Public Assessment Report

Decentralised Procedure

Zolpidem tartrate 5 mg film-coated tablets
Zolpidem tartrate 10 mg film-coated tablets

(zolpidem tartrate)

UK/H/1260/01-02/DC
UK licence numbers: PL 00057/1193-4

Pfizer Limited
LAY SUMMARY

On 11th February 2011, the MHRA granted Aurobindo Pharma Limited Marketing Authorisations (licences) for the medicinal products, Zolpidem tartrate 5 mg and 10 mg film-coated tablets (PL 20532/0148-9). These licences underwent Change of Ownership on 15th April 2011 and are now held by Pfizer Limited (PL 00057/1193-4). These are prescription-only medicines (POM).

Zolpidem is a hypnotic belonging to the group of benzodiazepine-like agents. It is used for short-term treatment of sleep disturbances. Treatment with benzodiazepines and benzodiazepine-like agents is only indicated for serious sleep disturbances.

The test products were considered to be generic versions of the UK reference products Stilnoct 5 mg and 10 mg tablets (PL 04425/0618 and 0619, Sanofi-Aventis) based on the data submitted by Pfizer Limited.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of Zolpidem tartrate 5 mg and 10 mg film-coated tablets outweigh the risks; hence Marketing Authorisations have been granted.
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## Module 1

### Information about Initial Procedure

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Zolpidem tartrate 10 mg film-coated tablets |
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<td>Active Substance</td>
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<tr>
<td>Form</td>
<td>Film-coated tablets</td>
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<td>Strength</td>
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<tr>
<td>MA Holder</td>
<td>Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ.</td>
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<td>Reference Member State (RMS)</td>
<td>UK</td>
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| Concerned Member States (CMS) | UK/H/1260/01/DC: Czech Republic, Hungary  
UK/H/1260/02/DC: Czech Republic, Hungary, Poland, Romania, Slovakia |
| Procedure Number | UK/H/1260/01-02/DC |
| Timetable | End of Procedure: Day 210 – 13th January 2011 |
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Zolpidem tartrate 5 mg and 10 mg film-coated tablets (PL 00057/1193-4) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Zolpidem tartrate 5 mg film-coated tablets
Zolpidem tartrate 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 / 10 mg zolpidem tartrate equivalent to 4.02 / 8.04 mg zolpidem.

Excipient: Each 5 / 10 mg film-coated tablet contains 41.6 / 83.2 mg lactose (as lactose monohydrate)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Zolpidem tartrate 5 mg film-coated tablets
White to off-white, circular, biconvex, film-coated tablets debossed with 'E' on one side and '78' on other side.

Zolpidem tartrate 10 mg film-coated tablets
White to off-white, oval shaped, biconvex, film-coated tablets debossed with 'E' on one side and '80' with a score line between '8' and '0' on other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For short-term treatment of insomnia.

Benzodiazepines or benzodiazepine-like medicinal products should only be used in insomnia of clinically relevant severity when the disorder is disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

For oral use
The medicinal product should be taken with fluid just before going to bed.

The duration of treatment should be as short as possible. In general it should be a few days to two weeks with a maximum, including the tapering off process, of four weeks.
The tapering off process should be tailored to the individual.

In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient’s status.

Adults:
The recommended daily dose for adults is 10 mg immediately before going to bed.

Elderly:
In elderly or debilitated patients who may be especially sensitive to the effects of zolpidem tartrate a dose of 5 mg is recommended. This dose should only be increased to 10 mg where the clinical response is inadequate and the medicinal product is well tolerated.
Patients with hepatic impairment

Patients with hepatic impairment who do not clear the medicinal product as rapidly as normal individuals, a dose of 5 mg is recommended. This dose should only be increased to 10 mg where the clinical response is inadequate and the medicinal product is well tolerated.

The total dose of zolpidem tartrate should not exceed 10 mg in any patient.

Children and adolescents under 18 years of age

Children and adolescents of less than 18 years of age must not be treated with Zolpidem tartrate.

4.3 Contraindications

- Hypersensitivity to zolpidem tartrate or to any of the excipients
- Myasthenia gravis
- Severe respiratory depression
- Obstructive sleep apnoea
- Severe hepatic insufficiency
- Children and adolescents of less than 18 years of age

4.4 Special warnings and precautions for use

General

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

General information relating to effects seen following administration of benzodiazepines or 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 of these products. The risk of dependence increases with dose and duration of treatment and is also greater in patients with a history of psychiatric disorders and/or alcohol or medicinal product abuse.

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

Rebound insomnia

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

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.

As the risk of withdrawal symptoms/rebound phenomena are more likely to develop after abrupt discontinuation of treatment, it is recommended to decrease the dose gradually.
**Duration of treatment**

The duration of treatment should be as short as possible (see section 4.2), but should not exceed 4 weeks including the tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration.

**Amnesia**

Benzodiazepines or benzodiazepine-like agents may induce anterograde amnesia. The condition usually occurs several hours after ingesting 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).

**Psychiatric and "paradoxical" reactions**

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

**Specific patient groups**

*Elderly or debilitated patients* should receive a lower dose: see recommended dosage (section 4.2).

Due to the myorelaxant effect there is a risk of falls and consequently of hip fractures particularly for elderly patients when they get up at night.

*Patients with renal insufficiency (see section 5.2)*

Although dose adjustment is not necessary, caution should be exercised.

*Patients with chronic respiratory insufficiency*

Caution should be observed when prescribing zolpidem tartrate since benzodiazepines have been shown to impair respiratory drive. It should also be taken into consideration that anxiety or agitation have been described as signs of decompensated respiratory insufficiency.

*Patients with severe hepatic impairment*

Benzodiazepines and benzodiazepine-like agents are not indicated for the treatment of patients with severe hepatic impairment as they may precipitate encephalopathy.

*Use in patients with psychotic illness:*

Benzodiazepines and benzodiazepine-like agents are not recommended for the primary treatment.

*Use in depression:*

Despite the fact that relevant clinical, pharmacokinetic and pharmacodynamic interactions with SSRI have not been demonstrated, zolpidem tartrate should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present. Due to the possibility of intentional overdose by the patient, the lowest amount of medicinal product that is feasible should be supplied to these patients.

Benzodiazepines and benzodiazepine-like agents should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

*Use in patients with a history of drug or alcohol abuse:*

Benzodiazepines and benzodiazepine-like agents should be used with extreme caution in patients with a history of alcohol or drug abuse. These patients should be under careful surveillance when receiving zolpidem tartrate since they are at risk of habituation and psychological dependence.

*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 of 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 behaviours, 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 behaviours (See section 4.5 and section 4.8).
The 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

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

Caution should be exercised when Zolpidem tartrate is used in combination with other CNS depressants (see section 4.4).

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 (see sections 4.8 and 5.1).

Co-administration of muscle relaxants may potentiate the muscle-relaxant effect - especially in elderly patients and at higher dosage (risk of falling!).

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

Zolpidem tartrate is metabolised by some enzymes of the cytochrome P450-family. The main enzyme is CYP3A4.

Rifampicin induces the metabolism of zolpidem tartrate, resulting in approximately 60% reduction in peak plasma concentrations and possibly decreased efficacy. Similar effects might be expected also with other strong inducers of cytochrome P450-enzymes (e.g. carbamazepine, and phenytoin).

Compounds that inhibit hepatic enzymes particularly CYP3A4 (e.g. azole antifungitcs, macrolide antibiotics, and grapefruit juice) may increase plasma concentrations and enhance the activity of zolpidem tartrate. However, when zolpidem tartrate is administrated with itraconazol (CYP3A4 inhibitor), the pharmacokinetic and pharmacodynamic effects are not significantly different. The clinical relevance of these results is unknown.

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

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

4.6 Pregnancy and lactation

Pregnancy

There are insufficient data to permit an assessment of the safety of Zolpidem tartrate during pregnancy.

Although animal studies have shown no teratogenic or embryotoxic effects, safety in pregnancy has not been established in humans.

Caution should be exercised when prescribing to pregnant women.

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspect that she is pregnant.

If, for compelling medical reason, 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 develop withdrawal symptoms in the postnatal period as a result of physical dependence.
**Breast-feeding**
Zolpidem tartrate passes into breast milk in minimal amounts. Zolpidem tartrate should therefore not be used during breast-feeding since effects on the infant have not been investigated.

**Fertility**:
In a rat reproduction study, there was no effect on fertility in males or females after daily oral doses of 4 to 100 mg base/kg or 5 to 130 times the recommended human dose in mg/m².

**4.7 Effects on ability to drive and use machines**
The medicinal product has major influence on the ability to drive and use machines. The ability to drive or to use machines may be adversely affected by sedation, amnesia, impaired concentration and impaired muscular function. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see section 4.5).

**4.8 Undesirable effects**
The following frequency data is the basis for the evaluation of undesirable effects:

- **Very common (>1/10)**
- **Common (>1/100 to < 1/10)**
- **Uncommon (>1/1,000 to < 1/100)**
- **Rare (>1/10,000 to < 1/1,000)**
- **Very rare (< 1/10,000)**
- **Not known (cannot be estimated 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.

These effects seem to be related with individual sensitivity and to appear more often within the hour following the medicinal product intake if the patient does not go to bed or does not sleep immediately (see section 4.2).

**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 tissue disorders**
- Not known: rash, pruritus, urticaria

**Musculoskeletal and connective tissue disorders**
- Not known: muscular weakness
4.9 Overdose

In reports of overdose with zolpidem tartrate alone, impairment of consciousness has ranged from somnolence to light coma. Besides visual disturbances, dystonia, ataxia and paradoxical reactions (restlessness, hallucinations) may occur. Individuals have fully recovered from overdoses up to 400 mg of zolpidem tartrate, 40 times the recommended dose.

General symptomatic and supportive measures should be used. Immediate gastric lavage should be used where appropriate. Intravenous fluids should be administered as needed. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Monitoring of respiratory and cardiovascular functions should be considered. Sedating drugs should be withheld even if excitation occurs.

Use of flumazenil may be considered when serious symptoms are observed. In the treatment of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Due to the high distribution volume and protein binding of zolpidem tartrate, haemodialysis and forced diuresis are not effective measures. Hemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem tartrate is not dialyzable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and Sedatives, Benzodiazepine related drugs ATC Code: N05CF02

Zolpidem tartrate, an imidazopyridine is a benzodiazepine-like hypnotic agent. In experimental studies it was shown that it has sedative effects at lower dosages than those required to exert anticonvulsant, myorelaxant or anxiolytic effects. These effects are related to a specific agonist action at central receptors belonging to the “GABA-omega” (BZ1 & BZ2) macromolecular receptor” complex, modulating the opening of the chloride ion channel. Zolpidem tartrate acts primarily upon omega (BZ1) receptor subtypes. The clinical relevance of this is not known.

5.2 Pharmacokinetic properties

Absorption
Zolpidem has both a rapid absorption and onset of hypnotic effect. Bioavailability is 70% following oral administration. It demonstrates linear kinetics in the therapeutic dose range. The therapeutic plasma level is between 80 and 200 ng/ml. Peak plasma concentration is reached at between 0.5 and 3 hours after administration.

Distribution
The distribution volume in adults is 0.54 l/kg and decreases to 0.34 l/kg in the elderly.

Protein binding amounts to 92%. 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.

Elimination
The elimination half-life is short, with a mean of 2.4 hours. 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.
Special populations
In patients with renal insufficiency, a moderate reduction in clearance is observed (independent of possible dialysis). The other pharmacokinetic parameters remain unaffected.

In elderly patients a reduced clearance has been observed. In a group of patients aged 81-95 years, the maximal plasma concentrations increased by around 80% without a significant change in the elimination half-life.

In patients with liver cirrhosis a 5-fold increase in AUC and a 3-fold increase in half-life was observed.

5.3 Preclinical safety data
Based on conventional studies of safety pharmacology, acute and chronic toxicity, toxicity to reproduction, genotoxicity and cancerogenic potential, preclinical data do not reveal any specific risk for humans.

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
Cellulose, microcrystalline
Sodium starch glycolate (Type A)
Magnesium stearate
Film-Coating:
Hypromellose
Macrogol 400
Titanium dioxide (E171)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
PVC/PVDC-Aluminium blister Pack sizes: 4, 5, 7, 8, 10, 14, 15, 20, 25, 28, 30, 40, 50, 56, 60, 70, 80, 84, 90, 98, 100, 105, 112, 150, 250 and 500 film-coated tablets.

HDPE bottle with white opaque polypropylene stock ribbed closure. Pack sizes of 30, 50, 100, 250 and 500.
The HDPE container contains Rayon coil as an absorbent to fill the void in it.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Pfizer Limited,
Ramsgate Road,
Sandwich,
Kent CT13 9NJ.
8 MARKETING AUTHORISATION NUMBER(S)
   PL 00057/1193
   PL 00057/1194

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   11/02/2011

10 DATE OF REVISION OF THE TEXT
    11/02/2011
Module 3
Patient Information Leaflet

Zolpidem tartrate 5 mg & 10 mg film-coated tablets

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

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

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

1. What Zolpidem tartrate is and what it is used for

Zolpidem is a hypnotic belonging to the group of benzodiazepine-like agents. It is used for short-term treatment of sleep disturbances.

Treatment with benzodiazepines and benzodiazepine-like agents is only indicated for serious sleep disturbances.

2. Before you take Zolpidem tartrate

DO NOT take Zolpidem tartrate if
- you are allergic (hypersensitive) to zolpidem tartrate or any of the other ingredients of Zolpidem tartrate tablets
- you suffer from a condition in which your muscles are weak and there is a risk of respiratory depression
- you have difficulty breathing (respiratory insufficiency)
- you suffer from difficulty breathing while asleep (sleep apnea syndrome)
- you suffer from severe liver damage (hepatic insufficiency)
- you are under the age of 18

Take special care with Zolpidem tartrate

Tell your doctor if:
- you suffer from chronic obstructive sleep apnoea (obesity)
- you have a history of drug or alcohol abuse
- you have a history of psychiatric illness
- you are depressed, think you are depressed or are being treated for depression. Zolpidem tablets may worsen or worsen pre-existing symptoms
- you are elderly

3. How to take Zolpidem tartrate

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

Taking this medicine
- Take this medicine by mouth
- Swallow the tablet whole with a drink of water
- Take just before bedtime. Make sure you have at least 7-8 hours for sleep after taking this medicine
- The usual length of treatment is 2 days to 4 weeks

Adolescents
- The recommended daily dose is 10 mg zolpidem tartrate, just before bedtime.

Elderly and debilitated patients
- A dose of 5 mg zolpidem tartrate/day is recommended.
- This dose should be increased only in exceptional cases.

Patients with impaired liver function
- In patients with impaired liver function a dose of 5 mg zolpidem tartrate/day is recommended.

Children and adolescents
- Zolpidem tartrate must not be used in children and adolescents of less than 18 years of age.

A daily dose of 10 mg should not be exceeded.

If you take more Zolpidem tartrate than you should
- In case of overdose, a doctor's advice is to be asked without delay.
- In case of overdose of Zolpidem tartrate alone, depression and psychiatric reactions have been reported at doses far above the range from extreme sleepiness up to light coma.

Side effects
- Nausea, restlessness, irritability, anxiety, dizziness, headache, visual disturbances, itching, increased sweating, insomnia, and memory loss. Motivation and reproductive performance may be impaired.

Driving and using machines
- Do not drive or use machines while taking if you experience sleepiness, memory defects, impaired concentration or impaired muscular function. This applies to a higher degree if you are not getting enough sleep.

Important information about some of the ingredients of Zolpidem tartrate
- Zolpidem tartrate tablet contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

4. Possible side effects

Some of the side effects that may occur are:
- Headache
- Nausea
- Dizziness
- Drowsiness
- Dry mouth
- Unusual tiredness

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 Zolpidem tartrate Tablets

Keep out of the reach of children.
- Store in a tight, light-resistant container.
- Store below 25°C.

6. Further information

Zolpidem tartrate 5 mg and 10 mg film-coated tablets

module 3

patient information leaflet

package leaflet: information for the user
PAR Zolpidem tartrate 5 mg and 10 mg film-coated tablets

If you forget to take Zolpidem tartrate
DO NOT take a double dose to make up for a forgotten dose. Continue intake of Zolpidem tartrate as prescribed by your doctor.

If you stop taking Zolpidem tartrate
Keep taking Zolpidem tartrate until your doctor tells you to stop. Do not stop taking Zolpidem tartrate suddenly, but tell your doctor if you want to stop. Your doctor will need to lower your dose and stop your tablets over a period of time.

When stopping this medicine you may experience side effects called withdrawal symptoms.
These include:
- headache or muscle pain
- lability or anxiety
- sadness
- sleep disturbances

In severe cases:
- a feeling of things being unreal (derealisation or disorientation)
- sounds seeming louder than usual that can be painful (hyperacusis)
- numbness and tingling of extremities
- hyperresponsivity to light, noise and physical contact
- hallucinations
- aphasic or clonic seizures

You may also experience a condition called rebound insomnia when stopping this medicine. This is an inability to sleep which may be worse than the insomnia you had before you started treatment. You may also experience mood changes, anxiety and restlessness. The risk of withdrawal symptoms and rebound insomnia is greater if you stop taking this medicine suddenly. Therefore your doctor may decide to gradually reduce the dose you take before you stop taking this medicine.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

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

Stop taking Zolpidem tartrate and see a doctor or go to a hospital straight away if:
- You have an allergic reaction. The signs may include: a rash, swelling or breathing problems, swelling of your face, hands or tongue.

Tell your doctor as soon as possible if you have any of the following side effects:

Common (affects less than 1 in 10 people)
- Headache
- Dizziness
- Insomnia
- Nausea
- Irritability
- Sleep disturbances

Uncommon (affects less than 1 in 100 people)
- Insomnia or shortness of breath
- Feeling of things being unreal (derealisation or disorientation)

Frequency unknown
- Feeling of things being unreal (derealisation or disorientation)
- Feeling of things being unreal (derealisation or disorientation)

Sleep Driving and other strange behaviour
There have been some reports of people doing things while asleep that they do not remember when waking up after taking a Zolpidem tartrate.
This includes sleep-driving, sleepwalking and having sex.

Alcohol and other medicines for depression can increase the chance that this side effect will happen.

Tell your doctor or pharmacist if any of the following side effects get serious or last longer than a few days:

Common (affects less than 1 in 10 people)
- Headache
- Dizziness
- Insomnia
- Nausea
- Irritability

Uncommon (affects less than 1 in 100 people)
- Feeling of things being unreal (derealisation or disorientation)

Frequency unknown
- Feeling of things being unreal (derealisation or disorientation)
- Feeling of things being unreal (derealisation or disorientation)

Talk to your doctor or pharmacist if any of the following side effects get serious or last longer than a few days, or if you notice any side effect not listed in this leaflet.

5. How to store Zolpidem tartrate Tablets

Keep out of the reach and sight of children.

Do not use Zolpidem tartrate after the expiry date.

This medicinal product does not require any special storage conditions.

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

6. Further Information

What Zolpidem tartrate contains
- The active substance is zolpidem tartrate.
- One film-coated tablet contains 5 mg zolpidem tartrate equivalent to 4.02 mg zolpidem.
- One film-coated tablet contains 10 mg zolpidem tartrate equivalent to 8.04 mg zolpidem.
- The other ingredients are:
  - Tablet core:
    - Lactose monohydrate, cellulose microcrystalline, sodium starch glycolate (type A), magnesium stearate.
  - Tablet film-coating:
    - Hypromellose, microcrystal 400, titanium dioxide (E 171)

What Zolpidem tartrate looks like and contents of the pack

Film-coated tablet.

Zolpidem tartrate 5 mg film-coated tablets are white to off-white, oval, brown, coated with 'Z' on one side and '1' on the other side.

Zolpidem tartrate 10 mg film-coated tablets are white to off-white, oval shaped, brown, coated with 'Z' on one side and '2' with a score line between 'D' and 'P' on the other side. The tablet can be divided into equal halves.

Blisters
Pack sizes: 4, 5, 7, 8, 10, 14, 15, 20, 25, 28, 30, 40, 50, 56, 60, 70, 84, 90, 98, 100, 105, 112, 150, 250 and 500 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Piller Limited,
Romagale Road,
Sandwich,
Kent CT 13 9NL.

Manufacturer

Piller Service Company,
Hog Weal 10, B - 19000,
Zwevegem,
Belgium.

PRIMAR PPM,
Zoo industrieel 20,
mont des Industries,
37620 Puil Sur Clise,
France.

Piller Italia s.r.l.,
Locatelli Marco Del Sereto,
03100 - Asolo Pioano (AP),
Italy.

This leaflet was last approved on 03/2011.

Ref: puZL_1_0.UK
Module 4

Labelling

Zolpidem tartrate 5 mg film-coated tablets

Blister pack presentation

Carton
Zolpidem tartrate #5 mg film coated tablets

Braille

Blister foil
HDPE container presentation – text only

PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT
Zolpidem tartrate 5 mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each film-coated tablet contains 5 mg zolpidem tartrate equivalent to 4.02 mg zolpidem.

3. LIST OF EXCIPIENTS
Contains lactose, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS
Film-coated tablet

   HDPE bottle:
   30 film-coated tablets
   50 film-coated tablets
   100 film-coated tablets
   250 film-coated tablets
   500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
<table>
<thead>
<tr>
<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer Limited,</td>
</tr>
<tr>
<td>Ramsgate Road,</td>
</tr>
<tr>
<td>Sandwich, Kent CT 13 9NJ</td>
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<table>
<thead>
<tr>
<th>12. MARKETING AUTHORISATION NUMBER(S)</th>
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<tr>
<td>PL 00057/1193</td>
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<table>
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<tr>
<th>13. BATCH NUMBER</th>
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</thead>
<tbody>
<tr>
<td>Lot</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>15. INSTRUCTIONS ON USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use as directed by a medical doctor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>16. INFORMATION IN BRAILLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem tartrate 5 mg film-coated tablets</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING HDPE TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Zolpidem tartrate 5 mg film-coated tablets

Zolpidem tartrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 5 mg zolpidem tartrate equivalent to 4.02 mg zolpidem.

3. LIST OF EXCIPIENTS

Contains lactose, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet.

30 film-coated tablets
50 film-coated tablets
100 film-coated tablets
250 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

---------

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

-----
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pfizer Limited,
Ramsgate Road,
Sandwich,
Kent CT13 9NJ

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 00057/1193

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

Use as directed by a medical doctor

16. **INFORMATION IN BRAILLE**

----------
Zolpidem tartrate 10 mg film-coated tablets

Blister pack presentation

Carton
Zolpidem tartrate 5 mg and 10 mg film-coated tablets

Braille

Zolpidem tartrate #10 mg film coated tablets

Blister foil
HDPE container presentation – text only

PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zolpidem tartrate 10 mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg zolpidem tartrate equivalent to 8.04 mg zolpidem.

3. LIST OF EXCIPIENTS

Contains lactose, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

HDPE bottle:
- 30 film-coated tablets
- 50 film-coated tablets
- 100 film-coated tablets
- 250 film-coated tablets
- 500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-------

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

-------

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-------
11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

   Pfizer Limited,
   Ramsgate Road,
   Sandwich,
   Kent CT 13 9NJ

12. **MARKETING AUTHORISATION NUMBER(S)**

   PL 00057/1194

13. **BATCH NUMBER**

   Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   POM

15. **INSTRUCTIONS ON USE**

   Use as directed by a medical doctor

16. **INFORMATION IN BRAILLE**

   Zolpidem tartrate 10 mg film-coated tablets
PARTICULARS TO APPEAR ON THE OUTER PACKAGING HDPE TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Zolpidem tartrate 10 mg film-coated tablets
Zolpidem tartrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg zolpidem tartrate equivalent to 8.04 mg zolpidem.

3. LIST OF EXCIPIENTS

Contains lactose, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet.

30 film-coated tablets
50 film-coated tablets
100 film-coated tablets
250 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-------

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

-------
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pfizer Limited,  
Ramsgate Road,  
Sandwich,  
Kent CT 13 9NJ

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 00057/1194

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

Use as directed by a medical doctor

16. **INFORMATION IN BRAILLE**
Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Aurobindo Pharma Limited Marketing Authorisations for the medicinal products Zolpidem tartrate 5 mg and 10 mg film-coated tablets (PL 20532/0148-9; UK/H/1260/01-02/DC) on 11th February 2011. These licences subsequently underwent Change of Ownership on 15th April 2011 and are now held by Pfizer Limited (PL 00057/1193-4). The products are prescription-only medicines.

These are generic applications for Zolpidem tartrate 5 mg and 10 mg film-coated tablets, submitted under Article 10.1 of Directive 2001/83 EC, as amended. The applications refer to the UK products, Stilnoct 5 mg and 10 mg tablets, originally licensed to Lorex Synthelabo Ltd (PL 04969/0017 and 0027) on 16th February 1993 and 16th September 1996 respectively. The licences for the reference products have undergone a series of Change of Ownership (CoA) procedures and were authorised to the current Marketing Authorisation Holder, Sanofi-Aventis (PL 04425/0618-9) on 3rd December 2009 and 26th January 2009 respectively. Stilnoct tablets are the innovator products in the UK and have been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the Reference Member State (RMS) in these Decentralised Procedures, Aurobindo Pharma Limited applied for Marketing Authorisations for Zolpidem tartrate 5 mg film-coated tablets in the Czech Republic and Hungary, and for Zolpidem tartrate 10 mg film-coated tablets in the Czech Republic, Hungary, Poland, Romania and Slovakia.

Zolpidem tartrate 5 mg and 10 mg film-coated tablets contain the active ingredient zolpidem tartrate, which is a benzodiazepine-related drug belonging to the pharmacotherapeutic group, hypnotics and sedatives (ATC code N05C F02). The tablets are indicated for the short-term treatment of insomnia. Benzodiazepines or benzodiazepine-like medicinal products should only be used in insomnia of clinically relevant severity when the disorder is disabling or subjecting the individual to extreme distress.

Zolpidem tartrate, an imidazopyridine is a benzodiazepine-like hypnotic agent. In experimental studies it was shown that it has sedative effects at lower dosages than those required to exert anticonvulsant, myorelaxant or anxiolytic effects. These effects are related to a specific agonist action at central receptors belonging to the ‘GABA-omega (BZ1 & BZ2) macromolecular receptor’ complex, modulating the opening of the chloride ion channel. Zolpidem tartrate acts primarily upon omega (BZ1) receptor subtypes. The clinical relevance of this is not known.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Zolpidem tartrate 10 mg film-coated tablets, to that of the reference product, Stilnoct 10 mg tablets (Sanofi-Aventis). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).
The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly 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 or 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 considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) 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.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market.
### II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Zolpidem tartrate 5 mg film-coated tablets  
Zolpidem tartrate 10 mg film-coated tablets |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
</tr>
</tbody>
</table>
| Pharmacotherapeutic classification (ATC code) | Hypnotics and Sedatives, Benzodiazepine  
related drugs  
(N05C F02) |
| Pharmaceutical form and strength(s)           | Film-coated tablets  
5 mg, 10 mg |
| Reference numbers for the Decentralised Procedure | UK/H/1260/01-02/DC |
| Reference Member State                        | United Kingdom |
| Member States concerned                       | UK/H/1260/01/DC: CZ, HU  
UK/H/1260/02/DC: CZ, HU, PO, RO, SK |
| Marketing Authorisation Number(s)             | PL 00057/1193-4 |
| Name and address of the authorisation holder  | Pfizer Limited,  
Ramsgate Road,  
Sandwich,  
Kent CT13 9NJ. |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

ACTIVE SUBSTANCE

Zolpidem tartrate

Nomenclature:

INN: Zolpidem tartrate

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

Structure:

\[
\text{Molecular formula: } C_{42}H_{48}N_6O_8 \\
\text{Molecular weight: } 764.9 \text{ g/mol} \\
\text{CAS No: } 99294-93-6 \\
\text{Physical form: White-almost white, crystalline, hygroscopic powder} \\
\text{Solubility: Slightly soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride}
\]

The active substance, zolpidem tartrate, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of zolpidem tartrate are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of zolpidem tartrate for inclusion in these medicinal products.
MEDICINAL PRODUCT

Description and Composition

Zolpidem tartrate 5 mg and 10 mg film-coated tablets are presented as white to off-white, biconvex, circular (5 mg) and oval-shaped (10 mg), film-coated tablets containing 5 mg or 10 mg of the active ingredient, zolpidem tartrate. The 10 mg tablets have a score-line on side and can be divided into equal halves (refer to SmPCs / patient information leaflet for full descriptions of individual tablets and their markings).

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A) and magnesium stearate making up the tablet core; and hypromellose, macrogol 400 and titanium dioxide (E171) comprising the film-coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic formulations, bioequivalent to the reference products, Stilnoct 5 mg and 10 mg tablets (Sanofi-Aventis).

Comparative dissolution and impurity data were provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacture

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

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted on the minimum production batch sizes and the results were satisfactory. The MAH has provided a commitment to validate full-scale production batches in accordance with the agreed protocol.

Finished product specification

The finished product specifications are provided for both release and shelf-life and are 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. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.
Container Closure System

Zolpidem tartrate 5 mg and 10 mg film-coated tablets are proposed to be packed in bulk packs for repackaging into marketable packs. The bulk pack consists of a clear Low Density Polyethylene (LDPE) bag as a primary packaging material, contained in triple-laminated bags.

The medicinal products are licensed for marketing in PVC (polyvinylchloride) - PVdC (polyvinylidene chloride) / aluminium foil blister strips, or in High-Density Polyethylene (HDPE) containers, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The licensed pack sizes are blister packs of 4, 5, 7, 8, 10, 14, 15, 20, 25, 28, 30, 40, 50, 56, 60, 70, 80, 84, 90, 98, 100, 105, 112, 150, 250 and 500 film-coated tablets, and HDPE container packs of 30, 50, 100, 250 and 500 film-coated tablets. The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support a shelf-life of 3 years. These medicinal products do not require any special storage conditions.

Bioequivalence Study

A bioequivalence study was submitted comparing the test product, Zolpidem tartrate 10 mg film-coated tablets, to the reference product, Stilnoct 10 mg tablets (Sanofi-Aventis). An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Quality Overall Summary

A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling (for blister presentations) have been provided. For the HDPE container presentation, text versions of the labelling have been provided. The PIL user testing report has been evaluated and is accepted. The labelling fulfils the statutory requirements for Braille.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes / presentations to the UK regulatory authority for approval before those packs are commercially marketed.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Zolpidem tartrate 5 mg and 10 mg film-coated tablets from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic and toxicological properties of zolpidem tartrate, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the innovator UK products, Stilnoct 5 mg and 10 mg tablets (Sanofi-Aventis).

There are no objections to approval of Zolpidem tartrate 5 mg and 10 mg film-coated tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS

Zolpidem tartrate 5 mg and 10 mg film-coated tablets are indicated for the short-term treatment of insomnia. Benzodiazepines or benzodiazepine-like medicinal products should only be used in insomnia of clinically relevant severity when the disorder is disabling or subjecting the individual to extreme distress.

The indications are consistent with those for the UK reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The recommended daily dose for adults is 10 mg immediately before going to bed. For elderly patients and patients with hepatic insufficiency, a starting dose of 5 mg is recommended, which may be increased as required. Children and adolescents of less than 18 years of age must not be treated with zolpidem tartrate.

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the UK reference products and is satisfactory.

TOXICOLOGY

The toxicology of zolpidem tartrate is well known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of zolpidem tartrate is well known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics – bioequivalence study

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Zolpidem tartrate 10 mg film-coated tablets, to that of the reference product, Stilnoct 10 mg tablets (Sanofi-Aventis). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for both the test and reference products.

This was an open-label, randomised, two-treatment, two-sequence, two-period, single dose crossover bioequivalence study conducted in 48 healthy adult human male subjects under fasting conditions. Following an overnight fast of at least 10 hours, a single dose of the
investigational products was administered orally, with 240 ml of water, to each subject in each period. A satisfactory washout period of 7 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 16.0 hours after administration of test or reference product. Plasma levels of zolpidem were detected by a validated LC-MS / MS method.

The primary pharmacokinetic parameters for this study were $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$.

Results:

48 subjects were enrolled in the study; 44 of these completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation, and non-inclusion in the pharmacokinetic analysis, of 4 subjects was satisfactorily justified.

Safety – Twenty-three adverse events were observed during the entire duration of the study. Vital signs showed no marked changes throughout the study. Most adverse events reported during the study were drowsiness, sometimes associated with vomiting. There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference Product (X)</td>
<td>Test Product (Y)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>150.101</td>
<td>157.490</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ (ng.h/ml)</td>
<td>595.273</td>
<td>600.942</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (ng.h/ml)</td>
<td>618.199</td>
<td>624.478</td>
</tr>
</tbody>
</table>

Conclusion on Bioequivalence

The results of the bioequivalence study show that the test and reference products are bioequivalent under fasting conditions, as the confidence intervals for $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$ for zolpidem fall within the acceptance criteria ranges of 80.00-125.00%, in line with current CHMP guidelines.

Satisfactory justification is provided for a bio-waiver for Zolpidem tartrate 5 mg film-coated tablets. As Zolpidem tartrate 5 mg and 10 mg film-coated tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10 mg strength can be extrapolated to the 5 mg strength tablets.
Clinical efficacy
No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of zolpidem tartrate is well-established from its extensive use in clinical practice.

Clinical safety
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of zolpidem tartrate is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)
The approved SmPCs are consistent with those of the UK reference products and are acceptable.

Patient Information Leaflet
The final PIL is in line with the approved SmPCs and is satisfactory. The PIL user testing has been evaluated and is accepted.

Labelling
The labelling is satisfactory.

Clinical overview
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

CONCLUSIONS
For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the reference UK products, Stilnoct 5 mg and 10 mg tablets (Sanofi-Aventis).

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended on medical grounds.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Zolpidem tartrate 5 mg and 10 mg 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 and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Zolpidem tartrate 10 mg film-coated tablets and the UK reference product, Stilnoct 5 mg tablets (Sanofi-Aventis).

As the proposed products, Zolpidem tartrate 5 mg and 10 mg film-coated tablets, meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10 mg strength were extrapolated to the 5 mg strength tablets, and omission of further bioequivalence studies on the lower strength can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with those of the UK reference products and are satisfactory.

The PIL is in line with the SmPCs and is satisfactory. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork (for blister presentations) complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. For the HDPE container presentation, text versions of the labelling have been provided. The MAH has committed to submitting mock-ups for unmarketed pack sizes / presentations to the UK regulatory authority for approval before those packs are marketed.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s Zolpidem tartrate 5 mg and 10 mg film-coated tablets are generic versions of the reference products, Stilnoct 5 mg and 10 mg tablets (PL 04425/0618 and 0619, Sanofi-Aventis). Extensive clinical experience with zolpidem tartrate is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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