Public Assessment Report

Zolpidem Tartrate 5mg Film-coated Tablets
Zolpidem Tartrate 10mg Film-coated Tablets

Zolpidem Tartrate

PL 17907/0123-4

Bristol Laboratories Limited

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Lay Summary

The MHRA granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Zolpidem 5mg and 10mg Film-coated Tablets to Bristol Laboratories Ltd on 19/05/2009.

Zolpidem tartrate is an imidazopyridine that is reported to have similar sedative properties to the benzodiazepines, but minimal anxiolytic, muscle relaxant, and anticonvulsant properties. It has a rapid onset and short duration of action, and is used as a hypnotic in the short-term management of insomnia. The usual dose by mouth is 10 mg taken immediately before retiring.

The test products were considered the same as the original products, Stilnoct Tablets 5mg and 10mg, (Sanofi-Synthelabo Ltd). No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Zolpidem 5mg and 10mg Film-coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.

Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Zolpidem 5mg and 10mg Film-coated Tablets to Bristol Laboratories Ltd on 19/05/2009. The products are prescription-only medicines.

These are two strengths of Zolpidem, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to the original products (PL 11723/0323-4) Stilnoct Tablets 5mg and 10mg, (Sanofi-Synthelabo Ltd).

The product contains the active ingredient Zolpidem tartrate. Zolpidem tartrate is an imidazopyridine that is reported to have similar sedative properties to the benzodiazepines, but minimal anxiolytic, muscle relaxant, and anticonvulsant properties. It has a rapid onset and short duration of action, and is used as a hypnotic in the short-term management of insomnia. The usual dose by mouth is 10 mg taken immediately before retiring.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

rINN:	Zolpidem Tartrate
Chemical name:	bis[N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]aceta mide] (2R,3R)-2,3-dihydroxybutanedioate,
Physical form:	A white or almost white, crystalline powder, hygroscopic.
Molecular formula:	(C19H21N3O)2,C4H6O6
Relative molecular mass:	764.9
Chirality:	The molecule is achiral
CAS:	99294-93-6
Therapeutic category:	Hypnotic

General Properties

Zolpidem is a white to off white odourless, water soluble microcrystalline solid. It is stable to heat and light and is stable in aqueous solution at pH values from 1.5 – 7.4.

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.

Active zolpidem tartrate 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.

Appropriate stability data have been generated supporting a retest period of 6 months, with no specific storage instructions.

DRUG PRODUCT

Other Ingredients

The other ingredients of Zolpidem 5mg and 10mg Film-coated Tablets are listed below.

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Pregelatinised starch
Sodium starch glycollate
Silica colloidal anhydrous
Magnesium stearate.

Film coating:
Hypromellose
Titanium dioxide (E171)
Talc
Macrogol 6000.

All excipients are Ph Eur, and therefore controlled by their respective monographs. Analytical methods are in line with respective monographs and do not need validating. Satisfactory certificates of analysis for tests carried out on receipt of excipients were provided.

Dissolution and impurity profiles

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

Manufacture

A description and flow-chart of the manufacturing method has 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
Both strengths are packed in blisters of 7 or 14 tablets, which are cartoned to give packs of 7, 14, 28, 56 or 84 tablets. Suppliers' and Finished product manufacturer's specifications and methods for 250µm thick PVC and 0.020mm thick aluminium lidding are provided. Satisfactory suppliers' Certificates of Analysis are provided together with confirmation the blister material conforms to Ph Eur monograph and the aluminium lidding foil conforms to ASIM: B-479 for food applications.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are "Do not store above 25 degrees".

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

PRE-CLINICAL ASSESSMENT

No pre-clinical data were submitted with these applications and none were required.

MEDICAL ASSESSMENT

Pharmacodynamics

Zolpidem tartrate is an imidazopyridine which preferentially binds the omega-1 receptor subtype (also known as the benzodiazepine-1 subtype) which corresponds to GABA-A receptors containing the alpha-1 sub-unit, whereas benzodiazepines non-selectively bind both omega-1 and omega-2 subtypes. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem tartrate. These effects are reversed by the benzodiazepine antagonist flumazenil.

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

In man: zolpidem tartrate decreases sleep latency and the number of awakenings, and increases sleep duration and sleep quality. These effects are associated with a characteristic EEG profile, different from that of the benzodiazepines. In studies that measured the percentage of time spent in each sleep stage, zolpidem tartrate has generally been shown to preserve sleep stages. At the recommended dose, zolpidem tartrate has no influence on the paradoxical sleep duration (REM). The preservation of deep sleep (stages 3 and 4 - slow-wave sleep) may be explained by the selective omega-1 binding by zolpidem tartrate. All identified effects of zolpidem tartrate are reversed by the benzodiazepine antagonist flumazenil.

Pharmacokinetics

Zolpidem tartrate 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 at between 0.5 and 3 hours.

The elimination half-life is short, with a mean of 2.4 hours (± 0.2 h) and a 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 binding indicating a lack of competition between zolpidem tartrate and its metabolites for binding sites.

The distribution volume in adults is 0.54 ± 0.02 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%).

Bioequivalence Study

An open label, randomised, two-treatment, two sequence, two period, two way cross-over single dose bioequivalence study in healthy adult male fasted (at least 10 hours) subjects was conducted. 26 healthy fasted male volunteers were enrolled; 24 subjects completed the study. Zolpidem 10mg Film-coated Tablets were compared to the reference product Silnoct 10mg Tablets. The bioequivalence study on the 10mg strength of Zolpidem Tablets was considered to be applicable to the 5mg strength as the drug displays linear pharmacokinetics.

Results

Results for main pharmacokinetic parameters

Parent drug		
Treatment Geometric Means (SD)		
	Test	Reference
C_{max} (ng/mL)	72.7755 (23.35050)	78.7337 (24.95339)
AUC_t (ng.h/mL)	245.3215 (109.98595)	260.9486 (115.75900)
AUC_∞ (ng.h/mL)	270.7830 (123.41316)	293.7788 (131.70134)
T_{max} (h)*	0.9375 (0.60005)	0.7604 (0.40700)
$T_{1/2}$	2.222 (1.0034)	2.675 (1.4968)
Bioequivalence results for log-transformed test/reference ratios. Point estimate (90% Confidence Interval)		
AUCt	84.87-103.22%	
AUCinf	83.56-101.53%	
Cmax	81.71-102.57%	

AUC_{0-t} / AUC_∞ is > 0.8, confirming adequate sampling duration.

The 90% confidence intervals for test/reference lie within the acceptance criteria specified in the Bioequivalence NfG and therefore, bioequivalence was demonstrated.

Efficacy

Efficacy is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

Safety

Safety is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

Expert Report
The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

Summary Of Product Characteristics
This is satisfactory.

Patient Information Leaflet
This is satisfactory.

Conclusions
The applicant appears to have demonstrated bioequivalence. Marketing authorisations should be granted for these products.

Overall Conclusion and Risk/Benefit Analysis

Quality

The important quality characteristics of Zolpidem 5mg and 10mg 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.

Pre-Clinical

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

Clinical

Bioequivalence has been demonstrated between the applicant's Zolpidem 5mg and 10mg Film-coated Tablets and the reference product. Given that linear kinetics apply between the 5mg and 10mg tablets, that proportional formulae for the capsules have been used and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 5mg tablets is not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Silnoct 10mg Tablets.

Risk/Benefit Analysis

The quality of the product 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 innovator products are interchangeable. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 18/07/2005.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 19/09/2005.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 05/05/2006, 19/11/2007 and 27/11/2007 and on the medical assessment on 18/11/2008.
4	The applicant provided further information in regard to the quality assessment on 21/07/2006, 20/11/2007 and 24/04/2008 and on the clinical assessment on 28/11/2008.
5	The application was determined on 19/05/2009.

Steps Taken after Assessment

No non-confidential changes have been made to the market authorisation.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zolpidem tartrate 5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Zolpidem tartrate 5mg Film-coated Tablets contains Zolpidem tartrate 5 mg as the active ingredient. It also contains Lactose monohydrate 29.50 mg .

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film Coated Tablets.

White to almost white, round, biconvex, film coated tablets with '5' embossing on one side containing 5mg Zolpidem tartrate.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The short-term treatment of insomnia in 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 tartrate acts rapidly and therefore should be taken immediately before retiring, or in bed.

The recommended daily dose for adults is 10 mg.

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.

Special Populations

Children

Safety and effectiveness of zolpidem in paediatric patients under the age of 18 years have not been established. Therefore, zolpidem should not be prescribed in this population (see section 4.4)

Elderly

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate therefore a 5mg dose is recommended. These recommended doses should not be exceeded.

Hepatic impairment

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

4.3 Contraindications

Zolpidem tartrate is contraindicated in patients with a hypersensitivity to zolpidem tartrate or any of the inactive ingredients, obstructive sleep apnoea, myasthenia gravis, severe hepatic insufficiency, acute and/or severe respiratory depression. In the absence of data, zolpidem tartrate should not be prescribed for children or patients with psychotic illness.

4.4 Special warnings and precautions for use

Respiratory insufficiency

As hypnotics have the capacity to depress respiratory drive, precautions should be observed if zolpidem is prescribed to patients with compromised respiratory function.

Hepatic Insufficiency: See section 4.2

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, and the patient should be carefully re-evaluated at regular intervals.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Elderly: See dose recommendations.

Paediatric patients:

Safety and effectiveness of zolpidem have not been established in patients below the age of 18 years. In an 8-week study in paediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%). (See section 4.2 Posology and method of administration).

Depression:

As with other sedative/hypnotic drugs, zolpidem tartrate should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present therefore the least amount of drug that is feasible should be supplied to these patients because of the possibility of intentional overdosage by the patient.
Pre-existing depression may be unmasked during use of zolpidem. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

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

General information relating to 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 and psychological dependence. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of psychiatric disorders and/or alcohol or drug abuse.

These patients should be under careful surveillance when receiving hypnotics.

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

Rebound insomnia

A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine or benzodiazepine-like agent recur in an enhanced form, may occur on withdrawal of 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.

There are indications that, in the case of benzodiazepines and benzodiazepine-like agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

Amnesia

Benzodiazepines or benzodiazepine-like agents may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours.

Other psychiatric and "paradoxical" reactions

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

Somnambulism and associated behaviours:

Sleep walking and other associated behaviours such as “sleep driving”, preparing and eating food, making phone calls or having sex, with amnesia for the event, have been reported in patients who had taken zolpidem and were not fully awake. The use of alcohol and other CNS-depressants with zolpidem appears to increase the risk of such behaviour, as does the use of zolpidem at doses exceeding the maximum recommended dose. Discontinuation of zolpidem should be strongly considered for patients who report such behaviour.

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.

- **Take into account**: 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, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines.Zolpidem tartrate appears to interact with sertraline. This interaction may cause increased drowsiness. Also, isolated cases of visual hallucinations were reported

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 enhance the activity of benzodiazepines and benzodiazepine-like agents.

Zolpidem tartrate is metabolised via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2. The pharmacodynamic effect of zolpidem tartrate is decreased when it is administered with rifampicin (a CYP3A4 inducer). However when zolpidem tartrate was administered with itraconazole (a CYP3A4 inhibitor) its pharmacokinetics and pharmacodynamics were not significantly modified. The clinical relevance of these results is unknown.

Co-administration of zolpidem with ketoconazole (200mg twice daily), a potent CYP3A4 inhibitor, prolonged zolpidem elimination half-life, increased total AUC, and decreased apparent oral clearance when compared to zolpidem plus placebo. The total AUC for zolpidem, when co-administered with ketoconazole, increased by factor of 1.83 when compared to zolpidem alone. A routine dosage adjustment of zolpidem is not considered necessary, but patients, should be advised that use of zolpidem with ketoconazole may enhance the sedative effects.

Since CYP3A4 plays an important role in zolpidem tartrate metabolism, possible interactions with drugs that are substrates or inducers of CYP3A4 should be considered.

Others: When zolpidem tartrate was administered with ranitidine or cimetidine, no significant pharmacokinetic interactions were observed.

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 tartrate 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 physician about stopping the product if she intends to become or suspects that she is pregnant.

If, for compelling medical reasons, zolpidem tartrate 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 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.

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

4.7 Effects on ability to drive and use machines

Vehicle drivers and machine operators should be warned that, as with other hypnotics, there may be a possible risk of drowsiness the morning after therapy. In order to minimise this risk a resting period of 7 to 8 hours is recommended between taking zolpidem tartrate and driving.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

Very Common ≥ 10%

Common ≥ 1 and < 10%

Uncommon ≥ 0.1 and <1%

Rare ≥ 0.01and < 0.1%

Very rare <0.01%

Not known: cannot be estimated based on available data.

There is evidence of a dose-relationship for adverse effects associated with zolpidem tartrate use, particularly for certain CNS and gastrointestinal events. As recommended in section 4.2 Posology and method of administration, they should in theory be less if zolpidem tartrate is taken immediately before retiring, or in bed. They occur most frequently in elderly patients.

Immune system disorders:
Not known: angioneurotic oedema

Psychiatric disorders:
Common: hallucination, agitation, nightmare
Uncommon: confusional state, irritability
Not known: restlessness, aggression, delusion, anger, psychosis, abnormal behaviour, sleep walking (See Section 4.4), dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation), libido disorder.

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

Nervous system disorders:
Common: somnolescence, headache, dizziness, exacerbated insomnia, anterograde amnesia: (amnestic effects may be associated with inappropriate behaviour)

Not known: depressed level of consciousness

Eye disorders:
Uncommon: diplopia

Gastro-intestinal Disorders:
Common: diarrhoea

Hepatobiliary disorders:
Not known: Liver enzymes elevated

Skin and subcutaneous disorders:
Not known: rash, pruritis, urticaria

Musculoskeletal and connective tissue disorders:
Not known: Muscular weakness

General disorders and administration site conditions:
Common: fatigue
Not know: gait disturbance, drug tolerance, fall (predominantly in elderly patients and when zolpidem was not taken in accordance with prescribing recommendation)

4.9 Overdose

Signs and symptoms:

In cases of overdose involving zolpidem tartrate alone or with other CNS depressant agents (including alcohol), impairment of consciousness ranging from somnolence to light coma and including fatal outcomes have been reported.

Individuals have fully recovered from zolpidem tartrate overdoses up to 400mg.

Overdose cases involving zolpidem tartrate among multiple CNS-depressant agents (including alcohol), have resulted in more severe symptomatology, including fatal outcomes.

Management
General symptomatic and supportive measures should be used. 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.

Flumazenil is reported to have an elimination half-life of about 40 to 80 minutes. Patients should be kept under close observation because of this short duration of action; further doses of flumazenil may be necessary. However,

flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

The value of dialysis in the treatment of an overdose has not been determined. Dialysis in patients with renal failure receiving therapeutic doses of zolpidem has demonstrated no reduction in levels of zolpidem.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Benzodiazepine related drugs

ATC Code : N05CF02

(GABA-A receptor modulator selective for omega-1 receptor subtype hypnotic agent).

Zolpidem tartrate is an imidazopyridine which preferentially binds the omega-1 receptor subtype (also known as the benzodiazepine-1 subtype) which corresponds to GABA-A receptors containing the alpha-1 sub-unit, whereas benzodiazepines non-selectively bind both omega-1 and omega-2 subtypes. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem tartrate. These effects are reversed by the benzodiazepine antagonist flumazenil.

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

In man: zolpidem tartrate decreases sleep latency and the number of awakenings, and increases sleep duration and sleep quality. These effects are associated with a characteristic EEG profile, different from that of the benzodiazepines. In studies that measured the percentage of time spent in each sleep stage, zolpidem tartrate has generally been shown to preserve sleep stages. At the recommended dose, zolpidem tartrate has no influence on the paradoxical sleep duration (REM). The preservation of deep sleep (stages 3 and 4 - slow-wave sleep) may be explained by the selective omega-1 binding

by zolpidem tartrate. All identified effects of zolpidem tartrate are reversed by the benzodiazepine antagonist flumazenil.

5.2 Pharmacokinetic properties

Zolpidem tartrate 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 at between 0.5 and 3 hours.

The elimination half-life is short, with a mean of 2.4 hours (± 0.2 h) and a 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 binding indicating a lack of competition between zolpidem tartrate and its metabolites for binding sites.

The distribution volume in adults is 0.54 ± 0.02 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 tartrate 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.

Zolpidem tartrate is metabolised via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2. Since CYP3A4 plays an important role in zolpidem tartrate metabolism, possible interactions with drugs that are substrates or inducers of CYP3A4 should be considered.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Pregelatinised starch
Sodium starch glycollate
Silica colloidal anhydrous
Magnesium stearate.

Film coating:
Hypromellose
Titanium dioxide (E171)
Talc
Macrogol 6000.

6.2 Incompatibilities

Not applicable

None known

6.3 Shelf life

Two years

6.4 Special precautions for storage

Do not store above 25ºC.

Store in the original package.

6.5 Nature and contents of container

Cartons of 7, 14, 28, 56 or 84 tablets containing PVC/Aluminium foil blister strips of 7 or 14 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside
Northbridge Road,
Berkhamsted, Hertfordshire
HP4 1EG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0123

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/05/2009

10 DATE OF REVISION OF THE TEXT

19/05/2009

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zolpidem tartrate 10 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Zolpidem tartrate 10mg Film-coated Tablets contains Zolpidem tartrate 10 mg as the active ingredient. It also contains Lactose monohydrate 59 mg .

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film Coated Tablets

Zolpidem tartrate 10mg Film-coated Tablets are white to almost white, caplet shaped, biconvex, film coated tablets with breakline on one side and ‘BL 10’ embossing on other side, containing 10mg zolpidem tartrate.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The short-term treatment of insomnia in 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 tartrate acts rapidly and therefore should be taken immediately before retiring, or in bed.

The recommended daily dose for adults is 10 mg.

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.

Special Populations

Children

Safety and effectiveness of zolpidem in paediatric patients under the age of 18 years have not been established. Therefore, zolpidem should not be prescribed in this population (see section 4.4)

Elderly

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate therefore a 5mg dose is recommended. These recommended doses should not be exceeded.

Hepatic impairment

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

4.3 Contraindications

Zolpidem tartrate is contraindicated in patients with a hypersensitivity to zolpidem tartrate or any of the inactive ingredients, obstructive sleep apnoea, myasthenia gravis, severe hepatic insufficiency, acute and/or severe respiratory depression. In the absence of data, zolpidem tartrate should not be prescribed for children or patients with psychotic illness.

4.4 Special warnings and precautions for use

Respiratory insufficiency

As hypnotics have the capacity to depress respiratory drive, precautions should be observed if zolpidem is prescribed to patients with compromised respiratory function.

Hepatic Insufficiency: See section 4.2

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, and the patient should be carefully re-evaluated at regular intervals.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Elderly: See dose recommendations.

Paediatric patients:

Safety and effectiveness of zolpidem have not been established in patients below the age of 18 years. In an 8-week study in paediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%). (See section 4.2 Posology and method of administration).

Depression:

As with other sedative/hypnotic drugs, zolpidem tartrate should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present therefore the least amount of drug that is feasible should be supplied to these patients because of the possibility of intentional overdosage by the patient. Pre-existing depression may be unmasked during use of zolpidem. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

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

General information relating to 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 and psychological dependence. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of psychiatric disorders and/or alcohol or drug abuse.

These patients should be under careful surveillance when receiving hypnotics.

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

Rebound insomnia

A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine or benzodiazepine-like agent recur in an enhanced form, may occur on withdrawal of 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.

There are indications that, in the case of benzodiazepines and benzodiazepine-like agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

Amnesia

Benzodiazepines or benzodiazepine-like agents may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours.

Other psychiatric and "paradoxical" reactions

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

Somnambulism and associated behaviours:

Sleep walking and other associated behaviours such as “sleep driving”, preparing and eating food, making phone calls or having sex, with amnesia for the event, have been reported in patients who had taken zolpidem and were not fully awake. The use of alcohol and other CNS-depressants with zolpidem appears to increase the risk of such behaviour, as does the use of zolpidem at doses exceeding the maximum recommended dose. Discontinuation of zolpidem should be strongly considered for patients who report such behaviour.

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.

- **Take into account**: 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, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines.Zolpidem tartrate appears to interact with sertraline. This interaction may cause increased drowsiness. Also, isolated cases of visual hallucinations were reported

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 enhance the activity of benzodiazepines and benzodiazepine-like agents.

Zolpidem tartrate is metabolised via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2. The pharmacodynamic effect of zolpidem tartrate is decreased when it is administered with rifampicin (a CYP3A4 inducer). However when zolpidem tartrate was administered with itraconazole (a CYP3A4 inhibitor) its

pharmacokinetics and pharmacodynamics were not significantly modified. The clinical relevance of these results is unknown.

Co-administration of zolpidem with ketoconazole (200mg twice daily), a potent CYP3A4 inhibitor, prolonged zolpidem elimination half-life, increased total AUC, and decreased apparent oral clearance when compared to zolpidem plus placebo. The total AUC for zolpidem, when co-administered with ketoconazole, increased by factor of 1.83 when compared to zolpidem alone. A routine dosage adjustment of zolpidem is not considered necessary, but patients, should be advised that use of zolpidem with ketoconazole may enhance the sedative effects.

Since CYP3A4 plays an important role in zolpidem tartrate metabolism, possible interactions with drugs that are substrates or inducers of CYP3A4 should be considered.

Others: When zolpidem tartrate was administered with ranitidine or cimetidine, no significant pharmacokinetic interactions were observed.

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 tartrate 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 physician about stopping the product if she intends to become or suspects that she is pregnant.

If, for compelling medical reasons, zolpidem tartrate 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 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.

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

4.7 Effects on ability to drive and use machines

Vehicle drivers and machine operators should be warned that, as with other hypnotics, there may be a possible risk of drowsiness the morning after therapy. In order to minimise this risk a resting period of 7 to 8 hours is recommended between taking zolpidem tartrate and driving.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

Very Common ≥ 10%

Common ≥ 1 and < 10%

Uncommon ≥ 0.1 and <1%

Rare ≥ 0.01and < 0.1%

Very rare <0.01%

Not known: cannot be estimated based on available data.

There is evidence of a dose-relationship for adverse effects associated with zolpidem tartrate use, particularly for certain CNS and gastrointestinal events. As recommended in section 4.2 Posology and method of administration, they should in theory be less if zolpidem tartrate is taken immediately before retiring, or in bed. They occur most frequently in elderly patients.

Immune system disorders:
Not known: angioneurotic oedema

Psychiatric disorders:
Common: hallucination, agitation, nightmare
Uncommon: confusional state, irritability
Not known: restlessness, aggression, delusion, anger, psychosis, abnormal behaviour, sleep walking (See Section 4.4), dependence (withdrawal

symptoms, or rebound effects may occur after treatment discontinuation), libido disorder.

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

Nervous system disorders:
Common: somnolence, headache, dizziness, exacerbated insomnia, anterograde amnesia: (amnestic effects may be associated with inappropriate behaviour)
Not known: depressed level of consciousness

Eye disorders:
Uncommon: diplopia

Gastro-intestinal Disorders:
Common: diarrhoea

Hepatobiliary disorders:
Not known: Liver enzymes elevated

Skin and subcutaneous disorders:
Not known: rash, pruritis, urticaria

Musculoskeletal and connective tissue disorders:
Not known: Muscular weakness

General disorders and administration site conditions:
Common: fatigue
Not know: gait disturbance, drug tolerance, fall (predominantly in elderly patients and when zolpidem was not taken in accordance with prescribing recommendation)

4.9 Overdose

Signs and symptoms:

In cases of overdose involving zolpidem tartrate alone or with other CNS depressant agents (including alcohol), impairment of consciousness ranging from somnolence to light coma and including fatal outcomes have been reported.

Individuals have fully recovered from zolpidem tartrate overdoses up to 400mg.

Overdose cases involving zolpidem tartrate among multiple CNS-depressant agents (including alcohol), have resulted in more severe symptomatology, including fatal outcomes.

Management:

General symptomatic and supportive measures should be used. 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.

Flumazenil is reported to have an elimination half-life of about 40 to 80 minutes. Patients should be kept under close observation because of this short duration of action; further doses of flumazenil may be necessary. However, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

The value of dialysis in the treatment of an overdose has not been determined. Dialysis in patients with renal failure receiving therapeutic doses of zolpidem has demonstrated no reduction in levels of zolpidem.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Benzodiazepine related drugs

ATC Code : N05CF02

(GABA-A receptor modulator selective for omega-1 receptor subtype hypnotic agent).

Zolpidem tartrate is an imidazopyridine which preferentially binds the omega-1 receptor subtype (also known as the benzodiazepine-1 subtype) which corresponds to GABA-A receptors containing the alpha-1 sub-unit, whereas benzodiazepines non-selectively bind both omega-1 and omega-2 subtypes. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem tartrate. These effects are reversed by the benzodiazepine antagonist flumazenil.

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

In man: zolpidem tartrate decreases sleep latency and the number of awakenings, and increases sleep duration and sleep quality. These effects are associated with a characteristic EEG profile, different from that of the benzodiazepines. In studies that measured the percentage of time spent in each sleep stage, zolpidem tartrate has generally been shown to preserve sleep stages. At the recommended dose, zolpidem tartrate has no influence on the paradoxical sleep duration (REM). The preservation of deep sleep (stages 3 and 4 - slow-wave sleep) may be explained by the selective omega-1 binding by zolpidem tartrate. All identified effects of zolpidem tartrate are reversed by the benzodiazepine antagonist flumazenil.

5.2 Pharmacokinetic properties

Zolpidem tartrate 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 at between 0.5 and 3 hours.

The elimination half-life is short, with a mean of 2.4 hours (± 0.2 h) and a 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 binding indicating a lack of competition between zolpidem tartrate and its metabolites for binding sites.

The distribution volume in adults is 0.54 ± 0.02 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 tartrate 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.

Zolpidem tartrate is metabolised via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2.

Since CYP3A4 plays an important role in zolpidem tartrate metabolism, possible interactions with drugs that are substrates or inducers of CYP3A4 should be considered.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Pregelatinised starch
Sodium starch glycollate
Silica colloidal anhydrous
Magnesium stearate.

Film coating:
Hypromellose
Titanium dioxide (E171)
Talc
Macrogol 6000.

6.2 Incompatibilities

Not applicable

Unknown

6.3 Shelf life

Two years

6.4 Special precautions for storage

Do not store above 25ºC.

Store in the original package.

6.5 Nature and contents of container

Cartons of 7, 14, 28, 56 or 84 tablets containing PVC/Aluminium foil blister strips of 7 or 14 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside
Northbridge Road,
Berkhamsted, Hertfordshire
HP4 1EG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0124

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/05/2009

10 DATE OF REVISION OF THE TEXT

19/05/2009

Labels and Leaflets

PACKAGE LEAFLET: INFORMATION FOR THE USER

Zolpidem tartrate 5 mg and 10 mg Film-coated Tablets

Read all of this leaflet carefully before you start taking this medicine. Even if you have used this medicine or a similar product before, you should read this text carefully as the information may have changed.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1.What Zolpidem tablets are and what they are used for

Zolpidem tartrate tablet is a sleeping tablet (hypnotic).
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. The duration of treatment usually varies from a few days to a maximum of four weeks. If you still have problems sleeping after you have finished taking your tablets, contact your doctor.

2.Before taking Zolpidem tablets

Do not take these tablets if you

- are allergic (hypersensitive) to Zolpidem tartrate or any of the other ingredients of Zolpidem tartrate tablets (these are listed in Section 6, Further Information). An allergic reaction may include a rash, itching, difficulty breathing or swelling of the face, lips, throat or tongue
- are pregnant or intend to become pregnant
- suffer from breathing difficulties
- suffer from sleep apnoea (stopping breathing for short periods while asleep)
- have liver disease
- have myasthenia gravis (weakness of the muscles)

Children must not take Zolpidem tablets.

If you are in any doubt about whether you have any of these conditions, do ask your doctor.

Taking special care

Check with your doctor or pharmacist before taking Zolpidem tablets if you

- have any kidney or liver problem
- have a history of mental illness
- are depressed, think you are depressed or being treated for depression.
- have ever had a history of alcohol or drug abuse.

Taking other medicines

Do not take any other medicine without asking your doctor or pharmacist first. This includes medicines which can be bought without a prescription. Some can cause drowsiness and should not be taken while taking these tablets.

These medicines include:

- antipsychotics (medicines to correct abnormal behavior e.g. chlorpromazine, prochlorperazine)
- hypnotics (sleeping pills e.g. nitrazepam and temazepam)
- anxiolytics (medicines to prevent anxiety e.g. diazepam)
- sedatives (medicines to make you feel calmer)
- antidepressants (e.g. sertraline and paroxetine)
- narcotic analgesics(painkillers e.g. codeine and morphine)
- antiepileptic medicines (e.g. phenytoin and phenobarbital)
- anaesthetics
- rifampicin
- some antihistamines (i.e. allergy treatment that makes you drowsy e.g. chlorphenamine)

Do not use Zolpidem tablets or any other sleeping medicine for longer than instructed by your doctor.

Taking Zolpidem tablets with alcohol

- DO NOT drink alcohol while you are being treated with these tablets. Alcohol can increase the side effects of any sleeping medicine.

Pregnancy and breastfeeding

- DO NOT take these tablets if you are pregnant or intend to become pregnant or are breastfeeding.
- Ask your doctor or pharmacist for advice before taking any medicine.

Driving or using machines

- As with other sleeping pills, there is a risk of drowsiness the morning after therapy.
- If you feel drowsy the day after taking these do NOT drive or operate machinery.
- A resting period of 7 to 8 hours is recommended between taking the medicine and driving or operating machinery.

Important information about some of the ingredients of Zolpidem tablets

If you have been previously told by your doctor you have intolerance to some sugars (lactose or milk sugars), contact your doctor before taking this medicine.

XXXXXX

3. How to take Zolpidem Tablets

- Always take the tablets exactly as your doctor has prescribed. You should check with your doctor or pharmacist if you are not sure.
- Take the tablets when you are ready to get into bed and go to sleep.
- Swallow the tablet(s) with a small glass of water.

You should not be treated with these tablets for longer than 4 weeks.

Dosage:
Adults: Take one 10mg tablet (or two 5mg tablets)

Elderly or debilitated adults: Take one 5mg tablet

Zolpidem tablets are not recommended for use in children.

If you take more tablets than you should:
If you or someone else swallows a lot of the tablets or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty (A&E) or your doctor immediately. Take your medicine in its original packaging with you in order to enable the doctor to identify your medication easily.

If you forget to take your tablets
If you forget to take a dose immediately before bed but remember during the night, only take the missed dose if you are still able to have 7-8 hours of uninterrupted sleep before you need to get up. If this is not the case, take the next dose before bed the next night. DO NOT take two doses at the same time. If you are worried ask your pharmacist or doctor for advice.

If you stop taking these tablets
Do not stop treatment suddenly without the advice of your doctor or else you may experience withdrawal effects such as headaches or muscle pain, anxiety, tension, restlessness, confusion, irritability and insomnia.

4. Possible side effects

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

Following side effects can occur during treatment with Zolpidem tablets:
- day-time drowsiness
- reduced alertness
- confusion
- diarrhoea
- nausea and vomiting
- fatigue
- headache
- dizziness
- muscle weakness
- unsteadiness and/or falls
- changes in libido
- skin reactions
- restlessness
- agitation
- irritability

If you notice any of the above listed side effects or any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. How to store

- Keep your tablets out of the reach and sight of children
- Do not take your tablets after the expiry date shown on the pack
- Only use them at the time when your doctor prescribes them. If you have any left over take them back to a pharmacist.
- Do not store above 25°C. Store in the original package.

6. Further Information

What Zolpidem 5mg and 10 mg tablets contains:
- The active ingredient is Zolpidem tartrate
- The other ingredients are lactose monohydrate, microcrystalline cellulose, pregelatinised starch, sodium starch glycollate, colloidal silicon dioxide, magnesium stearate, hypromellose, titanium dioxide (E171), purified talc, macrogol 6000

What the tablets look like and contents of the pack
- There are two strengths of Zolpidem tartrate tablets, 5mg and 10mg
- Zolpidem 5mg tablets are white to almost white, round, biconvex, film-coated tablets '5' embossing on one side and plain on the other side.
- Zolpidem 10mg tablets are white to almost white, caplet shaped, biconvex, film-coated tablets with break line on one side and 'BL 10' embossing on other side.

Zolpidem 5mg Tablets and Zolpidem 10mg Tablets are available in packs of 14, 28, 56 or 84 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder/Manufacturer
Name and address: Bristol Laboratories Limited,
Unit 3, Canalside,
Northbridge Road, Berkhamsted,
Hertfordshire, HP4 1EG
Telephone: 0044 (0)1442 200922
Fax: 0044 (0)1442 873717
Email: info@bristol-labs.co.uk

Zolpidem tartrate 5mg film-coated Tablets; PL 17907/0123
Zolpidem tartrate 10mg film-coated Tablets; PL 17907/0124

This leaflet was last approved in January 2009

To request a copy of this leaflet in braille, large print or audio format, please contact the licence holder at the address (or telephone, fax, email) above.

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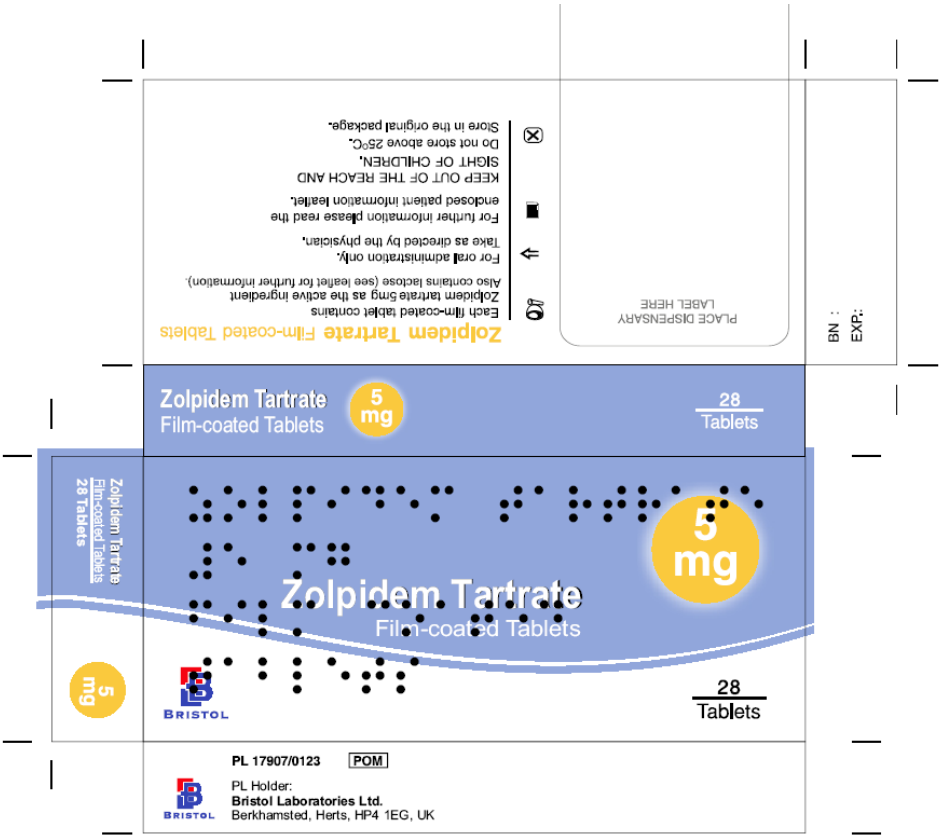
Zolpidem Tartrate Film-coated Tablets
Each film-coated tablet contains
Zolpidem tartrate 5mg as the active ingredient
Also contains lactose (see leaflet for further information).
For oral administration only.
Take as directed by the physician.
For further information please read the enclosed patient information leaflet.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Do not store above 25°C.
Store in the original package.
PLACE DISPENSARY LABEL HERE
BN :
EXP:
Zolpidem Tartrate 5mg Film-coated Tablets 28 Tablets
Zolpidem Tartrate
Film-coated Tablets
5 mg
28 Tablets
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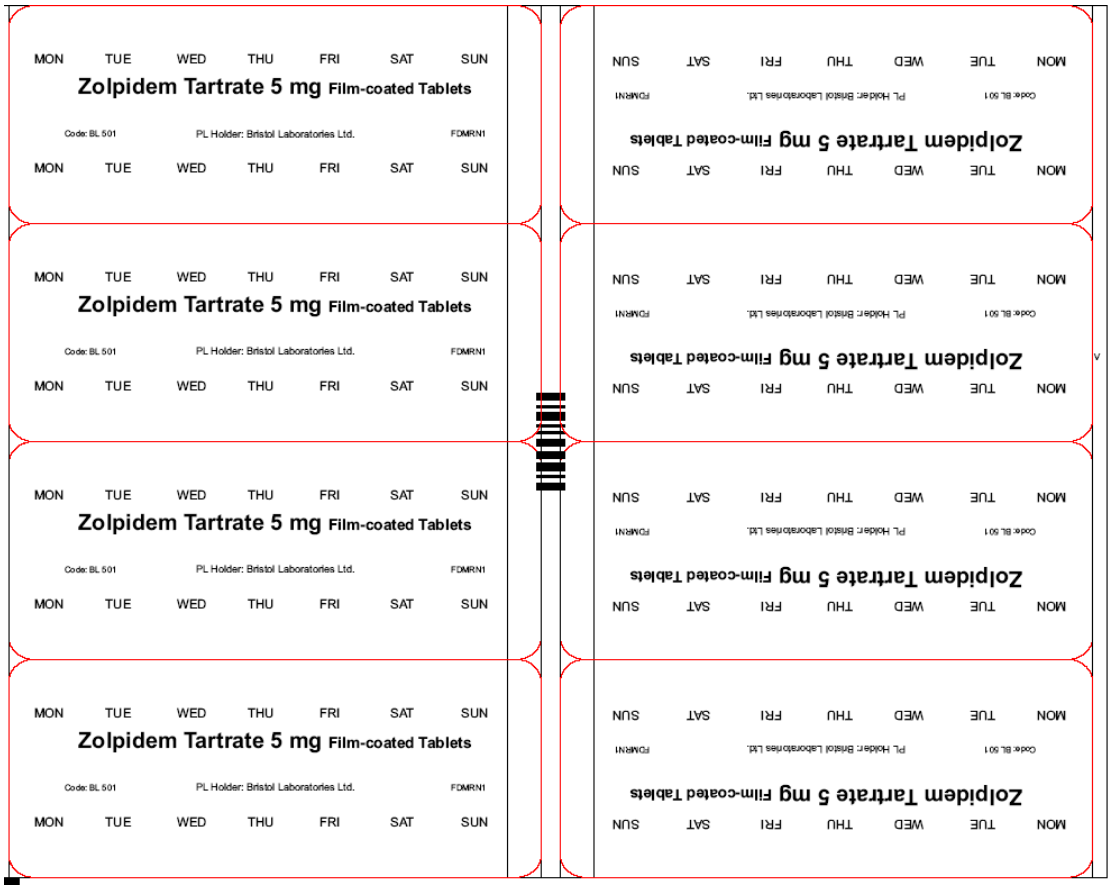
PL Holder:
Bristol Laboratories Ltd.
Berkhamsted, Herts, HP4 1EG, UK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Zolpidem Tartrate 5 mg Film-coated Tablets
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PL Holder: Bristol Laboratories Ltd.
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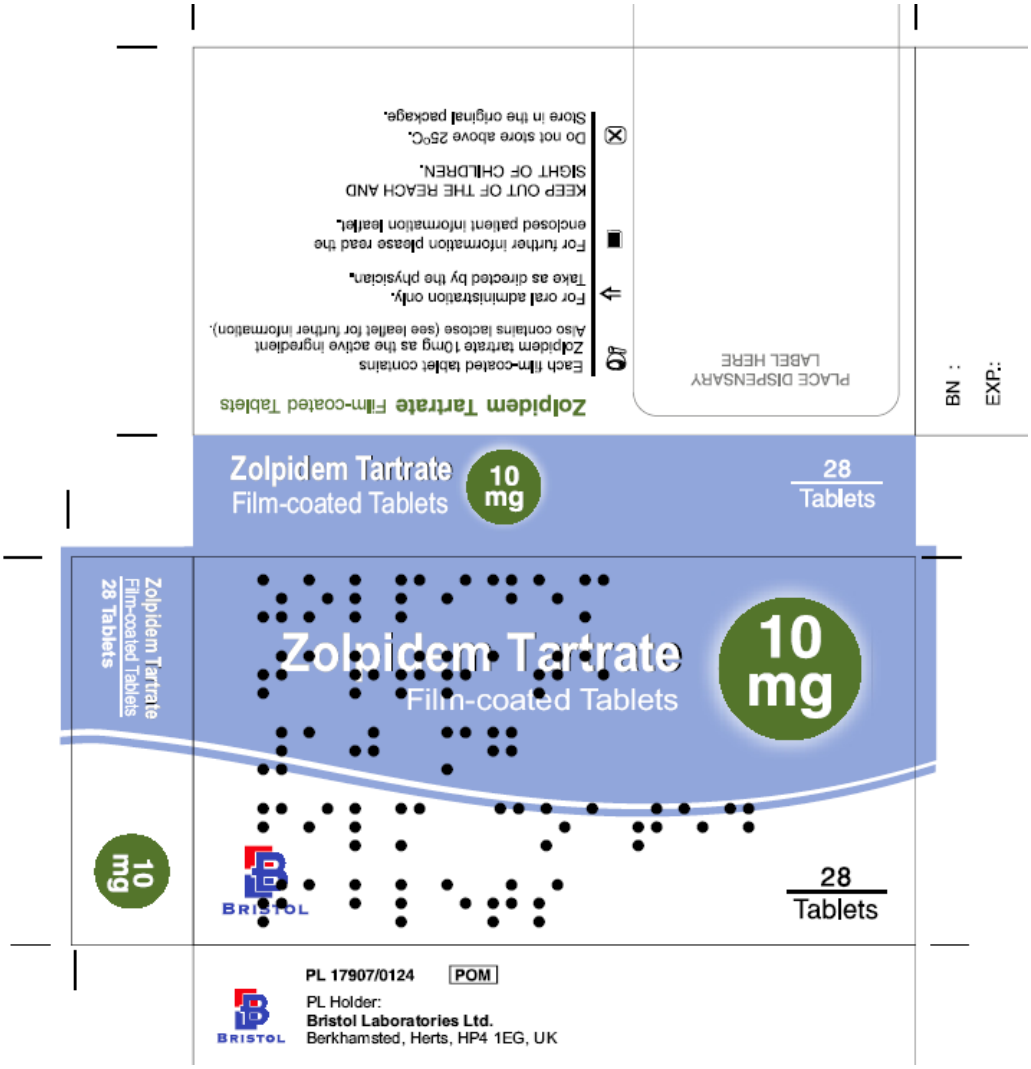
Zolpidem Tartrate Film-coated Tablets
Each film-coated tablet contains Zolpidem tartrate 10mg as the active ingredient Also contains lactose (see leaflet for further information).
For oral administration only. Take as directed by the physician.
For further information please read the enclosed patient information leaflet.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Do not store above 25°C. Store in the original package.
PLACE DISPENSARY LABEL HERE
BN :
EXP:
Zolpidem Tartrate
Film-coated Tablets
10 mg
28 Tablets
Zolpidem Tartrate
Film-coated Tablets
10 mg
28 Tablets
BRISTOL
Zolpidem Tartrate
Film-coated Tablets
10 mg
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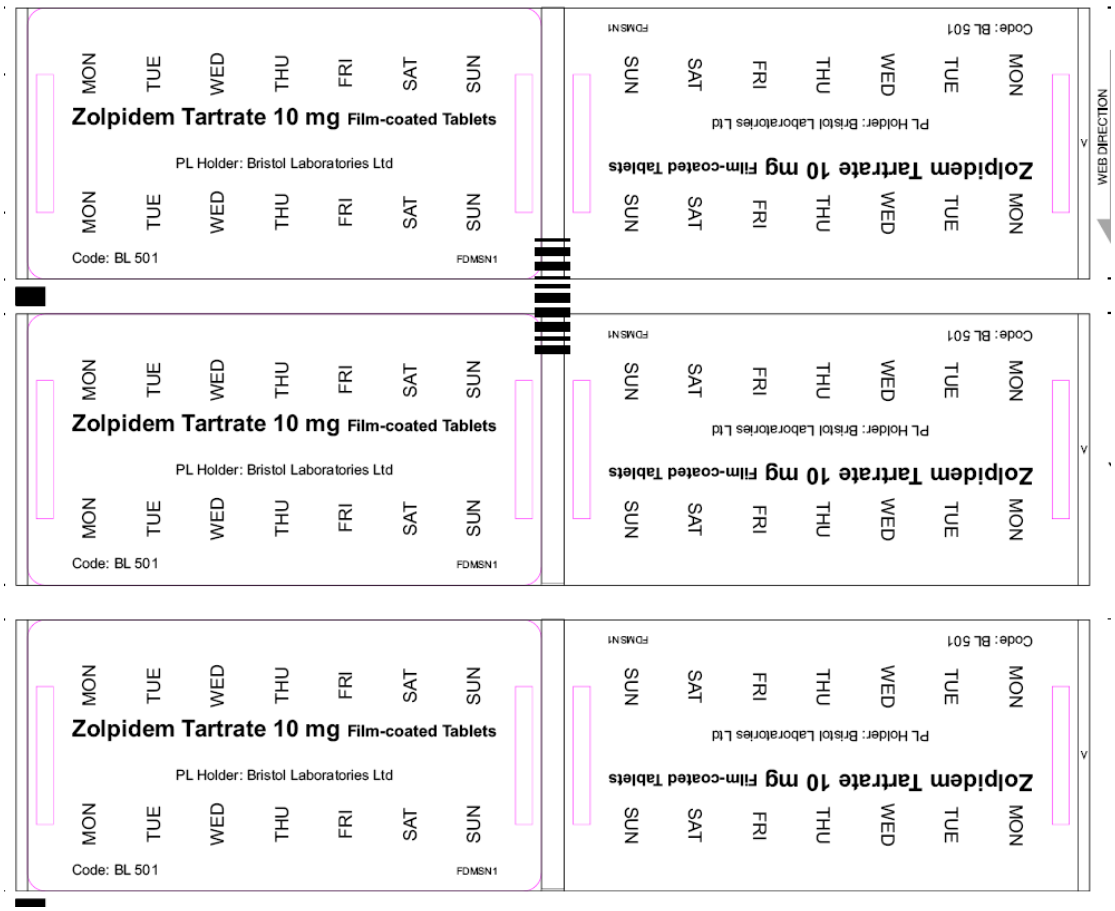
Bristol Laboratories Ltd.
Berkhamsted, Herts, HP4 1EG, UK
BRISTOL


MON TUE WED THU FRI SAT SUN
Zolpidem Tartrate 10 mg Film-coated Tablets
PL Holder: Bristol Laboratories Ltd
Code: BL 501
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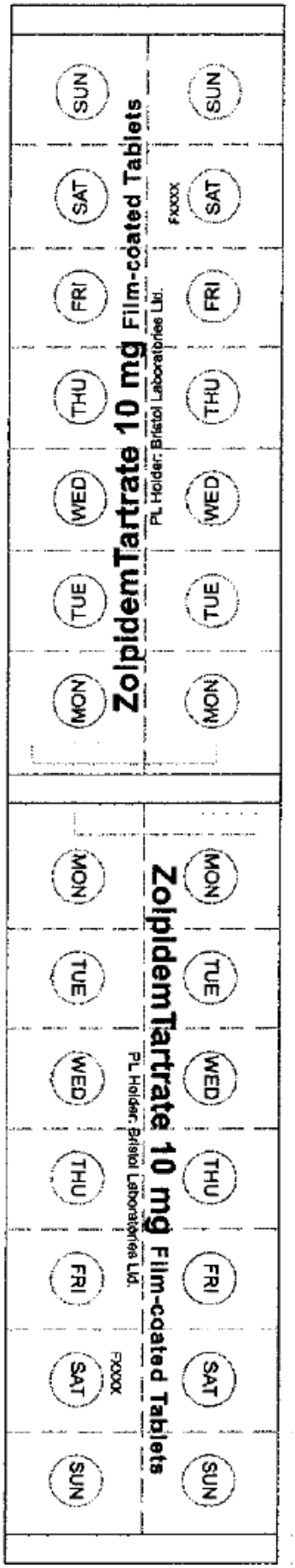
ZolpidemTartrate 10 mg Film-coated Tablets
PL Holder: Bristol Laboratories Ltd.
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SUN
ZolpidemTartrate 10 mg Film-coated Tablets
PL Holder: Bristol Laboratories Ltd.
FXXXX