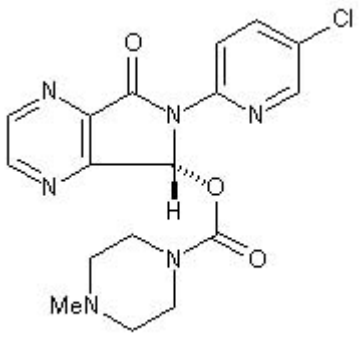
Imrest

Zopiclone

PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient	:	zopiclone
Chemical name	:	6-(5-chloro-2-pyridyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl-4-methylpiperazine-1-carboxylate
Structural formula	:	 and enantiomer

Molecular formula	:	$C_{17}H_{17}ClN_6O_3$	Molecular weight	:	388.8
			CAS Registry no.	:	43200-80-2

DESCRIPTION

Zopiclone is a fine white or slightly cream crystalline powder with a melting point of 176° to 178°C. It is practically insoluble in acetone, soluble in dimethyl formamide and hydrochloric acid 0.1 N and freely soluble in chloroform and dichloromethane.

Each Imrest tablet contains 7.5 mg of zopiclone and the following excipients: lactose anhydrous, calcium hydrogen phosphate anhydrous, maize starch, povidone, magnesium stearate and Opadry White Y-1-7000. The tablets are gluten free.

PHARMACOLOGY

Class

Zopiclone, a cyclopyrrolone derivative, is a short-acting hypnotic agent. Zopiclone belongs to a novel chemical class which is structurally unrelated to existing hypnotics. The pharmacological profile of zopiclone is similar to that of the benzodiazepines.

Site and Mode of Action

In sleep laboratory studies of 1 to 21 day duration in humans, zopiclone reduced sleep latency, increased the duration of sleep and decreased the number of nocturnal awakenings. Zopiclone delayed the onset of rapid eye movement (REM) sleep but did not reduce consistently the total duration of REM periods. The duration of stage 1 sleep was shortened and the time spent in stage 2 sleep increased. In most studies, stage 3 and 4 sleep tended to be increased, but no change and actual decreases have also been observed. The effect of zopiclone on stage 3 and 4 sleep differs from that of the benzodiazepines which suppress slow wave sleep. The clinical significance of this finding is not known.

Pharmacokinetics

Absorption

Zopiclone is rapidly absorbed and distributed after oral administration, the median T_{max}. being 1 hour (range 0.5 – 4 hours).

Distribution and Metabolism

A study of 16 healthy volunteers receiving a single dose of zopiclone 7.5 mg intravenously demonstrated the apparent volume of distribution of zopiclone to be 104 ± 15.5 L. Autoradiographic studies in the rat showed rapid distribution into the blood and peak tissue levels at 0.5 hours in the liver, small intestine, stomach, kidneys and adrenals. After 24 hours the total residual radioactivity in the body of the rat was 8%.

The bioavailability of the 7.5 mg tablets in humans is 76.3 ± 9.6%. An hepatic first-pass effect has been demonstrated. In fresh human plasma, zopiclone is approximately 45% protein bound in the 25 to 100 nanogram/mL concentration range.

Zopiclone is extensively and rapidly metabolised by the liver. A large number of metabolites have been isolated and characterised, with the two major ones being the N-oxide, produced by oxidation of the piperazine nitrogen, and the N-desmethyl, produced by oxidative demethylation of the N-methyl piperazine. Only the N-oxide analogue has weak pharmacological activity.

Elimination and Excretion

Zopiclone is rapidly eliminated, mainly by means of hepatic metabolism. The elimination half-life after a single oral dose is 5.57 ± 1.4 hours. The elimination half-life for the N-oxide metabolite is 4.44 ± 0.66 hours and that for the N-desmethyl metabolite is 7.28 ± 0.49 hours.

Renal clearance is 13.9 ± 7.0 mL/minute which further shows that the major elimination pathway is by hepatic metabolism.

The amount of renal excretion is also low: unchanged zopiclone 3.6%, the N-oxide metabolite 11.4% and the N-desmethyl metabolite 13.4%.

Elderly

In elderly patients, the absolute bioavailability is increased (94% versus 77% in young subjects) and the elimination half-life prolonged (approximately 7 hours).

Hepatic Insufficiency

In patients with hepatic insufficiency, the elimination half-life is prolonged (11.9 hours) and the time to peak plasma levels is delayed (3.5 hours).

Renal Insufficiency

In patients with mild to moderate renal insufficiency, the pharmacokinetics of zopiclone are not altered. Haemodialysis does not appear to increase the plasma clearance of the drug.

INDICATIONS

Short-term treatment of insomnia (two to four weeks).

CONTRAINDICATIONS

Patients with known hypersensitivity to zopiclone or any excipient.

Prior or concomitant use of alcohol.

Myasthenia gravis.

Severe impairment of respiratory function.

Acute cerebrovascular accident.

Sleep apnoea syndrome.

Severe hepatic insufficiency.

Imrest is contraindicated in Children.

PRECAUTIONS

Prolonged use of hypnotics is not recommended, especially in the elderly.

Dependence

Zopiclone should be prescribed for short periods only (2 to 4 weeks). Continuous long-term use is not recommended. Use of sedative-hypnotic agents like zopiclone may lead to the development of physical and psychological dependence or abuse. It is therefore recommended that after prolonged use the dose should be decreased gradually and the patient advised about such a possibility (see **ADVERSE EFFECTS**).

Risks of dependence or abuse increase with:

- dose and duration of treatment;
- history of alcohol and/or drug abuse; and
- use with alcohol or other psychotropics.

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 **ADVERSE EFFECTS**).

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
- they are able to have a full night's sleep.

Other Psychiatric and Paradoxical Reactions

Other psychiatric and paradoxical reactions have been reported (see **ADVERSE 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

Sleepwalking 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 and were not fully awake. The use of alcohol and other CNS-depressants with zopiclone appears to increase the risk of such behaviours, as does the use of zopiclone at doses exceeding the maximum recommended dose. Discontinuation of zopiclone would be strongly considered for patients who report such behaviours (see **INTERACTIONS WITH OTHER MEDICINES - Alcohol** and **ADVERSE EFFECTS**).

Depression, Suicidality, Psychosis and Schizophrenia

As with other hypnotics, zopiclone does not constitute a treatment of depression and may even mark its symptoms. Caution should be exercised if zopiclone is prescribed to depressed patients, including those with latent depression, particularly when suicidal tendencies may be present and protective measures may be required. 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

Epilepsy

Patients with a history of seizures should not be abruptly withdrawn from any CNS depressant drug, including zopiclone.

Severe Anaphylactic and Anaphylactoid Reactions

Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zopiclone. Some patients have had additional symptoms such as dyspnoea, throat closing, or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zopiclone should not be rechallenged with the drug.

Hepatic insufficiency

In patients with severe hepatic insufficiency (serum albumin less than 30 g/L or presence of gross oedema), the elimination of zopiclone may be significantly reduced. Treatment should be initiated at a dose of 3.75 mg and, if necessary, should be carried out at 7.5 mg.

Renal insufficiency

Zopiclone is removed by dialysis.

Respiratory insufficiency

Caution should be exercised in treating patients with chronic respiratory insufficiency. Treatment should be initiated at a dose of 3.75 mg and, if necessary, should be carried out at 7.5 mg.

As hypnotics have the capacity to depress respiratory drive, precautions should be observed if zopiclone is prescribed to patients with compromised respiratory function.

Hormonal Systems

Treatment of rats with zopiclone increases hepatic thyroid hormone metabolism of T_4, resulting in increases in thyroid stimulating hormone (TSH) and T_3 levels and decreases in T_4 levels. It is suggested that zopiclone not be administered to individuals with impaired thyroid hormone homoeostatic mechanisms or with conditions linked to hormonal imbalances.

Effects on Ability to Drive and use Machinery

As with all patients taking CNS depressant medications, patients receiving zopiclone should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy after zopiclone therapy. Abilities may be impaired on the day following use. It has been reported that the risk that zopiclone adversely affects driving ability is increased by concomitant intake of alcohol. Therefore, driving is not recommended after the concomitant intake of zopiclone and alcohol. Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these medications should be either eliminated or given in reduced dosage in the presence of zopiclone.

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 higher dose than recommended 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.

Risks from Concomitant Use of Opioids and Benzodiazepines

Concomitant use of benzodiazepines, 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**).

Abuse

Caution must be exercised in administering zopiclone to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative.

Use in the Elderly

Such patients may be particularly susceptible to the sedative effects of zopiclone and associated giddiness, ataxia and confusion, which may increase the possibility of a fall (see **DOSAGE AND ADMINISTRATION)**.

Paediatric use

The safe and effective dose in children and adolescents under 18 years of age has not been established (see **CONTRAINDICATIONS**).

Effects of Fertility

Zopiclone has been shown to severely reduce fertility in male rats treated with 50 mg/kg/day or greater. The significance of this finding for humans is not known.

Use in Pregnancy (Category C)

The use of Imrest during pregnancy is not recommended. Studies in animals have not shown evidence of an increased occurrence of foetal damage. However, zopiclone has been shown to cross the placenta and increase

postnatal mortality in rats given 10 mg/kg/day and above. Although the significance of this for humans is not known, it is likely that zopiclone may be harmful to the neonate.

Cases of reduced foetal movement and foetal heart rate variability have been described after administration of benzodiazepines and other sedative-hypnotic drugs, such as zopiclone, during pregnancy.

Administration of zopiclone during the last three months of pregnancy or during labour, has been associated with effects on the neonate, such as hypothermia, hypotonia, feeding difficulties and respiratory depression due to the pharmacological action of the product

Treatment should be as short as possible and should not exceed four weeks including the period of tapering off. 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 doctor regarding discontinuation of the product if she intends to become or suspects she is pregnant.

Use in Lactation

Zopiclone and/or its metabolites are excreted in breast milk, therefore should not be used in nursing mothers.

Use in Debilitated Patients

Such patients may be particularly susceptible to the sedative effects of zopiclone and associated giddiness, ataxia and confusion, which may increase the possibility of a fall (see **DOSAGE AND ADMINISTRATION**).

Carcinogenicity

Treatment with zopiclone by dietary administration for two years increased the incidence of thyroid carcinomas in male rats dosed with 100 mg/kg/day and increased the incidence of mammary carcinoma in female rats dosed with 100 mg/kg/day, probably due to interference with thyroid hormone and 17β-oestradiol metabolism. Studies with mice treated with zopiclone at dietary doses up to 100 mg/kg/day showed no evidence of drug-related carcinogenicity.

Genotoxicity

Genotoxicity studies, using a standard battery of tests, showed no evidence of gene mutations or chromosomal damage.

INTERACTIONS WITH OTHER MEDICINES

Alcohol

Concomitant intake with alcohol is not recommended. The sedative effect of Imrest may be enhanced when the product is used in combination with alcohol.

CNS Depressants

Additive CNS depressant effects should be expected if zopiclone is administered concomitantly with other medications which themselves produce CNS depression, e.g. barbiturates, benzodiazepines, alcohol, sedatives, tricyclic antidepressants, nonselective monoamine oxidase inhibitors (MAOIs) and other antidepressants, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines, narcotic analgesics, anaesthetics, neuroleptics, hypnotics, anxiolytics, antiepileptics (see **PRECAUTIONS**). In the case of narcotic analgesics, enhancement of euphoria may also occur leading to an increase in psychic dependence.

Other

Erythromycin has been reported to significantly increase zopiclone concentrations at 30 minutes and 1 hour after ingestion of zopiclone. The total area under the curve (AUC) of zopiclone increased by 80% in 10 healthy volunteers which indicates that erythromycin can inhibit the metabolism of drugs metabolised by CYP3A4. Accelerated absorption of zopiclone in the presence of erythromycin may lead to enhanced hypnotic effects.

Plasma levels of zopiclone may be increased when co-administered with CYP3A4 inhibitors such as erythromycin, clarithromycin, ketoconazole, itraconazole, and ritonavir.

Plasma levels of zopiclone may be decreased when co-administered with CYP3A4 inducers, such as rifampicin, carbamazepine, phenobarbital (phenobarbitone), phenytoin, and St. John's wort.

Opioids

The concomitant use of benzodiazepines, 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 **PRECAUTIONS**).

ADVERSE EFFECTS

The side-effect most commonly seen in clinical trials is taste alteration (bitter taste).

More Common Effects

Gastrointestinal. Bitter taste, dry mouth.

Nervous System. Drowsiness, headaches, fatigue.

Less Common Effects

Gastrointestinal. Heartburn, constipation, diarrhoea, nausea, coated tongue, bad breath, anorexia or increased appetite, vomiting, epigastric pains, dyspepsia.

Cardiovascular. Palpitations in elderly patients.

Reproductive. Impotence, ejaculation failure, libido disorder

Nervous system. Agitation, anxiety, loss of memory including retrograde amnesia, anterograde amnesia, confusion, dizziness, weakness, somnolence, asthenia, feeling of drunkenness, euphoria, depression, coordination abnormality, hypotonia, speech disorder, hallucinations (auditory and visual), behavioural disorders, aggression, tremor, rebound insomnia, nightmares, irritability, abnormal and/or inappropriate behaviour possibly associated with amnesia, sleepwalking (see **PRECAUTIONS - Somnambulism and Associated Behaviours**), restlessness, delusion, anger, dependence, ataxia, paresthesia, cognitive disorders such as memory impairment, disturbance in attention, speech disorder.

Withdrawal syndrome has been reported upon discontinuation (see **PRECAUTIONS**). Withdrawal symptoms vary and may include rebound insomnia, muscle pain, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations, 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. In very rare cases, seizures may occur.

Respiratory, Thoracic and Mediastinal Disorders. Dyspnea and respiratory depression have been reported.

Skin. Urticaria, tingling.

Allergic or cutaneous. Pruritus, rash, urticaria and thingling have been rarely reported. Angioedema and/or anaphylactic reactions have been reported very rarely.

Miscellaneous. Blurred vision, micturition, mild to moderate increases in serum transaminases and/or alkaline phosphatase have been reported very rarely. Falls, predominantly in elderly patients, diplopia and muscular weakness have been reported.

DOSAGE AND ADMINISTRATION

For oral use only. Use the lowest effective dose. Imrest should be taken in a single intake and not be readministered during the same night.

Adults

One tablet (7.5 mg) by oral administration shortly before retiring for a maximum of 2 to 4 weeks. This dose should not be exceeded. Depending on clinical response, the dose may be lowered to 3.75 mg.

Zopiclone is not recommended for long-term use (i.e. periods of more than 4 weeks). If used for long periods, treatment should be withdrawn gradually (see Precautions, Dependence and withdrawal).

Elderly

In elderly and/or debilitated patients an initial dose of 3.75 mg is recommended. The dose may be increased to a maximum of 7.5 mg if the starting dose does not offer adequate therapeutic effect, but in clinical trials, 25% of elderly patients treated with zopiclone experienced CNS side effects at the higher dose. Zopiclone should be used with caution in these patients (see **PRECAUTIONS**).

Paediatric

Zopiclone is contraindicated in children. Dosage has not been established.

Hepatic Insufficiency

The recommended dose is 3.75 mg depending on acceptability and efficacy. Up to 7.5 mg may be used with caution in appropriate cases.

Renal Impairment

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.

Alternative therapy

For long-term treatment of insomnia, alternative non-pharmacological methods should be considered. Effective practical management of insomnia must respond to the presenting characteristics of the complaint. Giving accurate information is a form of treatment; there is benefit in discussing some simple facts with the patient and relating them to the problem, thereby assisting the patient to place the sleep problem in its context. Sleep hygiene such as reduction of caffeine intake, should be exercised. Programs designed to establish an optimal sleeping pattern for the patient may also be useful as are relaxation techniques designed to assist the patient to deal with tension and intrusive thoughts in bed.

OVERDOSAGE

Symptoms

Overdose of zopiclone can be manifested by varying degrees of CNS 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. Overdosage could be life threatening 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 very rarely can result in fatal outcome.

Treatment

Symptomatic and supportive treatment in an adequate clinical environment is recommended, attention should be paid to respiratory and cardiovascular function. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Haemodialysis is of no value, due to large volumes of distribution of zopiclone. Flumazenil may be useful as an antidote. As in the management of overdosage with any medication, it should be borne in mind that multiple agents may have been taken.

In cases of overdosage, it is advisable to contact the Poisons Information Centre (13 11 26 – Australia) for advice on the management of overdose.

PRESENTATION AND STORAGE CONDITIONS

Imrest : White, film coated, oval tablet embossed with "Z" breakline "Z" on one side and "7.5" on the other; 2*, 10*, 30 and 100* tablet bottle* and blister pack.

*Not currently marketed

Store below 25°C

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

30/11/2004

DATE OF MOST RECENT AMENDMENT

16/01/2018

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