ZOLPIDEM 5MG TABLETS
PL 18909/0062
ZOLPIDEM 10MG TABLETS
PL 18909/0063

UKPAR

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The MHRA granted Arrow Generics Limited Marketing Authorisations (licences) for the medicinal product Zolpidem 5 and 10mg Tablets on 1st April 2010. These products, to be available by prescription only (POM) contain zolpidem tartrate and are used to help you sleep.

Zolpidem tartrate belongs to a group of medicines called hypnotics (sleep producers). These medicines work by acting on the brain to cause sedation.

No new or unexpected safety concerns arose from these generic abridged applications and it was, therefore, judged that the benefits of taking Zolpidem 5 and 10mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.
ZOLPIDEM 5MG TABLETS
PL 18909/0062
ZOLPIDEM 10MG TABLETS
PL 18909/0063

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Zolpidem 5 and 10mg Tablets (PL 18909/0062-3) could be approved.

The products are prescription-only medicines for the short term treatment of insomnia and situations where the insomnia is debilitating or is causing severe distress for the patient.

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Stilnox Tablets 5 and 10mg, which were originally granted licences in June 1987 to Synthelabo in France.

Zolpidem tartrate is a non-benzodiazepine hypnotic agent of the imidazopyridine class that binds selectively to the benzodiazepine \( \omega_1 \) receptor subtype of the GABA\(_A\) receptor in the central nervous system. It is indicated for the short term treatment of insomnia in situations where the insomnia is debilitating or is causing severe distress for the patient.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.
PHARMACEUTICAL ASSESSMENT

S. Active substance

INN: Zolpidem tartrate
Chemical name: bis[N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide](2R,3R)-2,3-dihydroxybutanedioate

Structure:

![Structure Diagram]

Molecular formula: \((C_{19}H_{21}N_{3}O)_{2}, C_{4}H_{6}O_{6}\)
Molecular weight: 765
Appearance: White or almost white, hygroscopic, crystalline powder

Zolpidem tartrate is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials 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.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
P. Medicinal Product
Other Ingredients
Other ingredients consist of the pharmaceutical excipients lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, talc, magnesium stearate, hypromellose, hydroxypropylcellulose and titanium dioxide.

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

With the exception of lactose monohydrate and magnesium stearate, none of the excipients are sourced from animal or human origin. A European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability has been provided by the supplier of magnesium stearate to show that it is manufactured in-line with current guidelines concerning the minimisation of transmission of BSE/TSE. The supplier of lactose monohydrate has confirmed that the lactose used is sourced from healthy animals, under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent tablet dosage form containing zolpidem tartrate that was comparable to Stilnox Tablets 5 and 10mg (Synthelabo, France).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
All strengths of tablets are packaged in polyvinylchloride/aluminium foil blister strips, which are enclosed in an outer carton. Each carton contains 28 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.
Stability of the product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with the storage conditions “Do not store above 25°C. Store in the original packaging.”

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.
**PRECLINICAL ASSESSMENT**

As the pharmacodynamic, pharmacokinetic and toxicological properties of zolpidem tartrate are well-known, no further preclinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a preclinical viewpoint.
CLINICAL ASSESSMENT

Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Zolpidem 10mg Tablets versus the reference product Stilnox 10mg Tablets (Sanofi-Synthelabo Limited, UK) in healthy adult volunteers under fasted conditions.

Volunteers were dosed with either treatment after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 24 hours post dose. The two treatment arms were separated by a 7-day washout period.

The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Reference</th>
<th>Test</th>
<th>90% Confidence Interval</th>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>146.5</td>
<td>139.1</td>
<td>83-107</td>
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<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/mL)</td>
<td>542.5</td>
<td>519.5</td>
<td>83-99</td>
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<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.h/mL)</td>
<td>551.9</td>
<td>527.6</td>
<td>83-98</td>
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<tr>
<td>Tmax (h)</td>
<td>0.86</td>
<td>0.83</td>
<td>80-113</td>
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The 90% confidence intervals for C<sub>max</sub> and AUC for test versus reference products are within predefined acceptance criteria. The data support the claim that the test product is bioequivalent to the reference product.

As the 5 and 10mg strengths of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the extrapolation of results and conclusions from the bioequivalence study on the 10mg strength to the 5mg strength is justified.

Efficacy
No new data on the efficacy have been submitted and none are required for these types of applications.

Safety
No new or unexpected safety issues were raised by the bioequivalence data.

SPC, PIL, Labels
The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of marketing authorisations is recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Zolpidem 5 and 10mg 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 risk-benefit balance.

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

EFFICACY
Bioequivalence has been demonstrated between the applicant’s 10mg Tablets and its respective reference product. As the 5mg and 10mg strengths of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength can be extrapolated to the 5mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with zolpidem tartrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

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<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation applications on 8\textsuperscript{th} October 2001</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 20\textsuperscript{th} March 2006</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 5\textsuperscript{th} December 2006, 15\textsuperscript{th} February 2008 and 12\textsuperscript{th} September 2008.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 25\textsuperscript{th} October 2007, 14\textsuperscript{th} April 2008 and 11\textsuperscript{th} February 2009.</td>
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<td>The applications were determined on 1\textsuperscript{st} April 2010.</td>
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ZOLPIDEM 5MG TABLETS  
PL 18909/0062  
ZOLPIDEM 10MG TABLETS  
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STEPS TAKEN AFTER ASSESSMENT

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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ZOLPIDEM 5MG TABLETS
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ZOLPIDEM 10MG TABLETS
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Zolpidem 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg Zolpidem tartrate.
For excipients, see 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Round white film-coated tablets, embossed “5” on one face.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
The short term treatment of insomnia and situations where the insomnia is debilitating or is causing severe distress for the patient.

4.2 Posology and method of administration
Route of administration: Oral

Zolpidem acts rapidly and therefore should be taken immediately before retiring, or in bed.

The recommended daily dose for adults is 10 mg. Elderly or debilitated patients may be especially sensitive to the effects of zolpidem and so a 5 mg dose is recommended for these patient groups. The recommended doses should not be exceeded.

Clearance and metabolism of zolpidem are reduced in hepatic impairment. Dosage should begin at 5 mg, with particular caution being exercised in elderly patients. In adults (under 65 years) dosage may be increased to 10 mg only where the clinical response is inadequate and the drug is well tolerated.

The duration of treatment should usually vary from a few days to two weeks with a maximum of four weeks including tapering off where clinically appropriate.

As with all hypnotics, long term use is not recommended and a course of treatment should not exceed four weeks.

Zolpidem is not suitable for use in children.

4.3 Contraindications
Zolpidem is contraindicated in patients with a hypersensitivity to zolpidem, obstructive sleep apnoea, myasthenia gravis, severe hepatic insufficiency, acute pulmonary insufficiency or respiratory depression. Zolpidem should not be prescribed for children or patients with psychotic illness.

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. The failure of insomnia to remit after a 7-14 day course of treatment may indicate the presence of a primary psychiatric or physical disorder which should be evaluated.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in depression: As with other sedative/hypnotic drugs, zolpidem should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present. The least amount of the drug that is practical should be supplied to these patients because of the possibility of intentional overdose by the patient.

Use in patients with a history of drug or alcohol abuse: Extreme caution should be exercised when prescribing for patients with a history of drug or alcohol abuse. These patients should be kept under careful surveillance when receiving Zolpidem or any other hypnotic, since they are at risk of habituation and psychological dependence.

General information relating to the hypnotic effects seen following administration of benzodiazepines and other hypnotic agents which should be taken into account by the prescribing physician are described below.

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

**Dependence**
Use of benzodiazepines or benzodiazepine-like agents may lead to the development of physical or psychological dependence of these products. The risk of dependence increased with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety and tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

**Rebound insomnia**
This is a transient syndrome in which the symptoms that led to treatment with benzodiazepine or benzodiazepine-like agents recur in an enhanced form may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

It is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur when the medicinal product is discontinued. Since the risk of withdrawal phenomena or rebound has been shown to be greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually where clinically appropriate.

**Amnesia**
Benzodiazepines or benzodiazepine-like agents may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product. To reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 7-9 hours.

**Psychiatric and “paradoxical” reactions**
Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepine or benzodiazepine-like agents. Should any of these occur, use of the product should be discontinued. These reactions are more likely to occur in the elderly.
4.5 Interaction with other medicinal products and other forms of interaction

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

Combination requiring caution
Combination with CNS depressants – enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, antiepileptic drugs, anaesthetics and sedative antihistamines.

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

Compounds which inhibit certain hepatic enzymes (particularly cytochrome p450) may also enhance the activity of benzodiazepines and benzodiazepine-like agents.

4.6 Pregnancy and lactation

Although animal studies have shown no teratogenic or embryotoxic effects, safety in pregnancy has not been established. As with all drugs Zolpidem should be avoided in pregnancy particularly during the first trimester.

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her doctor about stopping the product if she intends or suspects she is pregnant.

If, for compelling medical reasons, zolpidem is administered during the late phase of pregnancy, or during labour, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected due to the pharmacological action of the product.

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

Small quantities of zolpidem occur in breast milk. The use of zolpidem in nursing mothers is, therefore, not recommended.

4.7 Effects on ability to drive and use machines

Although studies have shown that during the day following medication with zolpidem, simulated vehicle driving is unaffected, vehicle drivers and machine operators should be warned that, as with other hypnotics, there is a possible risk of drowsiness the morning after therapy.

4.8 Undesirable effects

There is evidence of a dose-relationship for adverse effects associated with zolpidem use, particularly for certain CNS and gastrointestinal events. These occur most frequently in elderly patients.

In clinical trials side effects observed during the treatment at doses up to 10 mg included drowsiness, dizziness, diarrhoea, headache, nausea and vertigo.

Daytime drowsiness, dizziness, headache, asthenia, nausea and vomiting occasionally led to withdrawal of treatment in clinical trials of zolpidem.

Memory disturbance (anterograde amnesia), nightmares, nocturnal restlessness, depressive syndrome, episodes of confusion, perceptual disturbances or diplopia, tremor, unsteady gait and falls have been observed rarely in long-term clinical trials.
4.9 Overdose
In reports of overdose with zolpidem alone, impairment of consciousness has ranged from somnolence to light coma. Individuals have fully recovered from zolpidem overdoses up to 400 mg, 40 times the recommended dose.

General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate; intravenous fluids should be administered as needed. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Sedating drugs should be withheld even if excitation occurs. Use of flumazenil may be considered where serious symptoms are observed.

In the management of overdose with any medical product, it should be borne in mind that multiple agents may have been taken.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: GABA-A receptor agonist selective for omega-1-type-sub-unit hypnotic agent.

ATC-Code: N05C F02

Zolpidem is an imidazopyridine which selectively binds the omega-1 receptor subtype (also know as the benzodiazepam-1 subtype) which is the alpha unit of the GABA-A receptor complex. Whereas benzodiazepines non-selectively bind all three omega receptor subtypes, zolpidem preferentially binds the omega-1 subtype. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem. These effects are reversed by the benzodiazepine antagonist flumazenil.

In animals: The selective binding of zolpidem to omega-1 receptors may explain the virtual absence at hypnotic doses of myorelaxant and anticonvulsant effects in animals which are normally exhibited by benzodiazepines which are not selective for omega-1 sites.

In humans: The preservation of deep sleep (stages 3 and 4 – slow-wave sleep) may be explained by the selective omega-1 binding by zolpidem. All identified effects of zolpidem are reversed by benzodiazepine antagonist flumazenil.

5.2 Pharmacokinetic properties
Zolpidem has both a rapid absorption and onset of hypnotic action. Bioavailability is 70% following oral administration and demonstrates linear kinetics in the therapeutic dose range. Peak plasma concentration is reached between 0.5 and 3 hours.

The elimination half-life is short, with a mean of 2.4 hours (0.7-3.5) and duration of action of up to 6 hours.

Protein binding amounts to 92.5 ± 0.1%. First pass metabolism by the liver amounts to approximately 35%. Repeated administration has been shown not to modify protein indicating a lack of competition between zolpidem and its metabolites for binding sites.

The distribution volume in adults is 0.54 + 0.2 L/kg and decreases to 0.34 + 0.05 L/kg in the very elderly.

All metabolites are pharmacologically inactive and are eliminated in the urine (56%) and in the faeces (37%).

Zolpidem has been shown in trials to be non-dialysable.

Plasma concentrations in elderly subjects and those with hepatic impairment are increased. In patients with renal insufficiency, whether dialysed or not, there is a moderate reduction in clearance. The other pharmacokinetic parameters are unaffected.
5.3 Preclinical safety data
No data of therapeutic relevance.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Talc
Magnesium stearate

Film coating:
Hyromellose
Hydroxypropylcellulose
Titanium dioxide (E171)
Talc

6.2 Incompatibilities
None known.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 25°C. Store in the original packaging.

6.5 Nature and contents of container
Cartons of 28 tablets in transparent PVC and aluminium foil blister strips. The blister packs are enclosed in an outer carton.

6.6 Special precautions for disposal
No special requirements.

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

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0062 POM

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/04/2010

10 DATE OF REVISION OF THE TEXT
01/04/2010
1 NAME OF THE MEDICINAL PRODUCT
Zolpidem 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg Zolpidem tartrate.
For excipients, see 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Capsule-shaped, white film-coated tablets, embossed “Z” and “10” on one face, either side of a centre breakline. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
The short term treatment of insomnia and situations where the insomnia is debilitating or is causing severe distress for the patient.

4.2 Posology and method of administration
Route of administration: Oral

Zolpidem acts rapidly and therefore should be taken immediately before retiring, or in bed.

The recommended daily dose for adults is 10 mg. Elderly or debilitated patients may be especially sensitive to the effects of zolpidem and so a 5 mg dose is recommended for these patient groups. The recommended doses should not be exceeded.

Clearance and metabolism of zolpidem are reduced in hepatic impairment. Dosage should begin at 5 mg, with particular caution being exercised in elderly patients. In adults (under 65 years) dosage may be increased to 10 mg only where the clinical response is inadequate and the drug is well tolerated.

The duration of treatment should usually vary from a few days to two weeks with a maximum of four weeks including tapering off where clinically appropriate.

As with all hypnotics, long term use is not recommended and a course of treatment should not exceed four weeks.

Zolpidem is not suitable for use in children.

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Zolpidem is contraindicated in patients with a hypersensitivity to zolpidem, obstructive sleep apnoea, myasthenia gravis, severe hepatic insufficiency, acute pulmonary insufficiency or respiratory depression. Zolpidem should not be prescribed for children or patients with psychotic illness.

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The cause of insomnia should be identified wherever possible and the underlying factors treated before a hypnotic is prescribed. The failure of insomnia to remit after a 7-14 day course of treatment may indicate the presence of a primary psychiatric or physical disorder which should be evaluated.

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Use in patients with a history of drug or alcohol abuse: Extreme caution should be exercised when prescribing for patients with a history of drug or alcohol abuse. These patients should be kept under careful surveillance when receiving Zolpidem or any other hypnotic, since they are at risk of habituation and psychological dependence.

General information relating to the hypnotic effects seen following administration of benzodiazepines and other hypnotic agents which should be taken into account by the prescribing physician are described below.

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

Dependence
Use of benzodiazepines or benzodiazepine-like agents may lead to the development of physical or psychological dependence of these products. The risk of dependence increased with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety and tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound insomnia
This is a transient syndrome in which the symptoms that led to treatment with benzodiazepine or benzodiazepine-like agents recur in an enhanced form may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

It is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur when the medicinal product is discontinued. Since the risk of withdrawal phenomena or rebound has been shown to be greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually where clinically appropriate.

Amnesia
Benzodiazepines or benzodiazepine-like agents may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product. To reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 7-9 hours.

Psychiatric and “paradoxical” reactions
Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepine or benzodiazepine-like agents. Should any of these occur, use of the product should be discontinued. These reactions are more likely to occur in the elderly.

4.5 Interaction with other medicinal products and other forms of interaction
Not recommended
Concomitant intake with alcohol – the sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Combination requiring caution
Combination with CNS depressants – enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, antiepileptic drugs, anaesthetics and sedative antihistamines.
In the case of narcotic analgesics, enhancement of euphoria may also occur leading to an increase in psychological dependence.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome p450) may also enhance the activity of benzodiazepines and benzodiazepine-like agents.

4.6 Pregnancy and lactation

Although animal studies have shown no teratogenic or embryotoxic effects, safety in pregnancy has not been established. As with all drugs Zolpidem should be avoided in pregnancy particularly during the first trimester.

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her doctor about stopping the product if she intends or suspects she is pregnant.

If, for compelling medical reasons, zolpidem is administered during the late phase of pregnancy, or during labour, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected due to the pharmacological action of the product.

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

Small quantities of zolpidem occur in breast milk. The use of zolpidem in nursing mothers is, therefore, not recommended.

4.7 Effects on ability to drive and use machines

Although studies have shown that during the day following medication with zolpidem, simulated vehicle driving is unaffected, vehicle drivers and machine operators should be warned that, as with other hypnotics, there is a possible risk of drowsiness the morning after therapy.

4.8 Undesirable effects

There is evidence of a dose-relationship for adverse effects associated with zolpidem use, particularly for certain CNS and gastrointestinal events. These occur most frequently in elderly patients.

In clinical trials side effects observed during the treatment at doses up to 10 mg included drowsiness, dizziness, diarrhoea, headache, nausea and vertigo.

Daytime drowsiness, dizziness, headache, asthenia, nausea and vomiting occasionally led to withdrawal of treatment in clinical trials of zolpidem.

Memory disturbance (anterograde amnesia), nightmares, nocturnal restlessness, depressive syndrome, episodes of confusion, perceptual disturbances or diplopia, tremor, unsteady gait and falls have been observed rarely in long-term clinical trials.

4.9 Overdose

In reports of overdose with zolpidem alone, impairment of consciousness has ranged from somnolence to light coma. Individuals have fully recovered from zolpidem overdoses up to 400 mg, 40 times the recommended dose.

General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate; intravenous fluids should be administered as needed. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Sedating drugs should be withheld even if excitation occurs. Use of flumazenil may be considered where serious symptoms are observed.
In the management of overdose with any medical product, it should be borne in mind that multiple agents may have been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: GABA-A receptor agonist selective for omega-1-type-sub-unit hypnotic agent.

ATC-Code: N05C F02

Zolpidem is an imidazopyridine which selectively binds the omega-1 receptor subtype (also know as the benzodiazepam-1 subtype) which is the alpha unit of the GABA-A receptor complex. Whereas benzodiazepines non-selectively bind all three omega receptor subtypes, zolpidem preferentially binds the omega-1 subtype. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem. These effects are reversed by the benzodiazepine antagonist flumazenil.

In animals: The selective binding of zolpidem to omega-1 receptors may explain the virtual absence at hypnotic doses of myorelaxant and anticonvulsant effects in animals which are normally exhibited by benzodiazepines which are not selective for omega-1 sites.

In humans: The preservation of deep sleep (stages 3 and 4 – slow-wave sleep) may be explained by the selective omega-1 binding by zolpidem. All identified effects of zolpidem are reversed by benzodiazepine antagonist flumazenil.

5.2 Pharmacokinetic properties

Zolpidem has both a rapid absorption and onset of hypnotic action. Bioavailability is 70% following oral administration and demonstrates linear kinetics in the therapeutic dose range. Peak plasma concentration is reached between 0.5 and 3 hours.

The elimination half-life is short, with a mean of 2.4 hours (0.7-3.5) and duration of action of up to 6 hours.

Protein binding amounts to 92.5 ± 0.1%. First pass metabolism by the liver amounts to approximately 35%. Repeated administration has been shown not to modify protein indicating a lack of competition between zolpidem and its metabolites for binding sites.

The distribution volume in adults is 0.54 ± 0.2 L/kg and decreases to 0.34 ± 0.05 L/kg in the very elderly.

All metabolites are pharmacologically inactive and are eliminated in the urine (56%) and in the faeces (37%).

Zolpidem has been shown in trials to be non-dialysable.

Plasma concentrations in elderly subjects and those with hepatic impairment are increased. In patients with renal insufficiency, whether dialysed or not, there is a moderate reduction in clearance. The other pharmacokinetic parameters are unaffected.

5.3 Preclinical safety data

No data of therapeutic relevance.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Talc
Magnesium stearate

Film coating:
Hyromellose
Hydroxypropylcellulose
Titanium dioxide (E171)
Talc

6.2 Incompatibilities
None known.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 25°C. Store in the original packaging.

6.5 Nature and contents of container
Cartons of 28 tablets in transparent PVC and aluminium foil blister strips.
The blister packs are enclosed in an outer carton.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 18909/0063 POM

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/04/2010

10 DATE OF REVISION OF THE TEXT

01/04/2010
UKPAR Zolpidem 5 and 10mg Tablets
PL 18909/0062-3

PATIENT INFORMATION LEAFLET

Zolpidem 5mg Tablets
Zolpidem 10mg Tablets
(Zolpidem tartrate)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Zolpidem Tablets are and what they are used for
2. Before you take Zolpidem Tablets
3. How to take Zolpidem Tablets
4. Possible side effects
5. How to store Zolpidem Tablets
6. Further Information

1. WHAT ZOLPIDEM TABLETS ARE AND WHAT THEY ARE USED FOR

Your tablets contain zolpidem tartrate, which belongs to a group of medicines called hypnotics (sleep producing). These medicines work by acting on the brain to cause sleep.

Your doctor has prescribed Zolpidem Tablets to help you sleep. Sleeping problems do not usually last long and most people only need a short course of treatment.

2. BEFORE YOU TAKE ZOLPIDEM TABLETS

Do not take Zolpidem Tablets:
- If you are allergic (hypersensitive) to zolpidem tartrate
- If you are allergic to any of the other ingredients of Zolpidem Tablets (these are listed in section 6. Further Information)
- If you have breathing difficulties
- If you have sleep apnoea (stopping breathing for short periods while asleep)
- If you have liver disease
- If you have a muscle disease called "myasthenia gravis"

Take special care with Zolpidem Tablets

Talk to your doctor before taking the tablets if any of the following apply to you:
- If you are pregnant or intend to become pregnant, or if you are breast feeding (see section on Pregnancy and breast feeding, below).
- If you have ever been addicted to or have abused drugs or alcohol.

Taking other medicines

When Zolpidem Tablets are taken with the following medicines, they may make you feel drowsier than normal. Tell your doctor if you are taking:
- medicines to control abnormal behaviour (antipsychotics),
- medicines to help you sleep (hypnotics),
- medicines to prevent amnesia (anticonvulsants),
- medicines to make you feel calm (sedatives),
- medicines for depression,
- strong painkillers (narcotic analgesics),
- medicines for epilepsy,
- antihistamines (allergy treatments).

Tell your doctor or dentist that you are taking Zolpidem tablets if you are going to be given an anaesthetic.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Zolpidem Tablets with food and drink

Swallow your tablets whole and take with a small glass of water.

Do not drink alcohol while you are being treated with Zolpidem Tablets. Alcohol can increase the side effects of any sleeping medicine.

Pregnancy and breast feeding

Zolpidem Tablets should only be taken if your doctor decides that it is absolutely necessary. Tell your doctor if you are pregnant, trying to become pregnant or think you may be pregnant.

This medicine can be passed into breast milk. You should not take Zolpidem Tablets whilst breast feeding, unless you are told by your doctor.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

After taking Zolpidem Tablets you may feel drowsy. If you are affected in this way, you should avoid driving or using machines.

Important information about some of the ingredients of Zolpidem Tablets

These tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
UKPAR Zolpidem 5 and 10mg Tablets

3. HOW TO TAKE ZOLPIDEM TABLETS

Always take Zolpidem Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Zolpidem Tablets work quickly and should be taken when you are ready to go into bed and go to sleep. Your tablets should be taken by mouth and swallowed whole (do not chew), with Elderly or infirm adults.

The usual daily dose is one 5mg tablet.

Your doctor will tell you what dose you should be taking.

Do not use Zolpidem Tablets or any other sleeping medicine for longer than your doctor tells you to.

Zolpidem Tablets are not recommended for children.

If you take more Zolpidem Tablets than you should

If you (or someone else), has taken too many tablets, contact your doctor or hospital casualty department immediately for advice.

If you have taken too many tablets, you will become increasingly sleepy very quickly. If you go to the hospital or doctors surgery, do not go on your own – ask someone to take you and take the container and the remaining tablets with you.

If you forget to take Zolpidem Tablets

Do not take the missed dose unless you have a full 7–8 hours before you have to wake up. Do not take a double dose to make up for the one you missed.

If you stop taking Zolpidem Tablets

Do not stop taking your Zolpidem Tablets without speaking to your doctor first. You may experience side effects if you stop your medication suddenly.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Zolpidem Tablets can cause side effects, although not everybody gets them.

Side effects can include:
- dizziness
- drowsiness
- weakness
- nausea and/or vomiting (feeling or being sick).

In rare cases you may experience:
- memory difficulties
- nightmares
- restlessness at night
- tremor (shaking)
- depression
- irritability
- inappropriate behavior
- ophthalmic problems

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ZOLPIDEM TABLETS

Keep out of the reach and sight of children.

Do not store above 25°C. Store in the original package to protect from light.

Do not use after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

What Zolpidem Tablets contain
- The active substance in Zolpidem tartrate is 5mg or 10mg.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, hypromellose, hydroxypropylcellulose, titanium dioxide (E171) and talc.

What Zolpidem Tablets look like and contents of the pack

Your medicine is in the form of a film-coated tablet. There are two strengths available in blister pack of 28 tablets:

Zolpidem 5mg Tablets are round white tablets, embossed on one face with the number “5”

Zolpidem 10mg Tablets are white, capsule-shaped tablets, embossed on one face with the letter “2” and the number “10” either side of a score line.

Marketing Authorisation Holder
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Manufacturer
Lacer SA, Sardenya 360, 08025 Barcelona, Spain

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