

APO-ZOPICLONE

Zopiclone 7.5mg Tablets

Presentation

Apo-Zopiclone 7.5mg tablets are blue, oval, biconvex, film coated tablets, scored and engraved APO7.5 on one side. Each tablet contains 7.5mg zopiclone and typically weighs 165mg.

Uses

Actions

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

Its pharmacological properties are hypnotic, sedative, anxiolytic, anti-convulsant 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.

In sleep laboratory studies, zopiclone reduced sleep latency, increased the duration of sleep and decreased the number of nocturnal awakenings. Zopiclone delayed the onset of 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 although these results were variable. Zopiclone does not suppress slow wave sleep during stages 3 and 4 sleep. Negligible residual effects are seen the following morning. Rebound insomnia after cessation of treatment is not usually a feature. Dependence potential appears to be less pronounced with zopiclone than with benzodiazepines.

Pharmacokinetics

Zopiclone is rapidly and well absorbed after oral administration. Bioavailability is more than 75%, although an hepatic first-pass effect has been demonstrated. It is widely distributed and is reported to be about 45-80% bound to plasma proteins. The distribution volume is 91.8-104.6 litres. After the administration of 7.5mg doses, peak plasma concentrations of 60ng/ml were reached in less than 2 hours.

Zopiclone has an elimination half-life of approximately 5 hours and there is no significant accumulation of the product or its metabolites on repeated dosing.

It is extensively metabolised in the liver with approximately 5% of a dose being excreted in the urine and 16% in the faeces as unchanged zopiclone. A large number of metabolites have been isolated and characterised with the principal metabolites being the N-oxide derivative (approximately 12%) produced by oxidation of the piperazine nitrogen and the N-desmethyl (approximately 16%) produced by oxidative demethylation of the N-methyl piperazine. The N-oxide analogue has weak pharmacological activity, while the N-desmethyl metabolite is pharmacologically inert. Their apparent half-lives evaluated from the urinary data are approximately 4.5 and 7.4 hours respectively. Both metabolites are excreted renally. Other metabolites resulting from oxidative decarboxylation are partly eliminated via the lungs as carbon dioxide.

Special Patient Populations:

In elderly patients, the absolute bioavailability is increased and the elimination half-life prolonged to approximately 7 hours.

In patients with mild to moderate renal insufficiency, the pharmacokinetics of zopiclone are not altered. Zopiclone is removed by haemodialysis.

In patients with hepatic insufficiency, elimination half-life is substantially increased (11.9 hours), and the time to peak plasma levels delayed (3.5 hours). Lower doses are recommended.

Indications

Treatment of transient, short-term and chronic insomnia in adults including difficulties with falling asleep, nocturnal awakening and wakening.

Dosage and Administration

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

Treatment Duration:

Transient insomnia: 2 to 5 days

Short-term insomnia: 2 to 3 weeks

Chronic insomnia: long term treatment should only be considered after consultation with a specialist.

Adults

7.5mg by oral administration shortly before retiring for a maximum of 2 - 4 weeks. This dose should not be exceeded.

Depending on clinical response, the dose may be lowered to 3.75mg. Zopiclone is not recommended for long term use (i.e periods of more than 4 weeks).

If physical dependence is suspected treatment should be withdrawn gradually.

Treatment of 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 cases of renal insufficiency no accumulation of zopiclone or its metabolites has been detected, it is recommended that patients with impaired renal function start treatment with a dose of 3.75mg.

Elderly

3.75mg is advisable initially; depending on effectiveness and tolerance, the dose can be increased to 7.5mg.

Paediatric

Not established

Contraindications

Myasthenia gravis

Hypersensitivity to zopiclone

Respiratory failure

Severe sleep apnoea syndrome

Severe hepatic insufficiency

Use in children

Prior or concomitant use of alcohol

Warnings and Precautions

Risk of Dependence: Clinical experience to date with zopiclone suggests that the risk of dependence is minimal when the duration of treatment is limited to 4 weeks or less. Patients with a history of drug abuse or alcoholism, are using alcohol or psychotropics, or who have marked personality disorders, are at most risk of dependence. The decision to use zopiclone in such patients should be taken only with this clearly in mind. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms.

Rebound and Withdrawal: A greater risk of such phenomena cannot be excluded after abrupt discontinuation of zopiclone, especially in those whom physical dependence is suspected. It is therefore recommended to decrease the dosage gradually and advise the patient accordingly. The recommendation for tapering the dose is particularly important in patients with a history of seizures.

Anterograde 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 and that they are able to have a full night's sleep. Anterograde amnesia is a dose-related phenomenon and elderly subjects may be at particular risk.

Abnormal Thinking and Psychotic Behavioural Changes: Particular caution is warranted in patients with a history of violent behaviour and a history of unusual reactions to sedatives including alcohol and the benzodiazepines or benzodiazepine-like agents. Psychotic behavioural changes reported include bizarre behaviour, hallucinations and depersonalisation. The emergence of any new behavioural sign or symptom of concern requires careful and immediate evaluation.

Depression: Caution should be exercised if Apo-Zopiclone is prescribed to patients with signs and symptoms of depression that could be intensified by hypnotic drugs. The potential for self-harm (e.g.: intentional overdose) is high in patients with depression and thus the least amount of drug that is feasible should be available to them at any one time.

Patients should be closely monitored for any signs or symptoms of psychiatric disorders.

Patients should be advised to seek medical assistance immediately if they notice they are becoming depressed or have suicidal thoughts or change in behaviour. Patients may wish to consider asking a family member or close friend to help them stay alert to signs of depression or behavioural changes.

Confusion: The benzodiazepines and benzodiazepine-like agents affect mental efficiency e.g.: concentration, attention and vigilance. The risk of confusion is greater in the elderly and in patients with cerebral impairment.

Toxicology: No teratogenic or embryopathic effects have been demonstrated in animal experiments. High doses affect fertility and maternal performance. Zopiclone and its principal metabolites exerted no mutagenic or clastogenic activity in a series of *in vivo* and *in vitro* tests.

Long term administration of zopiclone to mice and rats continuously for two years at the highest test dose of 100mg/kg/day (equivalent to administration of 800 times the human therapeutic dose) was associated with increased incidence of species and sex dependent tumours, namely: lung, adenoma in female mice, subcutaneous carcinoma in male mice, thyroid follicular carcinoma in male rats and mammary carcinoma in female rats. This was, however, not evident at lower test doses equivalent to daily administration of 80 times the human therapeutic dose. Careful consideration of the results suggest the findings bear little meaningful relationship to potential carcinogenic threat to man.

Pregnancy and Lactation

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

Pregnancy:

Category C.

Studies have been performed in three animal species and have revealed no evidence of harm to the foetus due to zopiclone. Because animal studies are not always predictive of human response, the use of zopiclone during pregnancy is not 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 she is pregnant.

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

Lactation:

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

Use in Children

The safety and effectiveness of zopiclone in children and young adults below the age of 18 have not been established.

Effects on ability to drive and use machines

Because of its pharmacological properties, zopiclone may adversely affect the ability to drive or to use machines.

Adverse Effects

A withdrawal syndrome has been reported upon discontinuation of zopiclone. Withdrawal symptoms vary and may include: rebound insomnia, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations, panic attacks, muscle aches/cramps, gastrointestinal disturbances and irritability. In very rare cases seizures may occur.

The side-effect most commonly reported is a bitter or metallic taste in the mouth.

Drowsiness can sometimes occur and, more rarely, inco-ordination; patients should be cautioned about driving or operating machinery until it has been established that their performance is not affected.

Other side effects include dry mouth, headaches and fatigue.

Less common side effects include:

Gastrointestinal: heartburn, constipation, diarrhoea, nausea, coated tongue, bad breath, anorexia or increased appetite, vomiting, epigastric pains

Nervous System: agitation, anxiety, loss of memory including retrograde amnesia, confusion, dizziness, weakness, somnolence, asthenia, feeling of drunkenness, euphoria, depression, hypotonia, speech disorder, hallucinations, behavioural disorders, aggression, tremor, rebound insomnia, nightmares

Cardiovascular: palpitations, particularly in elderly patients

Dermatological: urticaria, tingling

Other: blurred vision, altered micturition, impotence, ejaculation failure

Interactions

As with all hypnotics, caution should be exercised over the concomitant use of alcohol or central depressant drugs.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines and benzodiazepine-like agents. Examples include cimetidine or erythromycin.

Overdosage

Overdose is usually manifested by varying degrees of central nervous system depression ranging from drowsiness to coma according to the quantity ingested. Overdose should not be life-threatening unless combined with other CNS depressants (including alcohol).

Symptomatic and supportive treatment in an adequate clinical environment is recommended; attention should be paid to respiratory and cardiovascular functions. Gastric lavage 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.

Pharmaceutical Precautions

Protect from light, light and moisture.
Store below 25°C.

Medicine Classification

Prescription Medicine

Package Quantities

Bottles of 100 and 500 tablets
Blister packs of 30 tablets.

Further Information

Tablets contain lactose and Brilliant Blue FCF and D&C Yellow No 10 as colouring agents.

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