PROFESSIONAL INFORMATION FOR ZOPICLONE-INNOVATA TABLETS

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE:

ZOPICLONE-INNOVATA 7.5 Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

ZOPICLONE-INNOVATA 7.5: Each Film-coated Tablet contains 7.5 mg zopiclone.

Contains: Sugar (lactose 31.50 mg)

For the full list of excipients, **see section 6.1**

3. PHARMACEUTICAL FORM:

ZOPICLONE-INNOVATA 7.5: White to off white, oval, biconvex film-coated tablets with breakline on one side.

The scoreline is not intended for the division of the tablets into two equal doses. The tablets should be swallowed whole.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

Short-term treatment of insomnia in adults.

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

4.2 Posology and method of administration

Posology

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

ZOPICLONE-INNOVATA should be taken in a single intake and not be re-administered during the same night.

Long-term use of **ZOPICLONE-INNOVATA** 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 section 4.4**).

Adults:

One tablet (7,5 mg **ZOPICLONE-INNOVATA**) orally, shortly before retiring. This dose should not be exceeded.

Elderly/Patients with hepatic impairment and chronic respiratory insufficiency:

A lower dose of 3,75 mg **ZOPICLONE-INNOVATA** should be employed to start treatment in these patients, and if necessary, the dose may be increased to 7,5 mg.

Patients with renal impairment:

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 **ZOPICLONE-INNOVATA**.

Method of Administration

Oral

4.3 Contraindications

ZOPICLONE-INNOVATA is contraindicated in patients with:

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

ZOPICLONE-INNOVATA should not be used in children and young adults under the age of 18.

Safety in pregnancy and lactation has not been established (**see section 4.6**).

4.4 Special warnings and precautions for use

Respiratory depression

As **ZOPICLONE-INNOVATA** has the capacity to depress respiratory drive, precautions should be observed if **ZOPICLONE-INNOVATA** is prescribed to patients with compromised respiratory function (**see section 4.8** (dyspnoea)).

Psychomotor impairment

ZOPICLONE-INNOVATA has CNS-depressant effects. The risk of psychomotor impairment, including impaired driving ability, is increased if: **ZOPICLONE-INNOVATA** is taken within 12 hours of performing activities that require mental alertness, a dose higher than the recommended dose is taken, or **ZOPICLONE-INNOVATA** is co-administered with other CNS depressants, alcohol, or with other medicines that increase the blood levels of zopiclone (**see section 4.5**).

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-INNOVATA** and in particular during the 12 hours following that administration (**see section 4.7**).

Risks from concomitant use with opioids

Concomitant use of opioids with benzodiazepines or other sedative-hypnotic medicines, including **ZOPICLONE-INNOVATA**, 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-INNOVATA** 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 section 4.5**).

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 **ZOPICLONE-INNOVATA** 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. **ZOPICLONE-INNOVATA** 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 **ZOPICLONE-INNOVATA** 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 **ZOPICLONE-INNOVATA**, 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 section 4.2**), 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 **ZOPICLONE-INNOVATA** 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 **ZOPICLONE-INNOVATA** (**see section 4.8**: 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 **ZOPICLONE-INNOVATA** and were not fully awake. The use of alcohol and other CNS-depressants with **ZOPICLONE-INNOVATA** appears to increase the risk of such behaviours, as does the use of **ZOPICLONE-INNOVATA** at doses exceeding the maximum recommended dose. Discontinuation of **ZOPICLONE-INNOVATA** should be

strongly considered for patients who report such behaviours (**see section 4.5**: **Alcohol, and section 4.8**: **Psychiatric disorders**).

Psychotic illness

ZOPICLONE-INNOVATA is not recommended for the primary treatment of psychotic illness.

Suicidality and depression

ZOPICLONE-INNOVATA 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 **ZOPICLONE-INNOVATA**. A causal relationship has not been established.

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

Excipients

ZOPICLONE-INNOVATA contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Alcohol

Concomitant intake of **ZOPICLONE-INNOVATA** with alcohol is not recommended. The sedative effect of **ZOPICLONE-INNOVATA** may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines (**see section 4.4: 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 **ZOPICLONE-INNOVATA** 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 **ZOPICLONE-INNOVATA** may be enhanced.

Since **ZOPICLONE-INNOVATA** is metabolised by the cytochrome P450 (CYP) 3A4 isoenzyme (see section 5.2), plasma levels of zopiclone may be increased when coadministered with CYP3A4 inhibitors, such as erythromycin, clarithromycin, ketoconazole, itraconazole, and ritonavir. A dose reduction for **ZOPICLONE-INNOVATA** may be required when it is coadministered with CYP3A4 inhibitors.

Conversely, plasma levels of **ZOPICLONE-INNOVATA** may be decreased when co-administered with CYP3A4 inducers, such as rifampicin, carbamazepine, phenobarbitone, phenytoin and St. John's Wort.

A dose increase of **ZOPICLONE-INNOVATA** may be required when it is co-administered with CYP3A4 inducers.

Opioids

The concomitant use of benzodiazepines and other sedative-hypnotic medicines, including **ZOPICLONE-INNOVATA**, and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect (**see section 4.4**).

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential

If **ZOPICLONE-INNOVATA** is prescribed to a woman of childbearing potential, she should be warned to contact her medical practitioner regarding discontinuation of **ZOPICLONE-INNOVATA** if she intends to become or suspects that she is pregnant.

Pregnancy.

The use of **ZOPICLONE-INNOVATA** during pregnancy is not recommended (**see section 4.3**).

Insufficient data are available on **ZOPICLONE-INNOVATA** to assess its safety during human pregnancy and lactation.

Cases of reduced foetal movement and foetal heart rate variability have been described after administration of benzodiazepines during the second and/or third trimester of pregnancy.

If **ZOPICLONE-INNOVATA** 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.

Breastfeeding

Although the concentration of zopiclone in the breast milk is very low, **ZOPICLONE-INNOVATA** should not be used by mothers who are breastfeeding (**see section 4.3**).

4.7 Effects on the ability to drive and use machines

Because of its pharmacological properties, and its effects on central nervous system, **ZOPICLONE-INNOVATA** causes drowsiness, dizziness 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:

- **ZOPICLONE-INNOVATA** is taken within 12 hours of performing activities that require mental alertness,
- a dose higher than the recommended dose is taken, or
- **ZOPICLONE-INNOVATA** 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 **ZOPICLONE-INNOVATA** and in particular during the 12 hours following that administration.

4.8 Undesirable effects

System Organ Class	Frequency	Side effects

Immune system disorders	*Less frequent*	Angioedema, anaphylactic reaction.
Psychiatric disorders	*Less frequent*	Nightmare, agitation, confusional state, libido disorder, irritability, aggression, hallucination.
	Frequency unknown	Restlessness, delusion, anger, abnormal behaviour (possibly associated with amnesia); somnambulism, dependence and withdrawal syndrome (**see section 4.4: Dependence, Withdrawal phenomena and Somnambulism and associated behaviours**)
Nervous system disorders	*Frequent*	Dysgeusia (bitter taste), residual somnolence.
	Less frequent	Dizziness, headache, anterograde amnesia.

	Frequency unknown	Ataxia, paraesthesia, cognitive disorders such as memory impairment, disturbance in attention, speech disorder
Eye disorders	*Frequency unknown*	Diplopia
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Dyspnoea
	Frequency unknown	Respiratory depression (**see section 4.4**)
Gastrointestinal disorders	*Frequent*	Dry mouth
	Less frequent	Nausea, vomiting
	Frequency unknown	Dyspepsia
Hepato-biliary disorders	*Less frequent*	Transaminases increased and/or blood alkaline phosphatase increased (mild to moderate)
Skin and subcutaneous tissue disorders	*Less frequent*	Rash, pruritus, urticaria
Musculoskeletal, connective tissue and bone disorders	*Frequency unknown*	Muscular weakness

General disorders and administration site conditions	*Frequency unknown*	Fatigue
Injury, poisoning and procedural complications	Frequent	Weight decrease
	Less frequent	Fall (predominantly in elderly patients)
	Frequency unknown	Incoordination

Withdrawal symptoms have been reported upon discontinuation of **ZOPICLONE-INNOVATA**. Withdrawal symptoms may vary and may include rebound insomnia and other symptoms (**see section 4.4 – Withdrawal phenomena**). In some cases, seizures may occur.

4.9 Overdose

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. 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anxiolysis, sedation, hypnosis, anticonvulsion and muscle relaxation.

ATC code: N05C F01.

Mechanism of action

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.

5.2 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 section 4.9**).

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.

6. Pharmaceutical particulars

6.1 List of excipients

Calcium hydrogen phosphate dihydrate, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, maize starch, opadry white (hypromellose, macrogol and titanium dioxide), starch pregelatinised.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 ˚C

Protect from moisture and sunlight

Keep out of reach of children

6.5 Nature and contents of container

ZOPICLONE-INNOVATA 7.5 mg Tablet: Tablets are packed in foil blister aluminium 0.02 mm plain & PVC film 250 mic transparent.

Available in blister packs of 10’s (1x10) tablets, 30’s (3x10) tablets, 60’s (6x10) tablets and 100’s (10x10) tablets.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Holder of certificate of registration

Innovata Pharmaceuticals

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. Registration numbers

TBI

9. Date of first authorization/Renewal of the authorization

TBI

10. Date of revision of the text

TBI