ZOLON F.C. TABLETS 7.5mg

Description
It is a white, oval-biconvex film-coated tablet, with a "S||T" scored on one side and a "404" scored on the other side.

Composition
Each tablet contains Zopiclone 7.5mg.

Mode of action
Zopiclone is an hypnotic agent, and a member of the cyclopyrrolone group of compounds. It rapidly initiates and sustains sleep without reduction of total REM sleep and with preservation of slow wave sleep. Negligible residual effects are seen the following morning. Its pharmacological properties include hypnotic, sedative, anxiolytic, anticonvulsant and muscle-relaxant actions. These are related to its high affinity and specific agonist action at central receptors belonging to the 'GABA' macromolecular receptor complex modulating the opening of the chloride ion channel. However, it has been shown that zopiclone and other cyclopyrrolones act on a different site to those of benzodiazepines including different conformational changes in the receptor complex.

Summary of pharmacodynamics and pharmacokinetics
Absorption:
Zopiclone is absorbed rapidly. Peak concentrations are reached within 1.5 - 2 hours and they are approximately 30 ng/ml and 60 ng/ml after administration of 3.75mg and 7.5mg respectively. Absorption is not modified by gender, food or repetition of doses.

Distribution:
The product is rapidly distributed from the vascular compartment. Plasma protein binding is weak (approximately 45%) and non saturable. There is very little risk of drug interactions due to protein binding. The volume of distribution is 91.8 - 104.6 litres. At doses between 3.75 - 15mg, plasma clearance does not depend on dose. The elimination half life is approximately 5 hours. After repeated administration, there is no accumulation, and interindividual variations appear to be very small.

Metabolism:
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. Their apparent half-lives (evaluated from the urinary data) are approximately 4.5 hours and 1.5 hours respectively. No significant accumulation is seen on repeated dosing (15mg) for 14 days. In animals, no enz me induction has been observed even at high doses.

Excretion:
The low renal clearance value of unchanged zopiclone (mean 8.4ml/min) compared with the plasma clearance (232ml/min) indicates that zopiclone clearance is mainly metabolic.

The product is eliminated by the urinary route (approximately 80%) in the form of free metabolites (n-oxide and n-desmethyl derivatives) and in the faeces (approximately 16%). Special patient groups: In elderly patients, notwithstanding a slight decrease in hepatic metabolism and lengthening of elimination half-life to approximately 7 hours, various studies have shown no plasma accumulation of drug substance on repeated dosing. In renal insufficiency, no accumulation of zopiclone or of its metabolites has been detected after prolonged administration. Zopiclone crosses dialysis membranes. In cirrhotic patients, the plasma clearance of zopiclone is clearly reduced by the slowing of the desmethylation process: dosage will therefore have to be modified in these patients.

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

Adverse reactions/side effects
A mild bitter or metallic after-taste is the most frequently reported adverse effect. Less commonly, mild gastrointestinal disturbances, including nausea and vomiting, dizziness, headache, drowsiness and dry mouth have occurred.

Psychological and behavioural disturbances, such as irritability, aggressiveness, confusion, depressed mood, anterograde amnesia, hallucinations and nightmares have been reported. Rarely these reactions may be severe and may be more likely to occur in the elderly. Rarely allergic and allied manifestations such as urticaria or rashes have been observed and, more rarely, light headedness and incoordination. Angioedema and/or anaphylactic reactions have been reported very rarely.

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.

Mild to moderate increases in serum transaminases and/or alkaline phosphatase have been reported very rarely.

Warning/Precautions
Use in hepatic insufficiency:
A reduced dosage is recommended, see : Recommended Dose.

Use in renal insufficiency:
A reduced dosage is recommended, see : Recommended Dose.

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 not more than 4 weeks.

Use of benzodiazepines and benzodiazepine-like agents (even at therapeutic doses) may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol and or drug abuse, or those who have marked personality disorders. The decision to use a hypnotic in such patients should be taken only with this clearly in mind. If physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion 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 or epileptic seizures. Rare cases of abuse have been reported.

Withdrawal:
The termination of treatment with Zopiclone is unlikely to be associated with withdrawal effects when duration of treatment is limited to 4 weeks. Patients may benefit from tapering of the dose before discontinuation.

Depression:
Zopiclone does not constitute a treatment for depression. Any underlying cause of the insomnia should also be addressed before symptomatic treatment to avoid under treating potentially serious effects of depression.

Tolerance:
Some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like agents may develop after repeated use for a few weeks. However, with Zopiclone there is an absence of any marked tolerance during treatment periods of up to 4 weeks.

Rebound insomnia
Rebound insomnia is a transient syndrome where the symptoms which led to treatment with a benzodiazepine or benzodiazepine-like agent recur in an enhanced form on discontinuation of therapy. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since the risk of withdrawal/rebound phenomena may be increased after prolonged treatment, or abrupt discontinuation of therapy, decreasing the dosage in a stepwise fashion may be helpful.

A course of treatment should employ the lowest effective dose for the minimum length of time necessary for effective treatment. A course of treatment should not continue for longer than 4 weeks including any tapering off.

Amnesia:
Amnesia is rare, but anterograde amnesia may occur, especially when sleep is interrupted or when retiring to bed is delayed after taking the tablet. Therefore, patients should ensure that they take the tablet when certain of retiring for the night and they are able to have a full night's sleep.

Driving:
It has been reported that the risk that zopiclone adversely affects driving ability is increased by the concomitant intake of alcohol. Therefore, it is recommended not to drive while taking zopiclone and alcohol concomitantly.

Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) which can occur as early as the first time the product is taken.

Complex Sleep - Related behaviors which may include sleep driving, making phone calls, preparing and eating food (while asleep).

Contraindications
Zopiclone is contraindicated in patients with myasthenia gravis, respiratory failure, severe sleep apnoea syndrome, severe hepatic insufficiency and those people with a hypersensitivity to zopiclone. As with all hypnotics Zopiclone should not be used in children.

Dosage and directions for use
Zolon Tablet is to be taken orally.

Adults: The recommended dose is 1 tab (7.5 mg zopiclone) by the oral route shortly before retiring. This dose should not be exceeded.

Elderly: A lower dose of 3.75 mg zopiclone should be employed to start treatment in the elderly.

Children: An appropriate dosage has not been established.

Patients With 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.

Use in pregnancy and lactation
Use during pregnancy:
Experience of use of zopiclone during pregnancy in humans is limited although there have been no adverse findings in animals. Use in pregnancy is therefore not recommended. If the product is prescribed to a woman of child bearing potential, she should be advised to contact her physician about stopping the product if she intends to become pregnant, or suspects that 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, hypnotic and respiratory depression can be expected.
Infants born to mothers who took benzodiazepines or benzodiazepine-like agents chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Use during lactation:
Zopiclone is excreted in breast milk and use in nursing mothers must be avoided.

Effects on ability to drive & use machine
Because of its pharmacological properties and its effect on central nervous system, Zopiclone 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.

Drug interactions
The sedative effect of zopiclone may be enhanced when used in combination with alcohol, concomitant use is therefore not recommended. In particular this could affect the patient's ability to drive or use machines.
In combination with CNS depressants an enhancement of the central depressive effect may occur.

The therapeutic benefit of co-administration with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drug , anaesthetics and sedative antihistamines should therefore be carefully weighed. Concomitant use of benzodiazepines or benzodiazepine-like agents with narcotic analgesics may enhance their euphoric effect and could lead to an increase in psychic dependence. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines and benzodiazepine-like agents.

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 metabolised by CYP3A4. As a consequence, the hypnotic effect of zopiclone may be enhanced.

Since zopiclone is metabolised by the cytochrome P450 (CYP) 3A4 isoenzyme (see section 5.2 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 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.

Overdosage, symptoms and treatment
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 serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression and coma. Other risk factors, such as combining zopiclone with other CNS depressants (including alcohol), the presence of concomitant illness and the debilitated state of the patient, may contribute to the severity of the symptoms and very rarely 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 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.

Storage conditions
Store at temperature below 30°C. Protect from light.

Shelf-life
36 months from the date of manufacture if kept as recommended.

Package
10 tablets x 10 blisters (PTP Package) per box.

Registration number
ZOLON F.C. TABLETS 7.5mg – MAL09020983AZ

Manufacturer
Taiwan Biotech Co., Ltd.,
22, Chieh Shou Road
Taoyuan, Taiwan, R.O.C.

Product Registration Holder
Sunward Pharmaceutical Sdn Bhd
No. 9,11,17, Jalan Kempas 4,
Taman Perindustrian Tampoi Indah,
81200 Johor Bahru, Johor, Malaysia.

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