Public Assessment Report

Decentralised Procedure

Zopiclone 3.75mg and 7.5mg Film-coated Tablets

Procedure No: UK/H/2575/001-2/DC

UK Licence No: PL 17907/0122 and PL 17907/0051

Bristol Laboratories Limited
LAY SUMMARY

On 23 June 2011, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations to Bristol Laboratories Limited for medicines called Zopiclone 3.75mg and 7.5mg Film-coated Tablets (PL 17907/0122 and 0051; UK/H/2575/001-2/DC).

These medicines are available on prescription from your doctor. Zopiclone 3.75mg and 7.5mg Film-coated Tablets induce sleep and are used in the short-term treatment of sleeplessness.

The active ingredient, zopiclone, is a sedative-hypnotic (sleeping pill), which belongs to a class of medicines called cyclopyrrolones. Zopiclone has properties similar to that of the benzodiazepines. You should use benzodiazepines or benzodiazepine-like substances only if you suffer from severe sleep disorders which cause you extreme distress.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Zopiclone 3.75mg and 7.5mg Film-coated Tablets outweigh the risks, and Marketing Authorisations were granted.
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### Module 1

**Information about the initial procedure**

| **Product Names** | Zopiclone 3.75mg Film-coated Tablets  
|                  | Zopiclone 7.5mg Film-coated Tablets |
| **Type of Application** | Generic, Article 10.1 |
| **Active Substance** | Zopiclone |
| **Form** | Film-coated tablets |
| **Strength** | 3.75mg and 7.5mg |
| **MA Holder** | Bristol Laboratories Ltd.  
|               | Unit 3, Canalside, Northbridge Road  
|               | Berkhamsted  
|               | Herts, HP14 1EG  
|               | UK |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Czech Republic, Germany, Hungary and Slovak Republic |
| **Procedure Number** | UK/H/2575/001-2/DC |
| **Timetable** | Day 210 – 18 May 2011 |
Module 2

1 NAME OF THE MEDICINAL PRODUCT
Zopiclone 3.75mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 3.75 mg zopiclone
Excipient: Each film-coated tablet contains 15.91 mg lactose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-Coated Tablets (Tablets)
Blue coloured, round, biconvex film coated tablets plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Short-term treatment of insomnia.
Benzodiazepines and benzodiazepine-like substances are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration
Treatment with Zopiclone should be for as short a period as possible.
The period of treatment should generally vary between a few days to 2 weeks, with a maximum of 4 weeks including the tapering off phase. In certain cases it may be necessary to prolong treatment to beyond the maximum period. If this is the case, however, it should only take place after re-evaluation of the patient’s condition.
The recommended dose for adults is 7.5 mg (two tablets). This dose should not be exceeded.
The product should be taken immediately before going to bed.
In the elderly, patients with hepatic insufficiency or chronic respiratory insufficiency, treatment should be started at a dosage of 3.75 mg.
Although no accumulation of zopiclone or its metabolites have been found in patients with renal insufficiency, it is advisable to begin treatment of patients with reduced renal function at 3.75 mg.

Paediatric patients
Zopiclone is contraindicated in children and adolescents under 18 (see section 4.3).

4.3 Contraindications
Zopiclone is contra-indicated in the following cases:
− Hypersensitivity to the active substance or to any of the excipients
− Myasthenia gravis
− Severe respiratory insufficiency
− Sleep apnoea syndrome
− Children and adolescents under 18 years of age
− Severe hepatic insufficiency

4.4 Special warnings and precautions for use
Before starting treatment with zopiclone any underlying cause of insomnia should be addressed carefully.

Dependence
The use of benzodiazepines and benzodiazepine-like substances can lead to physical and psychological dependence on these agents. The risk of dependence increases the higher the dose and the longer the period of treatment; the risk of dependence is also greater in patient with a history of alcohol or drug
abuse or those who have marked personality disorders. If physical dependence occurs, sudden discontinuation of the treatment will be accompanied by withdrawal symptoms. These may be expressed as headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise or physical contact, hallucinations or epileptic seizures. Rare cases of abuse have been reported.

**Rebound insomnia**

After discontinuation of treatment with a benzodiazepine or a benzodiazepine-like substance, a temporary syndrome may occur in which the symptoms which led to the treatment with the benzodiazepine or a benzodiazepine-like substance return in a more severe form. This syndrome may be accompanied by other reactions, including mood changes, anxiety and restlessness. Since the risk of withdrawal symptoms or rebound symptoms is greater after abrupt interruption of the treatment it is advisable to reduce the dosage gradually.

**Period of treatment**

The period of treatment should be as short as possible (see Posology and method of administration) but not longer than 4 weeks including the tapering off process. This period should only be exceeded after re-evaluation of the patient’s condition. It may be of benefit to inform the patient at the beginning of treatment that the treatment will be of short duration, and to explain precisely how to reduce the dose gradually. It is also important to point out to the patient the possibility of the occurrence of rebound phenomena in order to keep to a minimum any worries about the occurrence of such symptoms during the tapering off period of the treatment. In the case of benzodiazepines and benzodiazepine-like substances with a short period of action, there are indications that withdrawal symptoms may occur within the dosage interval, especially if the dose is high.

**Tolerance**

The hypnotic effect of short-acting benzodiazepines and benzodiazepine-like substances may diminish after repeated use for a few weeks. For zopiclone however, no pronounced tolerance has occurred during a treatment period of up to 4 weeks.

**Anterograde amnesia**

Benzodiazepines and benzodiazepine-like substances may cause anterograde amnesia, in particular a few hours after taking the product. In order to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see section 4.8 Undesirable effects).

**Psychiatric and paradoxical reactions**

It is known that reactions such as restlessness, agitation, irritability, aggression, delusions, outbursts of rage, nightmares, hallucination, psychoses, unsuitable behaviour and other behavioural disturbances may occur during the use of benzodiazepines and benzodiazepine-like substances. If this is the case administration of the medicinal product should be discontinued. The risk of these reactions is greater in children and the elderly.

**Somnambulism and associated behaviours**

Sleep walking and other associated behaviours such as “sleep driving”, preparing and eating food, or making phone calls, with amnesia for the event, have been reported in patients who have taken zopiclone and were not fully awake. The use of alcohol and other CNS-depressants with zopiclone appears to increase the risk of such behaviours, as does the use of zopiclone at doses exceeding the maximum recommended dose. Discontinuation of zopiclone should be strongly considered for patients who report such behaviours (see section 4.5).

**Specific patient groups**

For the elderly: see Posology and method of administration. A lower dose is advised for patients with chronic respiratory insufficiency due to the risk of respiratory depression. Benzodiazepines and benzodiazepine-like substances are not suitable for the treatment of patients with severe hepatic insufficiency, since they may promote the occurrence of encephalopathy. Benzodiazepines and benzodiazepine-like substances are not recommended as the primary treatment of psychoses. Benzodiazepines and benzodiazepine-like substances should not be used as the sole treatment of depression or anxiety linked with depression (suicide may be triggered in such patients). Benzodiazepines and benzodiazepine-like substances should be administered with extreme caution to patients with a previous history of alcohol or drug abuse.
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**4.5 Interaction with other medicinal products and other forms of interaction**

*Not recommended:*
Simultaneous ingestion with alcohol is not recommended because the sedative effect of zopiclone may be intensified. This may affect the ability to drive or operate machines.

*Take account of:*
Combination with other central depressive agents, such as antipsychotic agents (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressants, anti-epileptics, anaesthetics and sedative antihistamines may increase the suppressive effect of zopiclone on the central nervous system and should therefore be carefully weighed.

In the case of narcotic analgesics potentiation of euphoria may also occur, which can lead to increased psychological dependence.

Combination of zopiclone with muscle relaxants may increase the muscle relaxing effect.

Since zopiclone is metabolised by CYP3A4, the plasma levels of zopiclone and thus the effect of zopiclone may be increased when used in combination with drugs which inhibit CYP3A4, such as macrolide antibiotics, azole antifungals and HIV protease inhibitors, as well as grape fruit juice. Dose reduction should be considered if zopiclone is co-administered with CYP3A4 inhibitors. Drugs which induce CYP3A4, like phenobarbital, phenytoin, carbamazepine, rifampicine and products containing St John's wort, may reduce zopiclone plasma levels and thus the effect of zopiclone.

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

**4.6 Pregnancy and lactation**

*Pregnancy*
The safety of use in pregnant women has not been established.

Animal studies have shown that zopiclone partially crosses the placenta and does not have any teratogenic effects. Zopiclone should not be used during pregnancy unless clearly necessary.

If, for compelling medical reasons, zopiclone is prescribed during the last three months of pregnancy or during labour, effects on the neonate, such as hypothermia, hypotension, hypotonia, respiratory depression and decreased sucking reflex (“floppy infant syndrome”) may be expected due to the pharmacological properties of the product. Because of the development of physical dependence, withdrawal symptoms may occur in neonates of mothers who have used zopiclone for long periods during the last months of pregnancy.

If zopiclone is prescribed to women of child-bearing age, they should be advised that if they are planning to become pregnant or think they may be pregnant, they should contact their doctor about discontinuing the treatment.

*Lactation*
The safety of use during lactation has not been established.

Zopiclone and its metabolites are excreted in breast milk. Although the concentration in breast milk is very low, zopiclone should not be prescribed to women during the lactation period.

*Fertility*
Zopiclone caused a decrease in fertility in male rats (see section 5.3)

**4.7 Effects on ability to drive and use machines**

Sedation, amnesia, impaired concentration and impaired muscular function may reduce the capability to drive or operate machines. The risk is increased with concomitant alcohol intake. The risk is even higher when sleep duration is insufficient. Patients should be warned not to drive or operate machines...
until treatment has finished or it has been established that performance is unimpaired. Due to residual effects this warning should also be considered the morning after administration of zopiclone.

4.8 Undesirable effects
In this section frequencies of undesirable effects are defined as follows: Very common (>1/10); common (>1/100 to <1/10); uncommon (>1/1,000 to <1/100); rare (>1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

A bitter taste or metallic after taste is the most common adverse reaction of zopiclone.

The following side effects have been observed in patients treated with zopiclone:

**Immune system disorders**
Rare: allergic reactions, skin reactions like itching and skin rash (including urticaria).
Very rare: Anaphylactic reactions and angioedema.

Stevens-Johnson syndrome, Toxic epidermal necrolysis/Lyell’s syndrome, erythema multiforme.

**Psychiatric disorders**
Rare: Numbed emotions, confusion, and depression. Paradoxical reactions such as restlessness, agitation, irritability, aggression, delusions, outbursts of rage, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural disturbances,
Very rare: Decreased libido.
Not known: Physical and psychological dependence.

See also below under “Depression”, “Psychiatric and paradoxical reactions” and “Dependence”.

**Nervous system disorders**
Very common: A bitter or metallic taste (dysgeusia).
Common: Sleepiness during the following day, reduced alertness, headache, dizziness.
Rare: Amnesia, incoordination, ataxia (occurs chiefly at the beginning of treatment and generally disappear after repeated administration), light headedness.
Not known: somnambulism (see section 4.4).

See also below under “Amnesia”

**Eye disorders**
Rare: Double vision (occurs chiefly at the beginning of treatment and generally disappear after repeated administration).

**Gastrointestinal disorders**
Common: Gastro-intestinal problems (including nausea and vomiting), dyspepsia.
Rare: Dry mouth.

**Musculoskeletal and connective tissue disorders**
Rare: Muscle weakness.

**General disorders and administration site conditions**
Rare: Tiredness.

**Investigations**
Rare: Slight to moderate increases of serumtransaminases and/or alkaline phosphatase.

**Amnesia**
Anterograde amnesia may occur on therapeutic doses, and the risk is increased the higher the dose. Amnesia may be accompanied by inappropriate behaviour (see section 4.4).

**Depression**
Pre-existent depression may become manifest during the use of benzodiazepines and benzodiazepine-like substances (rare).
Psychiatric and paradoxical reactions
Reactions such as restlessness, agitation, irritability, aggression, delusions, outbursts of rage, nightmares, hallucinations, psychoses, inappropriate behavior and other behavioral disturbances may occur rarely or very rarely during the use of benzodiazepines and benzodiazepine-like substances. In some cases they may become quite severe with this agent. The risk of these reactions is greater in children and the elderly.

Dependence
Use may lead to physical dependence even at therapeutic dosages: discontinuation of the treatment may lead to withdrawal or rebound phenomena (see section 4.4). Psychological dependence may also occur. Misuse has been reported.

4.9 Overdose
In the few cases where overdosage with zopiclone has been reported, these reports were not accompanied by life-threatening effects unless the agent was ingested in combination with other medicaments which have a suppressive effect on the central nervous system, including alcohol. The most important phenomena are dizziness, lethargy and ataxia. Overdose of benzodiazepines or benzodiazepine-like agents is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma.

Treatment should be aimed at supporting vital functions and is chiefly symptomatic (e.g. induce vomiting, monitor the heart function and respiration).

Haemodialysis is not useful because of the high distribution volume of zopiclone. Flumazenil may be beneficial as an antidote. Flumazenil is not be used in mixed overdose or as a diagnostic test.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: hypnotic-sedative
ATC code N05C F01

Zopiclone is a benzodiazepine-like hypnotic agent which belongs to the group of cyclopyrrolones. The pharmacological properties are: sedation, anxiolysis, anticonvulsion, muscle relaxation. These effects are related to a specific agonistic effect on central receptors belonging to the GABA<sub>δ</sub> macromolecular complex which regulates the opening of chloride channels. These effects are similar to those of benzodiazepines.

5.2 Pharmacokinetic properties
Absorption
Zopiclone is swiftly absorbed. Maximum plasma concentrations are achieved after 1½ - 2 hours and are approximately 30 and 60 ng/ml after administration of 3.75 mg and 7.5 mg respectively. Absorption is the same in men and women and is not affected by simultaneous ingestion of food or repetition of doses.

Distribution
Zopiclone is swiftly distributed from the vascular compartment. The plasma protein binding is at least 45% and is not saturable.

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

The elimination half-life is approximately 5 hours at the recommended doses. No accumulation occurs after repeated administration and individual differences appear slight.

Less than 1.0% of the dose ingested by the mother is eliminated in breast milk.
Metabolism
The most important metabolites are the N-oxide derivative (pharmacologically active in animals) and the N-desmethyl metabolite (pharmacologically inactive in animals). Their apparent half-life times are approximately 4.5 hours and 7.4 hours respectively. No significant accumulation of the compound is seen following repeat dosing, (15mg) for 14 days.

Elimination
The low renal clearance of zopiclone (on average 8.4 ml/min) compared to the plasma clearance (232 ml/min) shows that zopiclone is cleared chiefly by metabolism. Zopiclone is eliminated in the urine (approximately 80%) in the form of unconjugated metabolites (N-oxide and N-desmethyl derivatives) and in the faeces (approximately 16%).

Special patient groups
In various trials with elderly patients, no accumulation of zopiclone was observed in the plasma after repeated doses, in spite of a slight reduction in the renal function and extension of the elimination half-life to approximately 7 hours.

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

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

5.3 Preclinical safety data
Hepatotoxic effects were elicited in repeated dose toxicity studies conducted in rats and dogs. In dogs anaemia were evident in some studies.

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

Increased incidence of mammary carcinomas in female rats at high multiples of the maximum plasma concentration from therapeutic doses in humans has been attributed to increased 17-beta-estradiol serum levels. Increased incidence in thyroid tumours in rats were associated with increased TSH serum levels. In humans zopiclone has no effects on thyroid hormones.

Fertility was impaired in two rat studies, whereas zopiclone had no adverse effects on fertility in rabbits.

Foetal developmental retardations and foetotoxic effects in rats and rabbits were observed only at doses well above the maximum human dosage. There was no evidence of a teratogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Lactose monohydrate
Calcium hydrogen phosphate dihydrate
Sodium Starch Glycolate (Type A)
Povidone K 30
Maize Starch
Colloidal Anhydrous Silica
Magnesium Stearate

Film-coating
Hypermellose
Titanium Dioxide E 171
Talc
Macrogol 6000
Indigo Carmine Al Lake E 132

6.2 Incompatibilities
Not applicable
6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container
PVC/PVDC/Al blister of 14 tablets.
Pack containing 28 tablets

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Ltd.
Unit 3, Canalside, Northbridge Road
Berkhamsted
Herts, HP4 1EG
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0122

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/06/2011

10 DATE OF REVISION OF THE TEXT
23/06/2011
1 NAME OF THE MEDICINAL PRODUCT
Zopiclone 7.5mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 7.5 mg zopiclone
Excipient: Each film-coated tablet contains 31.82 mg lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated Tablets (Tablets)
White to off white, round, biconvex film coated tablets with ‘BL’ embossing on one side and plain on
the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Short-term treatment of insomnia.

Benzodiazepines and benzodiazepine-like substances are only indicated when the disorder is severe,
disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration
Treatment with Zopiclone should be for as short a period as possible.

The period of treatment should generally vary between a few days to 2 weeks, with a maximum of
4 weeks including the tapering off phase. In certain cases it may be necessary to prolong treatment to
beyond the maximum period. If this is the case, however, it should only take place after re-evaluation
of the patient’s condition.

The recommended dose for adults is 7.5 mg (one tablet). This dose should not be exceeded.

The product should be taken immediately before going to bed.

In the elderly, patients with hepatic insufficiency or chronic respiratory insufficiency, treatment should
be started at a dosage of 3.75 mg.

Although no accumulation of zopiclone or its metabolites have been found in patients with renal
insufficiency, it is advisable to begin treatment of patients with reduced renal function at 3.75 mg.

4.4 Special warnings and precautions for use
Before starting treatment with zopiclone any underlying cause of insomnia should be addressed
carefully.

Contraindications
Zopiclone is contra-indicated in the following cases:
− Hypersensitivity to the active substance or to any of the excipients
− Myasthenia gravis
− Severe respiratory insufficiency
− Sleep apnoea syndrome
− Children and adolescents under 18 years of age
− Severe hepatic insufficiency

Dependence
The use of benzodiazepines and benzodiazepine-like substances can lead to physical and psychological
dependence on these agents. The risk of dependence increases the higher the dose and the longer the
period of treatment; the risk of dependence is also greater in patient with a history of alcohol or drug
abuse or those who have marked personality disorders. If physical dependence occurs, sudden
discontinuation of the treatment will be accompanied by withdrawal symptoms. These may be
expressed as headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise or physical contact, hallucinations or epileptic seizures. Rare cases of abuse have been reported.

**Rebound insomnia**
After discontinuation of treatment with a benzodiazepine or a benzodiazepine-like substance, a temporary syndrome may occur in which the symptoms which led to the treatment with the benzodiazepine or a benzodiazepine-like substance return in a more severe form. This syndrome may be accompanied by other reactions, including mood changes, anxiety and restlessness. Since the risk of withdrawal symptoms or rebound symptoms is greater after abrupt interruption of the treatment it is advisable to reduce the dosage gradually.

**Period of treatment**
The period of treatment should be as short as possible (see Posology and method of administration) but not longer than 4 weeks including the tapering off process. This period should only be exceeded after re-evaluation of the patient’s condition. It may be of benefit to inform the patient at the beginning of treatment that the treatment will be of short duration, and to explain precisely how to reduce the dose gradually. It is also important to point out to the patient the possibility of the occurrence of rebound phenomena in order to keep to a minimum any worries about the occurrence of such symptoms during the tapering off period of the treatment. In the case of benzodiazepines and benzodiazepine-like substances with a short period of action, there are indications that withdrawal symptoms may occur within the dosage interval, especially if the dose is high.

**Tolerance**
The hypnotic effect of short-acting benzodiazepines and benzodiazepine-like substances may diminish after repeated use for a few weeks. For zopiclone however, no pronounced tolerance has occurred during a treatment period of up to 4 weeks.

**Anterograde amnesia**
Benzodiazepines and benzodiazepine-like substances may cause anterograde amnesia, in particular a few hours after taking the product. In order to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see section 4.8 Undesirable effects).

**Psychiatric and paradoxical reactions**
It is known that reactions such as restlessness, agitation, irritability, aggression, delusions, outbursts of rage, nightmares, hallucination, psychoses, unsuitable behaviour and other behavioural disturbances may occur during the use of benzodiazepines and benzodiazepine-like substances. If this is the case administration of the medicinal product should be discontinued. The risk of these reactions is greater in children and the elderly.

**Somnambulism and associated behaviours**
Sleep walking and other associated behaviours such as “sleep driving”, preparing and eating food, or making phone calls, with amnesia for the event, have been reported in patients who have taken zopiclone and were not fully awake. The use of alcohol and other CNS-depressants with zopiclone appears to increase the risk of such behaviours, as does the use of zopiclone at doses exceeding the maximum recommended dose. Discontinuation of zopiclone should be strongly considered for patients who report such behaviours (see section 4.5).

**Specific patient groups**
For the elderly: see Posology and method of administration. A lower dose is advised for patients with chronic respiratory insufficiency due to the risk of respiratory depression. Benzodiazepines and benzodiazepine-like substances are not suitable for the treatment of patients with severe hepatic insufficiency, since they may promote the occurrence of encephalopathy. Benzodiazepines and benzodiazepine-like substances are not recommended as the primary treatment of psychoses. Benzodiazepines and benzodiazepine-like substances should not be used as the sole treatment of depression or anxiety linked with depression (suicide may be triggered in such patients). Benzodiazepines and benzodiazepine-like substances should be administered with extreme caution to patients with a previous history of alcohol or drug abuse.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
4.5 **Interaction with other medicinal products and other forms of interaction**

*Not recommended:*
Simultaneous ingestion with alcohol is not recommended because the sedative effect of zopiclone may be intensified. This may affect the ability to drive or operate machines.

*Take account of:*
Combination with other central depressive agents, such as antipsychotic agents (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressants, narcotic analgesics, anti-epileptics, anaesthetics and sedative antihistamines may increase the suppressive effect of zopiclone on the central nervous system and should therefore be carefully weighed.

In the case of narcotic analgesics potentiation of euphoria may also occur, which can lead to increased psychological dependence.

Combination of zopiclone with muscle relaxants may increase the muscle relaxing effect.

Since zopiclone is metabolised by CYP3A4, the plasma levels of zopiclone and thus the effect of zopiclone may be increased when used in combination with drugs which inhibit CYP3A4, such as macrolide antibiotics,azole antimycotics and HIV protease inhibitors, as well as grape fruit juice. Dose reduction should be considered if zopiclone is co-administered with CYP3A4 inhibitors. Drugs which induce CYP3A4, like phenobarbital, phenytoin, carbamazepine, rifampicine and products containing St John's wort, may reduce zopiclone plasma levels and thus the effect of zopiclone.

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

4.6 **Pregnancy and lactation**

*Pregnancy*
The safety of use in pregnant women has not been established.

Animal studies have shown that zopiclone partially crosses the placenta and does not have any teratogenic effects. Zopiclone should not be used during pregnancy unless clearly necessary.

If, for compelling medical reasons, zopiclone is prescribed during the last three months of pregnancy or during labour, effects on the neonate, such as hypothermia, hypotension, hypotonia, respiratory depression and decreased sucking reflex ("floppy infant syndrome") may be expected due to the pharmacological properties of the product. Because of the development of physical dependence, withdrawal symptoms may occur in neonates of mothers who have used zopiclone for long periods during the last months of pregnancy.

If zopiclone is prescribed to women of child-bearing age, they should be advised that if they are planning to become pregnant or think they may be pregnant, they should contact their doctor about discontinuing the treatment.

*Lactation*
The safety of use during lactation has not been established.
Zopiclone and its metabolites are excreted in breast milk. Although the concentration in breast milk is very low, zopiclone should not be prescribed to women during the lactation period.

*Fertility*
Zopiclone caused a decrease in fertility in male rats (see section 5.3)

4.7 **Effects on ability to drive and use machines**

Sedation, amnesia, impaired concentration and impaired muscular function may reduce the capability to drive or operate machines. The risk is increased with concomitant alcohol intake. The risk is even higher when sleep duration is insufficient. Patients should be warned not to drive or operate machines until treatment has finished or it has been established that performance is unimpaired. Due to residual effects this warning should also be considered the morning after administration of zopiclone.
4.8 Undesirable effects
In this section frequencies of undesirable effects are defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

A bitter taste or metallic after taste is the most common adverse reaction of zopiclone.

The following side effects have been observed in patients treated with zopiclone:

**Immune system disorders**
Rare: allergic reactions, skin reactions like itching and skin rash (including urticaria).
Very rare: Anaphylactic reactions and angioedema, Stevens-Johnson syndrome, Toxic epidermal necrolysis/Lyell’s syndrome, erythema multiforme.

**Psychiatric disorders**
Rare: Numbness, confusion, and depression. Paradoxical reactions such as restlessness, agitation, irritability, aggression, delusions, outbursts of rage, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural disturbances.
Very rare: Decreased libido.
Not known: Physical and psychological dependence.

See also below under “Depression”, “Psychiatric and paradoxical reactions” and “Dependence”.

**Nervous system disorders**
Very common: A bitter or metallic taste (dysgeusia).
Common: Sleepiness during the following day, reduced alertness, headache, dizziness.
Rare: Amnesia, incoordination, ataxia (occurs chiefly at the beginning of treatment and generally disappear after repeated administration), light-headedness.
Not known: Somnambulism (see section 4.4).

See also below under “Amnesia”

**Eye disorders**
Rare: Double vision (occurs chiefly at the beginning of treatment and generally disappear after repeated administration).

**Gastrointestinal disorders**
Common: Gastro-intestinal problems (including nausea and vomiting), dyspepsia.
Rare: Dry mouth.

**Musculoskeletal and connective tissue disorders**
Rare: Muscle weakness.

**General disorders and administration site conditions**
Rare: Tiredness.

**Investigations**
Rare: Slight to moderate increases of serum transaminases and/or alkaline phosphatase.

**Amnesia**
Anterograde amnesia may occur on therapeutic doses, and the risk is increased the higher the dose. Amnesia may be accompanied by inappropriate behaviour (see section 4.4).

**Depression**
Pre-existent depression may become manifest during the use of benzodiazepines and benzodiazepine-like substances (rare).
Psychiatric and paradoxical reactions
Reactions such as restlessness, agitation, irritability, aggression, delusions, outbursts of rage, nightmares, hallucinations, psychoses, inappropriate behavior and other behavioral disturbances may occur rarely or very rarely during the use of benzodiazepines and benzodiazepine-like substances. In some cases they may become quite severe with this agent. The risk of these reactions is greater in children and the elderly.

Dependence
Use may lead to physical dependence even at therapeutic dosages: discontinuation of the treatment may lead to withdrawal or rebound phenomena (see section 4.4). Psychological dependence may also occur. Misuse has been reported.

4.9 Overdose
In the few cases where overdosage with zopiclone has been reported, these reports were not accompanied by life-threatening effects unless the agent was ingested in combination with other medicaments which have a suppressive effect on the central nervous system, including alcohol. The most important phenomena are dizziness, lethargy and ataxia. Overdose of benzodiazepines or benzodiazepine-like agents is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma.

Treatment should be aimed at supporting vital functions and is chiefly symptomatic (e.g. induce vomiting, monitor the heart function and respiration).

Haemodialysis is not useful because of the high distribution volume of zopiclone. Flumazenil may be beneficial as an antidote. Flumazenil is not be used in mixed overdose or as a diagnostic test.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: hypnotic-sedative
ATC code N05C F01
Zopiclone is a benzodiazepine-like hypnotic agent which belongs to the group of cyclopyrrolones. The pharmacological properties are: sedation, anxiolysis, anticonvulsion, muscle relaxation. These effects are related to a specific agonistic effect on central receptors belonging to the GABA<sub>A</sub> macromolecular complex which regulates the opening of chloride channels. These effects are similar to those of benzodiazepines.

5.2 Pharmacokinetic properties
Absorption
Zopiclone is swiftly absorbed. Maximum plasma concentrations are achieved after 1½ - 2 hours and are approximately 30 and 60 ng/ml after administration of 3.75 mg and 7.5 mg respectively. Absorption is the same in men and women and is not affected by simultaneous ingestion of food or repetition of doses.

Distribution
Zopiclone is swiftly distributed from the vascular compartment. The plasma protein binding is at least 45% and is not saturable.

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

The elimination half-life is approximately 5 hours at the recommended doses. No accumulation occurs after repeated administration and individual differences appear slight.

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

Metabolism
The most important metabolites are the N-oxide derivative (pharmacologically active in animals) and the N-desmethyl metabolite (pharmacologically inactive in animals). Their apparent half-life times are approximately 4.5 hours and 7.4 hours respectively. No significant accumulation of the compound is seen following repeat dosing, (15mg) for 14 days.
Elimination
The low renal clearance of zopiclone (on average 8.4 ml/min) compared to the plasma clearance (232 ml/min) shows that zopiclone is cleared chiefly by metabolism. Zopiclone is eliminated in the urine (approximately 80%) in the form of unconjugated metabolites (N-oxide and N-desmethyl derivatives) and in the faeces (approximately 16%).

Special patient groups
In various trials with elderly patients, no accumulation of zopiclone was observed in the plasma after repeated doses, in spite of a slight reduction in the renal function and extension of the elimination half-life to approximately 7 hours.

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

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

5.3 Preclinical safety data
Hepatotoxic effects were elicited in repeated dose toxicity studies conducted in rats and dogs. In dogs anaemia were evident in some studies.

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

Increased incidence of mammary carcinomas in female rats at high multiples of the maximum plasma concentration from therapeutic doses in humans has been attributed to increased 17-beta-estradiol serum levels. Increased incidence in thyroid tumours in rats were associated with increased TSH serum levels. In humans zopiclone has no effects on thyroid hormones.

Fertility was impaired in two rat studies, whereas zopiclone had no adverse effects on fertility in rabbits.

Foetal developmental retardations and foetotoxic effects in rats and rabbits were observed only at doses well above the maximum human dosage. There was no evidence of a teratogenic potential.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet Core
Lactose monohydrate
Calcium hydrogen phosphate dihydrate
Sodium Starch Glycolate (Type A)
Povidone K 30
Maize Starch
Colloidal Anhydrous Silica
Magnesium Stearate

Film-coating
Hypermellose
Titanium Dioxide E 171
Talc
Macrogol 6000

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package in order to protect from light.
6.5 Nature and contents of container
PVC/PVDC/Al blister of 14 tablets.

Pack containing 28 tablets
Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Ltd.
Unit 3, Canalside, Northbridge Road
Berkhamsted
Herts, HP4 1EG
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0051

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/06/2011

10 DATE OF REVISION OF THE TEXT
23/06/2011
Module 3
Patient Information Leaflet

Zopiclone 3.75mg and 7.5mg Film-coated Tablets
UK/H/2575/001-2/DC

1. What Zopiclone Tablets are and what they are used for

Zopiclone belongs to a class of medicines called non-benzodiazepines. It has similar properties as benzodiazepines. You should take benzodiazepines or benzodiazepine-like substances only if you suffer from severe sleep disorders which cause you extreme distress.

Zopiclone, the active substance in Zopiclone Tablets, is a sedative-hypnotic drug (sleeping pill). It induces sleep and is used in the short-term treatment of sleeplessness.

2. Before you take Zopiclone Tablets

DO NOT take Zopiclone Tablets if:
- you are allergic (hypersensitive) to zopiclone or to any of the other ingredients of Zopiclone Tablets (see section 6. Further information)
- you suffer from any of the following diseases:
  - a serious muscle weakness caused by electrolyte disorders (an autoimmune disease),
  - acute respiratory insufficiency (a condition in which the gas exchange in the lungs is insufficient to meet the body's needs),
  - sleep apnoea syndrome (a sleep disorder characterized by pauses in breathing during sleep),
  - severe liver impairment
- you are a child or adolescent under 16 years of age.

Take special care with Zopiclone Tablets

Before treatment with Zopiclone Tablets:
- the cause of the sleep disturbances should be clarified
- underlying diseases should be treated.

Please tell your doctor if you have or have had any medical conditions or illnesses, especially any of the following:
- chronic respiratory insufficiency (caused by breathing or heart problems),
- unstable behaviour
- other serious medical conditions.

The risk of these reactions is higher in elderly patients. If you feel any of the symptoms listed above, you should stop taking Zopiclone Tablets. Ask your doctor for advice.

Sleepwalking (somniloquy) and associated behaviours

Sleepwalking and other associated behaviours such as "sleep driving", preparing and eating food, or making phone calls, with memory loss (amnesia) for the event, have been reported in patients who have taken zopiclone and were not fully aware of the risk such behaviours increase.

If alcohol or other medicines (such as nasiconal analgesics, antipsychotic agents, hypnotics or antidepressants) are used during treatment with zopiclone:

If zopiclone is used in doses exceeding the maximum recommended dose. If you develop such behaviours, please inform your doctor immediately. Your doctor may discontinue the treatment with zopiclone.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines, herbal remedies, health foods or supplements that you have obtained without a prescription.

The following medicines may increase the effect of Zopiclone:
- antipsychotics/cns depressants (used to treat psychoses),
- hypotensives (used to treat high blood pressure),
- sedative/hypnotics (used to treat anxiety),
- antiepileptic/anticonvulsants (used to treat epilepsy seizures),
- anxiolytics (used to treat anxiety),
- antihistamines (used to treat colds),
- antidepressants (used to treat depression),
- some medicines used to treat psychiatric conditions.

The combination of Zopiclone Tablets with muscle relaxants may enhance the muscle relaxation effect.

Tiredness and withdrawal reactions

During the use of benzodiazepines and benzodiazepine-like substances, the following reactions may occur:
- initial drowsiness
- agitation
- irritability
- depression
- anxiety
- palpitations
- feelings of being drunk
- sleep disturbances
- nightmares
- sleepwalking
- severe mental disorders characterized by alteration of personality and loss of contact with reality (psychoses).

Products containing St. John's wort (herb used to treat depression and anxiety).

Taking Zopiclone Tablets with food and drink:

You should not drink alcoholic beverages while you are on treatment with Zopiclone. Alcoholic drinks may increase the effect of the medicine. This may particularly affect your ability to drive or operate machines.

Avoid drinking grapefruit juice during the treatment. Grapefruit juice may enhance the effect of Zopiclone.

Pregnancy and breast-feeding

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

Please tell your doctor if you are pregnant, as it is not known if the medicine passes into breast milk. The use of zopiclone during pregnancy is not recommended yet.

Pregnancy

You should not take Zopiclone Tablets if you are pregnant. If zopiclone is used during the last three months of pregnancy, some effects on the newborn child may arise. These include low body temperature (hypothermia), and low blood pressure (hypotension), decreased muscle tone (hypotonia), very slow or shallow breathing (respiratory depression) and decreased sucking reflexes ("floppy infant syndrome"). Withdrawal symptoms may occur in newborns. This has been observed in children of mothers who have used zopiclone for long periods during the last months of pregnancy.

Your doctor will prescribe you Zopiclone Tablets only after weighing the risk against the benefits.

Breast-feeding

You should not take Zopiclone Tablets if you are breast-feeding. Zopiclone is excreted in breast milk.

Driving and using machines

You should not drive or operate machines until the treatment has finished or if it has been established that your performance is not impaired. Zopiclone may cause side effects which may affect your ability to drive and use machines. These are, for example:
- feeling numb (peripheral)
- loss of memory (amnesia)
- impaired coordination
- impaired muscle function.

The risk of these effects increases with alcohol intake and is even higher when the sleep duration is insufficient. The symptoms may affect you also in the next morning.

Important information about some of the ingredients of Zopiclone Tablets:

- Zopiclone Tablets contains milk sugar (lactose), if you have been told by your doctor that you have an intolerance to milk sugar, contact your doctor before taking this medicine.
Zopiclone 3.75mg and 7.5mg Film-coated Tablets

3. How to take Zopiclone

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

The usual dose is:

- Adults: The recommended dose is 7.5 mg zopiclone (two tablets of 3.75 mg or one tablet of 7.5 mg). This dose should not be exceeded.

- Children: You must not take Zopiclone Tablets if you are under 18 years of age.

Elderly patients, also with impaired liver or kidney function or chronic respiratory insufficiency (a condition in which the gases in the lungs is insufficient to meet the body's needs)

You should start the treatment at a dosage of 3.75 mg zopiclone.

Maximum dose:

A daily dose of 7.5 mg film-coated tablets of Zopiclone Tablets should not be exceeded.

Take Zopiclone Tablets just before going to bed. Make sure you will be able to have an uninterrupted sleep of 7-8 hours. Swallow the tablet with liquid (e.g. 1 glass of water), however not with grapefruit juice.

Please talk to your doctor if you think that the effect of Zopiclone Tablets is too weak or too strong.

Duration of the treatment:

Your treatment with Zopiclone Tablets should be as short as possible.

In general, it should last between a few days to 2 weeks. Your doctor will explain to you how to reduce the dose of Zopiclone Tablets gradually at the end of the treatment ( tapering off ). This measure (a slow withdrawal) or rebound symptoms (see section 4. "Take special care with Zopiclone ").

You should not take Zopiclone Tablets for longer than 4 weeks including the tapering off phase. Ask your doctor for advice if your symptoms do not improve within this period.

If you take more Zopiclone Tablets than you should:

If you have taken too many tablets, contact your doctor or nearest hospital casualty department immediately for advice.

Zopiclone overdose together with certain agents might be life-threatening.

These agents are drugs which have a suppressive effect on the central nervous system, including alcohol.

Overdose of benzodiazepines or barbiturates or substances usually causes depression of the central nervous system which ranges from drowsiness to coma. The most frequent symptoms are dizziness, loss of energy (lethargy) and difficulty coordinating muscle movements (ataxia).

If you forget to take Zopiclone Tablets:

If you forget to take a Zopiclone Tablet, do not take a double dose at the next time. Take the next dose as soon as possible. However, if you take the next dose more than 1 hour later, skip the missed dose and take the next dose as usual. Do not take a double dose.

4. Possible side effects

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

A minor taste or metallic after taste is the most common adverse reaction of Zopiclone.

The following side effects have been observed in patients treated with zopiclone.

Common (1 to 10 users in 100):

- difficulty coordinating muscle movements (ataxia), which occurs mainly at the beginning of the treatment and generally disappears after repeated use.
- light-headedness
- dizziness
- drowsiness
- dizziness and vertigo.
- gastrointestinal problems, including feeling sick (nausea) and vomiting.
- rate (1 to 10 users in 10,000):
- slight to moderate increases of certain liver enzymes (transaminases, alkaline phosphatase, bilirubin).
- loss of memory (amnesia) and
- confusion.

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

5. How to store Zopiclone Tablets:

Keep out of the reach and sight of children.

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

Do not take Zopiclone Tablets after the expiry date which is stated on the package and blister pack. The expiry date refers to the last day of that month.

Ask your pharmacist how to dispose of medicines no longer required.

What Zopiclone Tablets contain:

The active substance is zopiclone.

Each Zopiclone Tablet contains 3.75 mg or 7.5 mg of zopiclone.

The other ingredients are:

- Lactic acid monohydrate
- Calcium hydrogen phosphate dihydrate
- Sodium starch glycolate
- Povidone
- Croscarmellose sodium
- Magnesium stearate
- Hydroxypropyl, titanium dioxide E 171, talc, microcrystalline cellulose E 460.

What Zopiclone Tablets look like and contents of the pack:

Zopiclone Tablets 3.75 mg tablets are blue, round, biconvex film-coated tablets, plain on both sides.

Zopiclone Tablets 7.5 mg tablets are white, round, biconvex film-coated tablets, plain on both sides.

Zopiclone Tablets are available in packs containing 28 tablets in PVC/PVDC blister packs.

Marketing Authorisation Holder and Manufacturer:

Bristol Laboratories Ltd., Unit 3, Calefield, Northbridge Road, Berkhamsted, Herts, HP4 1EG

Telephone: 01442 851422 305929
Fax: 01442 855317
Email: info@bristol-labs.co.uk

This medicine is authorised in the Member States of the EEA under the following names:

- Zopiclone 3.75mg Film-coated Tablets
- Zopiclone 7.5mg Film-coated Tablets

Zopiclone 3.75mg Film-coated Tablets: PL 17967/0012
Zopiclone 7.5mg Film-coated Tablets: PL 17967/0001

This leaflet was last revised in May 2011

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20
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Zopiclone 3.75mg and 7.5mg Film-coated Tablets (PL 17907/0122 and 0051; UK/H/2575/001-2/DC) could be approved. The products are prescription-only medicines (POM) used in the short-term treatment of insomnia, when the disorder is severe, disabling or subjecting the patient to extreme distress.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Czech Republic, Germany, Hungary and Slovak Republic as Concerned Member States (CMS). The applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Zimovane LS 3.75mg film-coated tablets (Rhone-Poulenc Rorer, UK) and Zimovane 7.5mg film-coated tablets (Rhone-Poulenc Rorer, UK) which were first authorised in the UK on 06 May 1993.

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

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

A single-dose, bioequivalence study was submitted to support these applications, comparing the test product Zopiclone 7.5mg Film-coated Tablets (Bristol Pharmaceuticals Limited, UK) versus the reference product Zimovane 7.5mg film-coated tablets (Rhone-Poulenc Rorer, UK). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries...
with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites. The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 18 May 2011. After a subsequent national phase, licences were granted in the UK on 23 June 2011.

II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Zopiclone 3.75 mg Film-coated Tablets  
Zopiclone 7.5 mg Film-coated Tablets |
| Name(s) of the active substance(s) (INN) | Zopiclone |
| Pharmacotherapeutic classification (ATC code) | Hypnotic-sedative (N05C F01) |
| Pharmaceutical form and strength(s) | Film-coated tablets 3.75 mg and 7.5 mg |
| Reference numbers for the Decentralised Procedure | UK/H/2575/001/DC (PL 17907/0122)  
UK/H/2575/002/DC (PL 17907/0051) |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | Czech Republic, Germany, Hungary and Slovak Republic |
| Marketing Authorisation Number(s) | PL 17907/0051  
PL 17907/0122 |
| Name and address of the authorisation holder | Bristol Laboratories Ltd.  
Unit 3, Canalside, Northbridge Road  
Berkhamsted  
Herts, HP4 1EG  
UK |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

ACTIVE SUBSTANCE

INN:  Zopiclone
Chemical names:  (5RS)-6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate

Structure:

Molecular formula:  C₁₇H₁₇ClN₆O₃
Molecular Mass:  388.8
Appearance:  A white or slightly yellowish powder, practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, practically insoluble in ethanol (96 per cent). It dissolves in dilute mineral acids.

Zopiclone is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance zopiclone are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

MEDICINAL PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients in the tablet core and coating, namely lactose monohydrate, calcium hydrogen phosphate dihydrate, sodium starch glycolate (Type A), povidone K30, maize starch, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide (E171), talc, macrogl 6000. Additionally the 3.75mg strength tablet contains indigo carmine aluminium lake (E132). Appropriate justifications for the inclusion of each excipient have been provided.

With the exception of indigo carmine aluminium lake (E132), all excipients comply with their respective European Pharmacopoeia monograph. Indigo carmine aluminium lake (E132) is controlled to a suitable in-house specification and is in compliance with current EEC Directives concerning the use of colouring agents in foodstuff. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

No genetically modified organisms (GMO) have been used in the preparation of these products.
Pharmaceutical Development
The objective of the development programme was to produce safe, efficacious products which could be considered generic medicinal products of Zimovane LS 3.75 mg film-coated tablets (Rhone Poulenc Rorer, UK) and Zimovane 7.5 mg film-coated tablets (Rhone Poulenc Rorer, UK). Suitable pharmaceutical development data have been provided for these applications.

Comparative in-vitro dissolution and impurity profiles have been provided for these products versus their respective reference products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation on future full-scale (commercial) batches.

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, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The tablets are packaged in polyvinylchloride/polyvinylidene chloride/aluminium blisters in pack sizes of 28 film-coated 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 foodstuff.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches 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 package in order to protect from light.”

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL), Labels
The SmPCs, 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 they contains.
MAA Forms
The MAA forms are pharmaceutically satisfactory.

Expert Report
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of zopiclone are well-known, no further non-clinical studies are required and none have been provided.

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

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

The grant of Marketing Authorisations is recommended.
III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

The clinical pharmacology of zopiclone is well-known. With the exception of data from the below bioequivalence study, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

Pharmacokinetics

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, single-dose, open-label, two-treatment, two-sequence, two-period, crossover study comparing the pharmacokinetics of the test product Zopiclone 7.5mg Film-Coated Tablets (Bristol Laboratories Limited, UK) and the reference product Zimovane 7.5mg film-coated tablets (Rhone-Poulenc Rorer, UK) in healthy adult male subjects, under fasting conditions.

The subjects were given a 7.5mg dose of either treatment with about 240 ml of water after at least a 10-hour fast. Blood samples were collected before and up to 36 hours after each administration. The washout period between the two treatment arms was 7 days. The pharmacokinetic results are presented below:

Pharmacokinetic parameters (geometric mean, ratio and confidence intervals [CI]) for zopiclone (parent drug)

<table>
<thead>
<tr>
<th></th>
<th>Zopiclone 7.5mg (Test)</th>
<th>Zimovane 7.5mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>94.85</td>
<td>91.45</td>
<td>103.71</td>
<td>99.23-108.40</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/ml)</td>
<td>649.24</td>
<td>655.65</td>
<td>99.02</td>
<td>97.08-101.00</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng.h/ml)</td>
<td>669.67</td>
<td>675.43</td>
<td>99.15</td>
<td>97.15-101.19</td>
</tr>
</tbody>
</table>

AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
AUC<sub>0-inf</sub> area under the plasma concentration-time curve from time zero to infinity
C<sub>max</sub> maximum plasma concentration
90% geometric CI calculated from In-transformed data

Pharmacokinetic parameters (least square mean± standard deviation and ratio) for Zopiclone N-oxide (metabolite)

<table>
<thead>
<tr>
<th></th>
<th>Zopiclone 7.5 mg (Test)</th>
<th>Zimovane 7.5 mg (Reference)</th>
<th>Test/Ref Ratio(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>11.96±3.88</td>
<td>11.80±3.48</td>
<td>101.39</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng x hr/mL)</td>
<td>64.17±19.58</td>
<td>64.23±19.88</td>
<td>99.89</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng x hr/mL)</td>
<td>74.07±19.41</td>
<td>74.16±20.07</td>
<td>99.88</td>
</tr>
</tbody>
</table>

AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
AUC<sub>0-inf</sub> area under the plasma concentration-time curve from time zero to infinity
C<sub>max</sub> maximum plasma concentration
Pharmacokinetic parameters (least square mean ± standard deviation and ratio) for N-desmethyzopiclone (metabolite)

<table>
<thead>
<tr>
<th></th>
<th>Zopiclone 7.5 mg (Test)</th>
<th>Zimovane 7.5 mg (Reference)</th>
<th>Test/Ref Ratio(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>5.27±1.29</td>
<td>5.36±1.33</td>
<td>98.44</td>
</tr>
<tr>
<td>$\text{AUC}_{0\text{t}}$ (ng x hr/mL)</td>
<td>92.87±25.46</td>
<td>94.97±23.15</td>
<td>97.79</td>
</tr>
<tr>
<td>$\text{AUC}_{0\text{-}\infty}$ (ng x hr/mL)</td>
<td>107.46±27.15</td>
<td>108.14±25.03</td>
<td>99.35</td>
</tr>
</tbody>
</table>

$\text{AUC}_{0\text{-}\infty}$ area under the plasma concentration-time curve from time zero to infinity
$\text{AUC}_{0\text{t}}$ area under the plasma concentration-time curve from time zero to t hours
$C_{\text{max}}$ maximum plasma concentration

The Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) defines the confidence limits as 80% to 125% for $C_{\text{max}}$ and $\text{AUC}$ values. The 90% confidence intervals of the test/reference ratio of geometric means for $\text{AUC}_{0\text{t}}, \text{AUC}_{0\text{-}\infty}$ and $C_{\text{max}}$ lie within the acceptable limits. Thus, the data support the claim that the test product Zopiclone 7.5 mg Film-coated Tablets (Bristol Laboratories Limited, UK) is bioequivalent to the reference product Zimovane 7.5 mg film-coated tablets (Rhone Poulenc Rorer, UK).

As the 3.75mg and 7.5mg strength products meet the criteria for a biowaver specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions of the bioequivalence study with the 7.5mg tablet strength can be extrapolated to the 3.75mg tablet strength.

**Efficacy**
The efficacy of zopiclone is well-known. No new efficacy data have been submitted and none are required for applications of this type.

**Safety**
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues were highlighted by the bioequivalence study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPCs, PIL and labels are clinically acceptable. The SmPCs are consistent with those for the originator products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

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

**Pharmacovigilance System and Risk Management Plan**
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for these products.
Conclusion
The grant of Marketing Authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Zopiclone 3.75mg and 7.5mg 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.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of zopiclone are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 7.5mg strength tablets and the reference product. As the 3.75mg and 7.5mg strengths of the product meet the biowaiver criteria specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions of the bioequivalence study with the 7.5mg tablet strength can be extrapolated to the 3.75mg tablet strength product.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are acceptable. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in-line with current guidelines. The labelling is in-line with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that the applicant’s and the reference products are interchangeable. Extensive clinical experience with zopiclone is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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