine you are taking affects liver enzymes, the information leaflet should give an explanation).

If you are going into hospital for an operation, tell the doctor that you are taking Zopiclone Tablets.

Do not take any other medicines whilst you are taking Zopiclone Tablets without asking your doctor or pharmacist first. This includes medicines that can be bought without a prescription.

**Pregnancy**

Zopiclone Tablets are not recommended for use during pregnancy or whilst breast-feeding.

**Driving**

Some patients feel drowsy the morning after taking zopiclone. Do not attempt skilled tasks such as driving or using dangerous machinery unless you are sure you are not affected.

**Alcohol**

Alcohol affects the way zopiclone works and you should not drink alcohol whilst taking these tablets.

**3. HOW TO TAKE ZOPICLONE TABLETS**

Always take this medicine as prescribed by your doctor. Do not take more than your doctor told you to. Read and follow the instructions on the pharmacist's label. If you're not sure about anything please ask your doctor or pharmacist.

The usual dose is one 7.5 mg tablet shortly before going to bed.

If you are elderly the usual dose is one 3.75 mg tablet shortly before going to bed.

If you have liver or kidney disease, the usual starting dose is one 3.75 mg tablet shortly before going to bed.

Zopiclone Tablets are not for use in children.

Swallow your tablet whole without sucking, chewing or breaking.

Your doctor will only prescribe you zopiclone for a short period of time – no more than 4 weeks. If you take zopiclone for longer than this, the medicine may not work as well; you may become dependent; and you may have withdrawal symptoms when you stop taking the tablets.

Only take this medicine when you want to go to sleep. If you forget to take your medicine do not try to catch up the missed dose. Take your next tablet at the usual time.

If you take more tablets than you should, contact your doctor immediately or go to the nearest hospital casualty department. Take the pack and any remaining tablets with you, if you still have them.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Zopiclone Tablets can have unwanted side effects.

The most commonly reported side effect is a bitter or metallic after-taste. Less commonly, stomach upsets including nausea and vomiting, dizziness, headache, drowsiness, and dry mouth.

Effects on mood and behaviour have been reported such as irritability, aggressiveness, confusion, depressed mood, memory loss, hallucinations, and nightmares. These reactions are more likely to occur in the elderly. Rarely, they may be severe.

Rarely, allergic reactions such as rash or reddening and swelling of the skin; and more rarely lightheadedness and poor coordination have been seen.

There have been very rare reports of more serious allergic reactions such as anaphylactic shock and angioedema (symptoms include difficulty breathing and red wheals on the body).

Very rarely, changes in blood enzymes have been reported.

Tell your doctor if you notice any other side effects not mentioned in this leaflet or a change in your general health whilst taking Zopiclone Tablets.

**5. HOW TO STORE ZOPICLONE TABLETS**

Keep medicines out of the reach and sight of children.

Do not take after the expiry date on the carton or label.

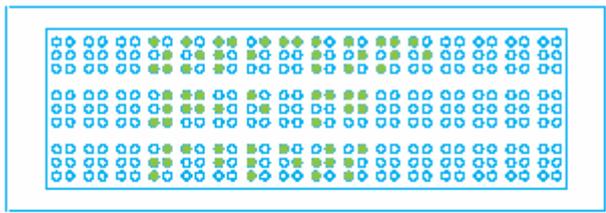
Blister Packs: Do not store your Zopiclone Tablets above 25°C. Store in the original package.

HDPE/PP Containers (only available for 7.5 mg tablets): Do not store above 25°C. Keep the container tightly closed.

If you notice any visible signs of deterioration in the tablets, such as chipped, broken or discoloured tablets, take them to your pharmacist for advice before taking them.

If you have any tablets left after taking all the doses prescribed to you, please return these to your pharmacist.

Leaflet Approved: March 2007

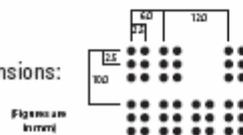


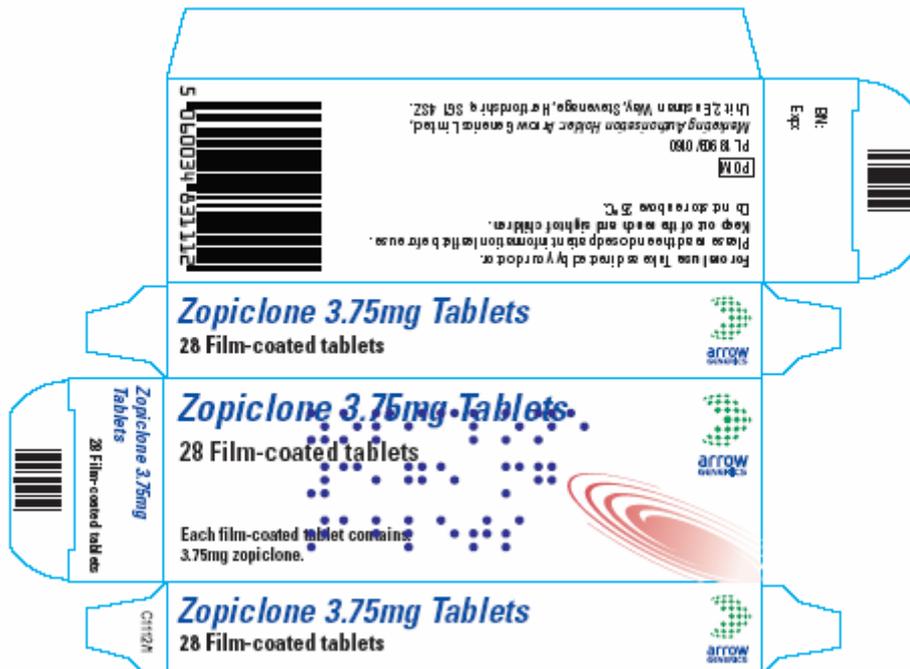
Outline of front panel showing female (universal) die position (cyan circles) overlaid with male die position (green dots).

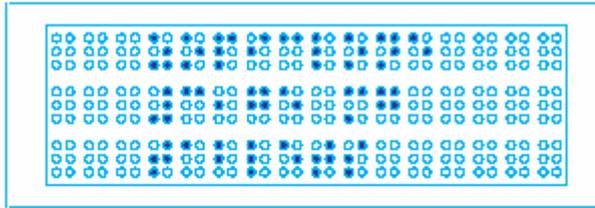
Braille text reads as follows in English:

z o p i c l o n e  
 # 7 . 5 m g (Note: # = number sign)  
 t a b l e t s

Note: dies comply with Marburg Medium cell dimensions:







Outline of front panel showing female (universal) die position (cyan circles) overlaid with male die position (blue dots).

Braille text reads as follows in English:

z o p i c l o n e

# 3 . 7 5 m g (Note: # = number sign)

t a b l e t s

Note: dies comply with Marburg Medium cell dimensions:

