PROFESSIONAL INFORMATION FOR IMOVANE TABLETS (CLEAN COPY),

DATED 19 FEBRUARY 2020

SCHEDULING STATUS: S5

PROPRIETARY NAME AND DOSAGE FORM:

IMOVANE TABLETS

COMPOSITION:

Each tablet contains: Zopiclone 7,5 mg.

Other excipients are: Calcium hydrogen phosphate, lactose, magnesium stearate, sodium starch glycolate, wheat starch and the film-coating contains: hypromellose, macrogol 6000 and titanium dioxide.

Contains sugar (lactose): IMOVANE contains 31,6 mg lactose per tablet.

CATEGORY AND CLASS:

A 2.2 Sedatives, hypnotics.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Zopiclone is a hypnotic medicine, a member of the cyclopyrrolone group of compounds. Its pharmacological properties are: hypnotic, sedative, anxiolytic, anticonvulsant and 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.

Pharmacokinetic properties:

Absorption:

Zopiclone is rapidly absorbed. Peak concentrations are reached within 1,5 to 2 hours and they are approximately 30 to 60 ng/ml after administration of 3,75 mg and 7,5 mg, respectively. Absorption is not modified by food.

Distribution:

Zopiclone is rapidly distributed from the vascular compartment. Plasma protein binding is weak (approximately 45 %) and non-saturable. The distribution volume is 91,8 to 104,6 litres.

Metabolism:

After repeated administration, there is no accumulation of zopiclone and its metabolites. Interindividual variations appear to be low.

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.

Elimination:

At recommended doses, the elimination half-life of the unchanged zopiclone is approximately 5 hours.

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.

Zopiclone is eliminated by the urinary route (approximately 80 %) mainly in the form of free metabolites (N-oxide and N-demethyl derivatives) and in the faeces (approximately 16 %).

Special patient populations:

Elderly: 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 zopiclone on repeated dosing.

Renal impairment: In renal insufficiency, no accumulation of zopiclone or of its metabolites has been detected after prolonged administration. Zopiclone is removed by haemodialysis; however, haemodialysis is of no value in treating overdose due to the large volume of distribution of zopiclone (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT).

Hepatic impairment: In cirrhotic patients, the plasma clearance of zopiclone is reduced by approximately 40 % in relation to the decrease of the demethylation process. Therefore, dosage will have to be modified in these patients.

INDICATIONS:

Short-term treatment of insomnia in adults.

IMOVANE is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

CONTRAINDICATIONS:

IMOVANE is contraindicated in patients with:

- A hypersensitivity to zopiclone, or any of the excipients of IMOVANE
- myasthenia gravis
- respiratory failure
- severe sleep apnoea syndrome
- severe hepatic insufficiency.

IMOVANE should not be used in children and young adults under the age of 18.

Safety in pregnancy and lactation has not been established (see HUMAN REPRODUCTION).

WARNINGS AND SPECIAL PRECAUTIONS:

Respiratory depression

As IMOVANE has the capacity to depress respiratory drive, precautions should be observed if IMOVANE is prescribed to patients with compromised respiratory function (see SIDE EFFECTS (dyspnoea)).

Psychomotor impairment

IMOVANE has CNS-depressant effects. The risk of psychomotor impairment, including impaired driving ability, is increased if: IMOVANE is taken within 12 hours of performing activities that require mental alertness, a dose higher than the recommended dose is taken, or IMOVANE is co-administered with other CNS depressants, alcohol, or with other medicines 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 IMOVANE and in particular during the 12 hours following that administration (see Effects on ability to drive and use machines).

Risks from concomitant use with opioids

Concomitant use of opioids with benzodiazepines or other sedative-hypnotic medicines, including IMOVANE, 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 IMOVANE concomitantly with opioids, prescribe the lowest effective dosages and minimum duration of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation (see INTERACTIONS).

Cause of insomnia:

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

Dependence

There is a potential for abuse and the development of physical and psychological dependence, especially with prolonged use and high doses. Cases of dependence have been reported more frequently in patients treated with IMOVANE for longer than 4 weeks. The risk of abuse and dependence is also greater in patients with a history of psychiatric disorders and/or alcohol or drug abuse. IMOVANE should be used with extreme caution in patients with current or a history of alcohol or drug abuse.

Withdrawal phenomena

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of rebound insomnia, headaches, muscle pain, extreme anxiety, tremor, sweating, agitation, tension, restlessness, confusion, nightmares, delirium, palpitations, tachycardia and irritability.

In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact or hallucinations. Seizures may also occur.

Rebound insomnia

A transient syndrome whereby, the symptoms that led to treatment with IMOVANE recur in an enhanced form may occur on discontinuation of treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

The risk of withdrawal or rebound phenomena is greater after abrupt discontinuation of IMOVANE, especially after prolonged treatment. It is, therefore, recommended to decrease the dosage gradually.

Duration of Treatment

The duration of treatment should be as short as possible (see DOSAGE AND DIRECTIONS FOR USE), 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 a 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 product is being discontinued.

Tolerance

Some loss of efficacy of IMOVANE may develop after repeated use.

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's sleep.

Other psychiatric and paradoxical reactions

Other psychiatric and paradoxical reactions are known to occur when using IMOVANE (see SIDE EFFECTS: Psychotic disorders). These reactions are more likely to occur in the elderly.

Somnambulism and associated behaviours

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

Psychotic illness

IMOVANE is not recommended for the primary treatment of psychotic illness.

Suicidality and depression

IMOVANE should not be used alone to treat depression or anxiety with 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 IMOVANE. A causal relationship has not been established.

Sedative/hypnotic medicines, such as IMOVANE should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present, therefore the lowest possible quantity of IMOVANE 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 IMOVANE. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

Hyperglycaemia and lactose intolerance

IMOVANE tablets contain lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus. IMOVANE contains 31,6 mg lactose per tablet.

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take IMOVANE.

Effects on ability to drive and use machines

Because of its pharmacological properties, and its effects on central nervous system, IMOVANE causes drowsiness and impaired concentration and may adversely affect the ability to drive or use machines.

The risk of psychomotor impairment, including impaired driving ability, is increased if:

- IMOVANE is taken within 12 hours of performing activities that require mental alertness,
- a dose higher than the recommended dose is taken, or
- IMOVANE is co-administered with other CNS depressants, alcohol, or with other medicines 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 IMOVANE and in particular during the 12 hours following that administration.

INTERACTIONS:

Alcohol

Concomitant intake of IMOVANE with alcohol is not recommended. The sedative effect of IMOVANE may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines (see WARNINGS AND SPECIAL PRECAUTIONS: Effects on ability to drive and use machines).

Combination with CNS depressants

Caution should be exercised with the concomitant use of central depressant medicines such as neuroleptics, hypnotics, anxiolytics/sedatives, antidepressants, narcotic analgesics,

antiepileptic medicines, anaesthetics and sedative antihistaminics, as the central depressive effect of IMOVANE may be enhanced in these cases.

In the case of narcotic analgesics, enhancement of euphoria may also occur.

CYP450 inhibitors and inducers

The AUC of zopiclone is increased by 80 % in the presence of erythromycin which indicates that erythromycin can inhibit the metabolism of medicines metabolised by CYP 3A4. As a consequence, the hypnotic effect of IMOVANE may be enhanced.

Since IMOVANE is metabolised by the cytochrome P450 (CYP) 3A4 isoenzyme (see Pharmacokinetic properties), 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 IMOVANE may be required when it is co-administered with CYP3A4 inhibitors.

Conversely, plasma levels of IMOVANE may be decreased when co-administered with CYP3A4 inducers, such as rifampicin, carbamazepine, phenobarbitone, phenytoin and St. John's Wort. A dose increase of IMOVANE may be required when it is co-administered with CYP3A4 inducers.

Opioids

The concomitant use of benzodiazepines and other sedative-hypnotic medicines, including IMOVANE, and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect (see WARNINGS AND SPECIAL PRECAUTIONS).

HUMAN REPRODUCTION:

The use of IMOVANE during pregnancy is not recommended (see CONTRAINDICATIONS).

Insufficient data are available on IMOVANE to assess its safety during human pregnancy and lactation.

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.

If IMOVANE is used during the last three months of pregnancy or during labour, effects on the neonate, such as hypothermia, hypotonia, feeding difficulties and respiratory depression can be expected, due to the pharmacological action of zopiclone.

Moreover, infants born to mothers who took sedative/hypnotic medicines 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 IMOVANE is prescribed to a woman of childbearing potential, she should be warned to contact her medical practitioner regarding discontinuation of IMOVANE if she intends to become or suspects that she is pregnant.

Lactation:
Although the concentration of zopiclone in the breast milk is very low, IMOVANE should not be used by mothers who are breastfeeding (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE:

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.
IMOVANE should be taken in a single intake and not be re-administered during the same night.

Long-term use of IMOVANE is not recommended. 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 process, 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, since the risk of abuse and dependence increases with the duration of treatment (see WARNINGS AND SPECIAL PRECAUTIONS).

Adults:

One tablet (7,5 mg IMOVANE) orally, shortly before retiring. This dose should not be exceeded.

Elderly patients, Patients with impaired liver function, and

Chronic respiratory insufficiency:

A lower dose of 3,75 mg IMOVANE (half a tablet) should be employed to start treatment in these patients, and if necessary, the dose may be increased to 7,5 mg.

Renal insufficiency:

Accumulation of zopiclone or its metabolites has not been seen during treatment of insomnia in patients with renal insufficiency. However, it is recommended that patients with impaired renal function should start treatment with 3,75 mg.

SIDE EFFECTS:

The following 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

Unknown: restlessness, delusion, anger, abnormal behaviour (possibly associated with amnesia); somnambulism, dependence and withdrawal syndrome (see WARNINGS AND SPECIAL PRECAUTIONS: *Dependence, Withdrawal phenomena* and *Somnambulism and associated behaviours*)

Nervous system disorders

Common: dysgeusia (bitter taste), residual somnolence

Uncommon: dizziness, headache

Rare: anterograde amnesia

Unknown: ataxia, paraesthesia, cognitive disorders such as memory impairment, disturbance in attention, speech disorder

Eye disorders

Unknown: diplopia

Respiratory, thoracic and mediastinal disorders:

Rare: dyspnoea

Unknown: respiratory depression (see WARNINGS AND SPECIAL PRECAUTIONS)

Gastrointestinal disorders

Common: dry mouth

Uncommon: nausea, vomiting

Unknown: dyspepsia

Hepato-biliary disorders

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

Skin and subcutaneous tissue disorders

Rare: rash, pruritus, urticaria

Musculoskeletal and connective tissue disorders

Unknown: muscular weakness

General disorders and administration site conditions

Uncommon: fatigue

Injury, poisoning and procedural complications

Rare: fall (predominantly in elderly patients)

Unknown: incoordination

Withdrawal symptoms have been reported upon discontinuation of IMOVANE. Withdrawal symptoms may vary and may include rebound insomnia and other symptoms (see WARNINGS AND SPECIAL PRECAUTIONS – *Withdrawal phenomena*). In very rare cases, seizures may occur.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdose is usually manifested by varying degrees of central nervous system depression according to the quantity ingested. In mild cases, symptoms include drowsiness, confusion, and lethargy; in more serious cases, symptoms may include ataxia, hypotonia, hypotension, methaemoglobinaemia, respiratory depression and coma. Overdose may be life-threatening especially when 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 can result in fatal outcome. Symptomatic and supportive treatment in an 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. Haemodialysis is of no value due to the large volume of distribution of zopiclone. Flumazenil may be a useful antidote.

IDENTIFICATION:

White, film-coated, elliptical tablets, with a breakline on one side.

PRESENTATION:

Blister packs of 30 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 ºC and protect from light.

Keep out of reach of children.

REGISTRATION NUMBER:

T/2.2/104

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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