Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zimovane 7.5mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 7.5mg zopiclone
Excipients : also contains lactose monohydrate and wheat starch
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)
Product imported from the UK
White elliptical film-coated tablets with a score line on one side, plain on the reverse

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short-term treatment of insomnia

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

4.2 Posology and method of administration

Treatment should be as short as possible. Generally the duration of treatment varies from a few days to two weeks with a maximum, including tapering off of four weeks. 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. The product should be taken just before retiring for the night.

Dose
The recommended dose for adults is 7.5mg. This dose should not be exceeded.
Treatment of the elderly and patients with impaired liver function or chronic respiratory insufficiency should be initiated on a dose of 3.75mg and if necessary increased to 7.5mg.

Although in case of renal insufficiency no accumulation of zopiclone or of its metabolites has been detected, it is recommended that patients with impaired renal function should start treatment with 3.75mg.

4.3 Contraindications

Myasthenia gravis
Hypersensitivity to zopiclone
Severe respiratory insufficiency
Severe sleep apnoea syndrome
Severe hepatic insufficiency
Use in children.

4.4 Special warnings and precautions for use

Tolerance
Some loss of efficacy to the hypnotic effects of benzodiazepines and benzodiazepine-like agents may develop after repeated use for a few weeks. However with zopiclone there is an absence of any marked tolerance for treatment periods of up to 4 weeks.

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

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

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

The risk of rebound insomnia and withdrawal phenomena after abrupt discontinuation of zopiclone cannot be excluded, especially after prolonged treatment. It is, therefore recommended to decrease the dosage gradually and to advise the patient accordingly. (See also section 4.8 Undesirable Effects.

Duration of treatment
The duration of treatment should be as short as possible (see section 4.2 Posology and Method of Odministration) depending on the indication, but should not exceed 4 weeks for insomnia including 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 and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued.
There are indications that, in the case of benzodiazepines and benzodiazepine-like agents with short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

Amnesia
Benzodiazepines and benzodiazepine-like agents may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have uninterrupted sleep of 7 - 8 hours (see section 4.8 Undesirable Effects)

Psychiatric and paradoxical reactions
Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychosis, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines and benzodiazepine-like agents. Should this occur, use of the drug should be discontinued.

These reactions are more likely to occur in children and the elderly.

Specific patient groups
Elderly should be given a reduced dose (see section 4.2 Posology and Method of Odministration). A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression. Benzodiazepines and benzodiazepine-like agents are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.

Benzodiazepines and benzodiazepine-like agents are not recommended for the primary treatment of psychotic illness.
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).

Benzodiazepines and benzodiazepine-like agents should be used with extreme caution in patients with a history of alcohol or drug abuse.

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

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended - Concomitant intake with alcohol

The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Take into account - Combination with CNS depressants

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative anti-histamines.

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

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450), may enhance the activity of benzodiazepines and benzodiazepine-like agents. To a lesser degree this also applies to benzodiazepines and benzodiazepine-like agents that are metabolised only by conjugation.

The effect of erythromycin on the pharmacokinetics of zopiclone has been studied in 10 healthy subjects. The AUC of zopiclone is increased by 80% in the 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.

Since zopiclone is metabolised by the cytochrome P450 (CYP) 3A4 isoenzyme (see section 5.2 Pharmacokinetics), plasma levels may be increased when co-administered with CYP 3A4 inhibitors, such as erythromycin, clarithromycin, ketoconazole, itraconazole and ritonavir. A dose reduction for zopiclone may be required when it is administered with CYP 3A4 inhibitors. Conversely, plasma levels of zopiclone may be decreased when co-administered with CYP 3A4 inducers, such as rifampicin, carbamazepine, phenobarbital, phenytoin, and St. John's wort. A dose increase for zopiclone may be required when it is co-administered with CYP 3A4 inducers.

4.6 Fertility, pregnancy and lactation

Insufficient data are available on zopiclone to assess its safety during pregnancy and lactation, therefore its use is not recommended.

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 suspects that she is pregnant.

Administration of the medicinal product during the last three months of pregnancy or during labour is only allowed on strict medical indication as, due to the pharmacological action of the product, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression can be expected.

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

Since benzodiazepines and benzodiazepine-like agents are found in the breast milk, zopiclone should not be administered to breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also Interactions). Patients should be advised not to drive or to operate machinery until it is established that their performance is not impaired.

4.8 Undesirable effects

For this product no modern clinical documentation is available to determine frequency of adverse effects.

Bitter taste is the most common side effect observed with Zopiclone.

	Frequency	
MedDRA SOC	***Very rare (<1/10,000)***	***Not known***
Investigations	Transaminases increased, alkaline phosphatise increased	
Nervous system disorders		Taste bitter, drowsiness, alertness decreased, confusion, headache, dizziness, muscle weakness, ataxia, double vision, anterograde amnesia.
Gastrointestinal disorders		Gastrointestinal disorder
General disorders and administration site conditions		Fatigue
Immune system disorders	Angioedema, anaphylactic reaction	Allergic reaction (such as pruritus or rash)
Psychiatric disorders		Affective blunting, libido disorder, restlessness, agitation, irritability, aggressiveness, delusion, rage, nightmare, hallucination, psychosis, abnormal behaviour, drug dependence physical, drug dependence psychic.

Drowsiness, affective blunting, alertness decreased, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision occur predominantly at the start of the therapy and usually disappear with repeated administration.

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour (see Section 4.4 Special Warnings and Special Precautions for Use).

Pre-existing depression may be unmasked during benzodiazepines and benzodiazepine-like agents use.

Reactions like restlessness agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychosis and abnormal behaviour are more likely to occur in children and the elderly.

Dependence
Use (even at therapeutic doses) may lead to the development of physical dependence. Psychic dependence may occur. Abuse of benzodiazepines and benzodiazepine-like agents has been reported. Discontinuation of the therapy may result in withdrawal or rebound phenomena. Withdrawal syndrome has been reported upon discontinuation of zopiclone (see 4.4 Special Warnings and Special Precautions for Use).

Withdrawal symptoms vary and may include rebound insomnia, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations, and irritability. In very rare cases seizures may occur.

4.9 Overdose

As with other benzodiazepines and benzodiazepine-like agents, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol). In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Following overdose with any medicinal product, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Hemodialysis is of no value due to the large volume of distribution of zopiclone. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Overdose is usually manifested by varying degrees of central nervous system depression ranging from drowsiness to coma according to the quantity ingested. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, and coma.

Overdose should not be life threatening unless combined with other CNS depressants (including alcohol). Other risk factors such as the presence of concomitant illness and the debilitated state of the patient, may contribute to the severity of symptoms and very rarely can result in fatal outcome.

Symptomatic and supportive treatment in adequate clinical environment is recommended, attention should be paid to the respiratory and cardiovascular functions. Gastric lavage is only useful when preformed soon after ingestion. Haemodialysis is of no value due to the large volume of distribution of zopiclone.

Flumazenil may be useful as an antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N05CF01.

Zopiclone is a benzodiazepine-like hypnotic agent, a member of the cyclopyrrolone group of compounds. Its pharmacological properties are: hypnotic, sedative, anxiolytic, anti-convulsant, muscle-relaxant.

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.

5.2 Pharmacokinetic properties

Absorption

Zopiclone is absorbed rapidly. Peak concentrations are reached within 1h30 to 2h and they are approximately 30, 60 and 115 ng/ml after administration of 3.75mg, 7.5mg and 15mg respectively. Absorption is not modified by sex, time of intake or repetition of doses.

Distribution

The product is rapidly distributed from the vascular compartment. Plasma protein binding is weak (approximately 45%) and non saturable. There is very little risk of drug interactions due to protein binding.

Plasma level decrease:
At doses between 3.75 and 15mg, the decrease in plasma level does not depend on dose. The elimination half life is approximately 5 hours.

After repeated administration, there is no accumulation and inter-individual variations appear to be very low.

During lactation, the kinetic profiles of zopiclone in breast milk and in plasma are similar. The estimated percentage of the dose ingested by a nursing child would not exceed 0.2% of the dose administered to the mother over 24 hours.

Metabolism

Zopiclone is extensively metabolised in humans to two major metabolites, N-oxide zopiclone (pharmacologically active in animals) and N-desmethyl zopiclone (pharmacologically inactive in animals). An *in vitro* study indicates that cytochrome P450 (CYP) 3A4 is the major isoenzyme involved in the metabolism of zopiclone to both metabolites, and that CYP2C8 is also involved with N-desmethyl zopiclone formation. Their apparent half-lives evaluated from urinary data are approximately 4.5 hours and 7.4 hours, respectively. In animals, no enzyme induction has been observed even at high doses.

Elimination

The low renal clearance value of unchanged zopiclone (mean 8.4 ml/min) compared with the plasma clearance (232 ml/min) indicates that zopiclone clearance is mainly metabolic. The product is eliminated by the urinary route (approximately 80%) in the form of free metabolites (N-oxide and N-demethyl derivatives) and in the faeces (approximately 16%).

Physio-pathological variations

In elderly patients, notwithstanding a slight decrease in hepatic metabolism and a lengthening of elimination half-life to approximately 7 hours, various studies have shown no plasma accumulation of zopiclone on repeated dosing. In renal insufficiency no accumulation of Zopiclone or of its metabolites has been detected after prolonged administration Zopiclone crosses the dialysing membrane, however, haemodialysis is of no value in treating overdose due to the large volume of distribution of zopiclone.

In cirrhotic patients, the plasma clearance of zopiclone is clearly reduced by the slowing of the desmethylation process: dosage will therefore have to be modified in these patients.

5.3 Preclinical safety data

None

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Calcium hydrogen phosphate dihydrate
Wheat starch
Sodium starch glycolate
Magnesium stearate
Film-Coating:
Hypromellose
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product shall be the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package to protect from light and moisture.

6.5 Nature and contents of container

Over-labelled cardboard carton containing 2 blister strips (14 tablets per strip).
Pack size : 28 tablets

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

G & A Licensing Limited
Ballymurray
Co. Roscommon
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1447/65/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th January 2010

10 DATE OF REVISION OF THE TEXT