**IMOVANE® 7.5 mg**
Zopiclone
film-coated scored tablets

This package insert is continually updated: please read carefully before using a new pack. In case of any question, please contact your physician or pharmacist.

## Composition

Active ingredient: zopiclone. Each tablet contains 7.5 mg zopiclone.
Excipients: lactose, calcium hydrogen phosphate, wheat starch, sodium starch glycollate, magnesium stearate. Film coating: hypromellose, titanium dioxide (E171), macrogol 6000.
Excipients with known effect: lactose, wheat starch (containing gluten) (see Warnings and precautions).

## Properties

Pharmacotherapeutic class: HYPNOTICS and SEDATIVES (N: Nervous system)
Zopiclone is a cyclopyrrolone, related to the benzodiazepine drugs. 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 $GABA_A$ macromolecular complex, modulating the opening of the chloride ion channel. Zopiclone reduces the time to onset of sleep and the frequency of nocturnal awakenings, increases the duration of sleep and improves both the quality of sleep and the quality of awakening.
In insomniac patients, zopiclone decreases stage I, increases stage II, while preserving or prolonging the deep sleep stages (III and IV) and the paradoxical sleep.

Zopiclone is rapidly absorbed. Peak concentrations are reached within 1.5-2 hours and they are approximately 60 ng/ml after administration of 7.5 mg. Absorption is not modified by food. Plasma protein binding is weak (approximately 45 %) and non saturable. After repeated administration, there is no accumulation of zopiclone and its metabolites. Inter-individual variations appear to be low. An in vitro study indicates that cytochrome P450 (CYP) 3A4 is the major isoenzyme involved in the metabolism of zopiclone. The principal metabolites are the N-oxide derivative (active) and the N-demethyl metabolite (inactive). Their apparent half-lives evaluated from urinary data are approximately 4.5 hours and 7.4 hours respectively. At recommended doses, the elimination half-life of the unchanged zopiclone is approximately 5 hours. Zopiclone is eliminated by the urinary route (approximately 80 %) mainly in the form of free metabolites and in the faeces (approximately 16 %). In renal insufficiency, no accumulation of zopiclone or of its metabolites has been detected after prolonged administration. In cirrhotic patients, the plasma clearance of zopiclone is reduced by approximately 40 % in relation with the decrease of the demethylation process. Therefore, dosage will have to be modified in these patients. In elderly patients, notwithstanding a slight decrease in hepatic metabolism and lengthening of elimination half-life to approximately 7 hours, various studies have not shown plasma accumulation of drug substance on repeated dosing.

## Therapeutic indications

IMOVANE is intended for treatment of short-term treatment of insomnia in adults (including difficulties with falling asleep, nocturnal awakening, and early wakening).

How should this medicinal product be used
*Strictly follow the recommended dosage unless directed otherwise by the physician.*

## Dosage and method of administration

Use the lowest effective dose. IMOVANE should be taken in a single intake and not be re-administered during the same night.
Adults: the recommended dose is one 7.5 mg IMOVANE tablet by oral route. This dose should not be exceeded.

As with all hypnotics, long-term use of zopiclone is not recommended. Treatment should be as short as possible and should not exceed four weeks including the period of tapering off. Extension beyond

the maximum treatment period should not take place without re-evaluation of the patient's status, since the risk of abuse and dependence increases with the duration of treatment.

The product must be taken just before retiring for the night.

**Treatment duration**
Treatment should be as short as possible and should not exceed four weeks including the period of tapering off. Extension beyond the maximum treatment period should not take place without re-evaluation of the patient's status.

**Special populations**
In elderly and in patients with impaired liver function or chronic respiratory insufficiency: a starting dose of 3.75 mg zopiclone (half a tablet) is recommended initially. The dosage subsequently may be increased to 7.5 mg.
In patients with renal insufficiency: although no accumulation of zopiclone or of its metabolites has been detected in cases of renal insufficiency, it is recommended that patients with impaired renal function should start treatment with 3.75 mg.
The safe and effective dose of zopiclone has not been established in children and young adults less than 18 years.

**Contraindications**
IMOVANE is contraindicated in patients:

- With myasthenia gravis
- With hypersensitivity to zopiclone or any of the excipients
- With respiratory failure
- With severe sleep apnea syndrome
- With severe hepatic insufficiency
- Who have previously experienced complex sleep behaviors after taking IMOVANE

**Warnings and precautions**
The cause of insomnia should be identified wherever possible and the underlying factors treated before a hypnotic is prescribed.

*Respiratory depression*
As hypnotics have the capacity to depress respiratory drive, precautions should be observed if zopiclone is prescribed to patients with compromised respiratory function (see Undesirable effects).

*Psychomotor impairment*
Like other sedative/hypnotic drugs, zopiclone has CNS-depressant effects.
The risk of psychomotor impairment, including impaired driving ability, is increased if:
zopiclone is taken within 12 hours of performing activities that require mental alertness, a dose higher than the recommended dose is taken, or zopiclone is co-administered with other CNS depressants, alcohol, or with other drugs that increase the blood levels of zopiclone (see Interactions). Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle following administration of zopiclone and in particular during the 12 hours following that administration (see Driving a vehicle or performing other hazardous tasks).

*Risks from concomitant use with opioids:*
Concomitant use of opioids with benzodiazepines or other sedative-hypnotic drugs, including zopiclone, may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe zopiclone concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation (see Interactions).

*Dependence*
Use of zopiclone may lead to the development of abuse and/or physical and psychological dependence.

The risks of dependence increases with dose and duration of treatment. Cases of dependence have been reported more frequently in patients treated with zopiclone for longer than 4 weeks. The risk of abuse and dependence is also greater in patient with a history of psychiatric disorders and/or alcohol or drug abuse. Zopiclone should be used with extreme caution in patients with current or a history of alcohol or drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms.

*Rebound insomnia*
A transient syndrome, whereby the symptoms that led to treatment with sedative/hypnotic agents recur in an enhanced form, may occur on withdrawal of hypnotic treatment. Since the risk of such phenomena is greater after abrupt discontinuation of zopiclone, especially after prolonged treatment, it is, therefore, recommended to decrease the dosage gradually and to advise the patient accordingly (see Undesirable effects).

*Tolerance*
Some loss of efficacy of other hypnotics may develop after repeated use. However, there is an absence of marked tolerance with zopiclone for treatment periods up to 4 weeks.

*Amnesia*
Anterograde amnesia may occur, especially when sleep is interrupted or when retiring to bed is delayed after the intake of the tablet.

To reduce the possibility of anterograde amnesia, patients should ensure that they:
- take the tablet strictly when retiring for the night.
- are able to have a full night sleep.

*Other psychiatric and paradoxical reactions*
Other psychiatric and paradoxical reactions (see Undesirable effects) like restlessness, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, inappropriate behaviour and other adverse behavioural effects are known to occur when using sedative/hypnotic agents like zopiclone. Should this occur, use of zopiclone should be discontinued. These reactions are more likely to occur in the elderly.

*Somnambulism and associated behaviours*
Complex sleep behaviors, including sleep-walking, sleep-driving, and engaging in other activities while not fully awake, may occur following the first or any subsequent use of zopiclone. Patients can be seriously injured or injure others during complex sleep behaviors. Such injuries may be fatal. Other complex sleep behaviors (e.g., preparing and eating food, making phone calls, or having sex) have also been reported. Patients usually do not remember these events. Postmarketing reports have shown that complex sleep behaviors may occur with zopiclone alone at recommended doses, with or without the concomitant use of alcohol or other central nervous system (CNS) depressants (see Interactions). Discontinue zopiclone immediately if a patient experiences a complex sleep behavior (see Contraindications).

*Suicidality and depression*

Several epidemiological studies show an increased incidence of suicide and suicide attempt in patients with or without depression, treated with benzodiazepines and other hypnotics, including zopiclone. A causal relationship has not been established.

As with other sedative/hypnotic drug, zopiclone should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present, therefore the lowest possible quantity of zopiclone that should be supplied to these patients to reduce the risk of intentional overdosage by the patient. Pre-existing depression may be unmasked during use of zopiclone. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

*Use in children*
The safe and effective dose of zopiclone has not been established in children and young adults less than 18 years.

*Excipients with known effect*
*Lactose:*
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

*Wheat starch (containing gluten):*
This medicine contains only very low levels of gluten (from wheat starch) and is very unlikely to cause problems in the case of coeliac disease. One 7.5mg tablet contains no more than 6 micrograms of gluten. Patients with wheat allergy (different from coeliac disease) should not take this medicine.

Driving a vehicle or performing other hazardous tasks
Because of its pharmacological properties and its effect on central nervous system, IMOVANE may adversely affect the ability to drive or to use machines. The risk of psychomotor impairment, including impaired driving ability, is increased if:
- zopiclone is taken within 12 hours of performing activities that require mental alertness,
- a dose higher than the recommended dose is taken, or
- zopiclone is co-administered with other CNS depressants, alcohol, or with other drugs that increase the blood levels of zopiclone.

Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle following administration of zopiclone and in particular during the 12 hours following that administration.

Pregnancy
The use of zopiclone is not recommended during pregnancy.

Zopiclone crosses the placenta.

A large amount of data collected from cohort studies has not demonstrated evidence of the occurrence of malformations following exposure to benzodiazepines during the first trimester of pregnancy. However, in certain epidemiological case-control studies, an increased incidence of cleft lip and palate was observed with benzodiazepines.

Cases of reduced fetal movement and fetal heart rate variability have been described after administration of benzodiazepines during the second and/or third trimester of pregnancy.
Administration of zopiclone during late phase of pregnancy or during labour has been associated with effects on the neonate, such as hypothermia, hypotonia, feeding difficulties (which may result in poor weight gain) and respiratory depression can be expected, due to the pharmacological action of the product.

Moreover, infants born to mothers who took sedative/hypnotics 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. Appropriate monitoring of the newborn in the postnatal period is recommended.

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

Lactation
Although the concentration of zopiclone in the breast milk is very low, zopiclone should not be used by nursing mothers.

Overdose
In case of overdose, contact immediately your physician.

*Signs and symptoms*
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, confusion, and lethargy; in more severe cases, symptoms may include ataxia, hypotonia, hypotension, methaemoglobinaemia, 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.

*Management*
Symptomatic and supportive treatment in adequate clinical environment is recommended; attention should be paid to respiratory and cardiovascular functions. Gastric lavage or activated charcoal is only useful when performed soon after ingestion. Hemodialysis is of no value due to the large volume of distribution of zopiclone. Flumazenil may be a useful antidote.

**Interactions**
*In order to avoid possible interactions with other medicines inform your physician or pharmacist about any other current treatment.*

***Association not recommended:***
*Alcohol*
Concomitant intake with alcohol or alcohol containing-medicinal products is not recommended. The sedative effect of zopiclone may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

***Associations to be taken into account:***
*Combination with CNS depressants*
Enhancement of the central depressive effect may occur in cases of concomitant use with CNS depressants: neuroleptics, hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, anesthetics and sedative anti-histaminics. In the case of narcotic analgesics, enhancement of euphoria may also occur leading to an increase in psychic dependence.

*CYP450 inhibitors and inducers*
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 presence of erythromycin which indicates that erythromycin can inhibit the metabolism of drugs metabolized by CYP 3A4. As a consequence, the hypnotic effect of zopiclone may be enhanced.

Since zopiclone is metabolized by the cytochrome P450 (CYP) 3A4 isoenzyme, plasma levels of zopiclone may be increased when co-administered with CYP3A4 inhibitors, such as erythromycin, clarithromycin, ketoconazole, itraconazole, and ritonavir. A dose reduction for zopiclone may be required when it is co-administered with CYP3A4 inhibitors. Conversely, plasma levels of zopiclone may be decreased when co-administered with CYP3A4 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 CYP3A4 inducers (see Warnings and precautions).

*Opioids*
The concomitant use of benzodiazepines and other sedative-hypnotic drugs, including zopiclone, and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see Warnings and precautions).

**Undesirable effects**
*Please tell your physician or pharmacist, if you experience any adverse effect with the use of this product.*
*The following CIOMS frequency rating is used, when applicable:*
*Very common ≥ 10%; Common ≥ 1 and ≤ 10%; Uncommon ≥ 0.1 and < 1%; Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%; Unknown (cannot be estimated from available data).*

Immune system disorders
Very rare: angioedema, anaphylactic reaction

Psychiatric disorders
Uncommon: nightmare, agitation
Rare: confusional state, libido disorder, irritability, aggression, hallucination
Not known: restlessness, delusion, anger, abnormal behaviour (possibly associated with amnesia) and, complex sleep behaviors, including somnambulism (see Warnings and precautions: Somnambulism and associated behaviour), dependence, withdrawal syndrome (see below).

Nervous system disorders
Common: dysgeusia (bitter taste), somnolence (residual)
Uncommon: dizziness, headache
Rare: anterograde amnesia
Not known: ataxia, paresthesia, cognitive disorders such as memory impairment, disturbance in attention, speech disorder

Eye disorders
Not known: diplopia

Respiratory, thoracic and mediastinal disorders
Rare: dyspnea
Not known: respiratory depression

Gastrointestinal disorders
Common: dry mouth
Uncommon: nausea
Not known: dyspepsia

Hepatobiliary disorders
Very rare: transaminases increased and/or blood alkaline phosphatase increased (mild to moderate)

Skin and subcutaneous tissue disorders
Rare: rash, pruritus

Musculoskeletal and connective tissue disorders
Not known: muscular weakness

General disorders and administration site conditions
Uncommon: fatigue

Injury, poisoning and procedural complications
Rare: fall (predominantly in elderly patients)

Withdrawal syndrome has been reported upon discontinuation of Imovane. Withdrawal symptoms vary and may include rebound insomnia, muscle pain, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, irritability. In severe cases the following symptoms may occur: derealisation, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations. In very rare cases, seizures may occur.

**Storage**
Store below 30°C.
Keep out of the reach of children.

**Expiry date**
Do not use later than the date of expiry indicated on the outer packaging.

**Presentation**
Box of 14 or 20 tablets in PVC/aluminium blisters.

**Manufacturer**
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