PACKAGE INSERT TEMPLATE FOR ZOLPIDEM TABLET

Brand or Product Name
[Product name] Tablet 10mg

Name and Strength of Active Substance(s)

Zolpidem Tartrate…..10mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)
eg White, circular flat beveled edge tablets marked '10' on one side]

Pharmacodynamics
Pharmacologically, zolpidem binds selectively to the omega-1 subclass (or BZ1) of benzodiazepine receptors in the brain without binding to peripheral benzodiazepine receptors. This has been corroborated by the observation that zolpidem has little or no muscle relaxant properties.

Zolpidem has been shown to reduce sleep latency (time to fall asleep), decrease the number of awakenings, and to increase total sleep time. While REM sleep is not significantly decreased, the onset of REM is delayed. The REM/non-REM ratio is not significantly altered. Slow wave (stages 3 and 4) sleep time is increased. This more closely resembles natural sleep than does hypnosis induced by the benzodiazepines; this may result in fewer adverse reactions related to disturbance of normal sleep patterns.

Pharmacokinetics

Absorption

Zolpidem is rapidly absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations occurring within 3 hours.

Bioavailability, Oral, tablets: 70%

Effect of food: decreased systemic exposure (decreased Cmax and AUC; increased Tmax)

Distribution
Zolpidem is about 92% bound to plasma proteins.
The distribution volume in adults is 0.54L/kg
Zolpidem is distributed into breast milk.

Metabolism
Liver, extensive
Zolpidem undergoes first-pass metabolism. It is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4;

Elimination
Zolpidem has an elimination half-life of about 2.5 hours. The inactive metabolites of zolpidem are excreted in the urine and faeces.
Zolpidem is not dialysable.

Populations at risk
• In patients with renal insufficiency, whether dialysed or not, a moderate decrease in clearance is observed. Other kinetic parameters remain unchanged.
• In patients with hepatic insufficiency, the bioavailability of zolpidem is increased. Clearance is reduced and elimination half-life prolonged (about 10 hours).

Indication
Indications are limited to treatment of severe sleep disorders in the following cases:
• Occasional insomnia,
• Transient insomnia.

Recommended Dosage
The treatment should always be implemented at the lowest effective dose and maximum dosage never exceeded.
The usual dose for adults is one 10-mg tablet daily.
The medicinal product should always be taken just before going to bed.
In elderly subjects or subjects presenting with hepatic insufficiency: dosage should be halved, i.e. 5 mg.
Dosage must never exceed 10 mg per day.
Safety and effectiveness of zolpidem in paediatric patients under the age of 18 years have not been established. Therefore, zolpidem should not be prescribed in this population.
Zolpidem can be prescribed either continuously or on demand, depending on the patient's symptoms.

Treatment duration
The treatment period should be as short as possible, from a few days to four weeks, including the tapering period
The patient should be advised to take the treatment as follows:
- 2 to 5 days for occasional insomnia (e.g. during a trip)
- 2 to 3 weeks for transient insomnia (e.g. during a troubled period).
Very short treatment periods do not require any gradual treatment discontinuation.
For certain patients, it may be necessary to continue treatment for longer than four weeks, in which case careful and repeated reassessment of the patient's condition is necessary.

Mode of Administration
Oral

Contraindications

• hypersensitivity to the active substance or any of the ingredients in the product,

• severe respiratory insufficiency,

• sleep apnoea syndrome,

• severe, acute or chronic hepatic insufficiency (risk of encephalopathy),

• myasthenia.

• due to the lactose content, this medicinal product is contraindicated in the event of

congenital galactosaemia, glucose or galactose malabsorption syndrome or lactase

deficiency.

Warnings and Precautions

Insomnia must systematically be assessed and its causes treated before a hypnoticis prescribed.

Underlying comorbid physical or psychiatric disorders; worsening of insomnia, failure of insomnia to remit after 7 to 10 days, or emergence of new behavioral or cognitive abnormalities may indicate the presence of a primary medical and/or psychiatric illness.

Anaphylaxis (severe allergic reaction) and *angioedema* (severe facial swelling) may occur as early as the first dose or subsequent doses.

Pharmacological tolerance: After repeated administration over several weeks, the sedating or hypnotic effect of benzodiazepines and related substances may gradually decrease.

Abrupt withdrawal or rapid dose decrease; may cause severe withdrawal symptoms.Some symptoms are frequent and appear commonplace: insomnia, headaches, marked anxiety, myalgia, muscle tension and irritability.Other symptoms are rarer: agitation or even confusion, paresthesia of fingers and toes, hyperreactivity to light, sound and physical contact, depersonalisation, derealisation, hallucinations and convulsions. Withdrawal symptoms may appear during the days following treatment discontinuation. With short-acting benzodiazepines, certain withdrawal symptoms may occur between two consecutive intakes, especially at high doses.

Rebound insomnia: This transient syndrome is a worsening of the initial insomnia for which the benzodiazepines and related substances were prescribed.

Amnesia and impaired psychomotor function: Anterograde amnesia and impaired psychomotor function may occur within hours of intake. To reduce these risks, the product should be taken just before going to bed, or even in bed ,and in optimal conditions for uninterrupted sleepof 7-8 hours.

Behavioral changes (eg, hallucinations, bizarre behavior, agitation, and depersonalization) have been reported

Somnambulism and associated behaviours: Sleep-related behaviors, complex, have been reported; possibility of patients performing activities while asleep (eg, sleep-driving, making phone calls, preparing/eating food, engaging in sexual intercourse) with no memory afterwards;, has been reported in patients who had taken zolpidem and were not fully awake. Increased risk with doses higher than recommended and concomitant use of CNS depressants and alcohol; discontinuation may be necessary if sleep-driving occurs.

Treatment duration: The patient must be clearly informed of treatment duration depending on the type of insomnia.

Concurrent use of alcohol; avoid this combination

Concomitant use with other sedative-hypnotics (including other zolpidem products) at bedtime or the middle of the night is not recommended.

Patients with major depression: Since insomnia may be a symptom of depression, the depression must be treated. If insomnia persists, the patient's condition must be reassessed. Benzodiazepines and related substances should not be used alone in patients with a major depressive episodesince they enable depression to evolve with persistence or worsening of suicidal tendencies.The lowest amount of zolpidem must be prescribed and supplied to them in order to limit the possibility of intentional overdose (innovator)

*Gradual discontinuation of treatment***:** Patients must be warned of the possibility of rebound insomnia, so that potential insomnia resulting from symptoms related to such discontinuation, even if gradual, may be minimised. The patient must be informed that this period may be difficult.

Children: Zolpidem should not be given to children aged under 18 years.

Elderly subjects, patients with hepatic insufficiency: Dosage should be reduced (i.e. by half) because of the risk of accumulation

Great care must be taken when prescribing benzodiazepines and related substances to elderly patients, because of the risk of sedation and/or muscle relaxant effects which may lead to falls.

In patients with *respiratory insufficiency*, the depressant effect of benzodiazepines and related substances must be taken into account (especially since anxiety and agitation may be signs of respiratory function decompensation requiring hospitalisation in an intensive care unit).

Myasthenia gravis, sleep apnea and respiratory impairment; may depress respiratory drive

Diseases or conditions that affect metabolism or hemodynamic response

Very great care is required in the event of *history of alcoholism or drug addiction* (medicinal products or not)

Effects on the ability to drive and use machines
Drivers and machine operators should be informed of the risk of drowsiness associated with the use of this medicinal product. Any combination with other sedating medicinal products is to be avoided or taken into account when driving or using machines. The risk of impaired vigilance is exacerbated if patients do not get sufficient sleep.

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Interactions with Other Medicaments
Concurrent use of rifampicin and zolpidem may result in decreased plasma concentration and pharmacodynamic effect of zolpidem.

Concurrent use of deferasirox and CYP3A4 substrates may result in reduced plasma concentrations of CYP3A4 substrate.

Concurrent use of primidone and CYP3A4 substrates may result in decreased exposure of CYP3A4 substrates.

Concurrent use of zolpidem and ketoconazole may result in increased plasma concentrations and pharmacodynamic effects of zolpidem. Slight increase in sedation.

Concurrent use of ciprofloxacin and zolpidem may result in increased zolpidem plasma concentrations.

Concurrent use of fluvoxamine and zolpidem may result in decreased zolpidem clearance and increased exposure.

Concurrent use of zolpidem and ritonavir may result in an increased risk of extreme sedation and respiratory depression.

Concurrent use of zolpidem and the following may result in decreased zolpidem plasma concentrations:

- Carbamazepine
- St John's Wort

Concurrent use of zolpidem and the following drugs may result in an increased risk of hallucinations:

- Sertraline
- Venlafaxine
- Fluoxetine
- Bupropion

Buprenorphine: Enhanced risk of respiratory depression that may prove fatal. Carefully assess the risk/benefit ratio of this combination.

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Other Central nervous system depressants:
Morphine derivatives (analgesics, cough suppressants and replacement treatments, other than buprenorphine); neuroleptics; barbiturates; anxiolytic agents; other hypnotics; sedating antidepressants; sedating H1 antihistamines; central anti-hypertensive drugs; baclofen; thalidomide; pizotifen.

Enhanced central nervous system (CNS)-depressant effects. Impaired vigilance may prove dangerous when driving or using machines. Dosage adjustments may be necessary when zolpidem is administered with sedative/hypnotic drugs because of the potentially additive effects Moreover, for morphine derivatives (analgesics, cough suppressants and replacement treatments), barbiturates: enhanced risk of respiratory depression which may prove fatal in the case of overdose.

Concurrent use of zolpidem and food may result in decreased zolpidem plasma concentrations. Zolpidem should not be administered with or immediately after a meal.

Concurrent use of zolpidem and alcohol may result in increased sedation.

Statement on Usage During Pregnancy and Lactation
Pregnancy
Insufficient clinical data are currently available concerning exposure during the first trimester of pregnancy.

By analogy with related drugs (benzodiazepines):
• If high-doses of zolpidem are being taken during the second and/or third trimesters of pregnancy, a reduction in active fetal movements and in fetal heart rate variability may occur.
• Treatment towards the end of pregnancy with benzodiazepines, even at a low dosage, may cause signs of impregnation in the neonate, such as axial hypotonia and difficulty in suckling which gives rise to poor weight gain. These signs are reversible, but may last for 1 to 3 weeks, depending on the half-life of the benzodiazepine prescribed. At high doses, reversible respiratory depression or apnea and hypothermia may appear in the neonate. Furthermore, a neonatal withdrawal syndrome is possible, even if no signs of impregnation are present. This is characterized in particular by overexcitability, agitation and tremor in the neonate, occurring some time after delivery. The time to onset depends on the elimination half-life of the drug and may be considerable if the latter is long. Hence it is preferable, as a precautionary measure, not to use zolpidem at any stage during pregnancy.

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High doses of zolpidem should not be administered during the last trimester of pregnancy, as hypotonia and respiratory distress may occur in newborns at delivery. Withdrawal symptoms may occur in newborns a few days or weeks after birth.

Lactation
Breast-feeding is not recommended during treatment

Adverse Effects / Undesirable Effects
Gastrointestinal Effects: diarrhea, nausea, constipation, indigestion, xerostomia

Immunologic Effects: allergy

Neurologic Effects: dizziness, drugged state, headache, somnolence, asthenia, ataxia, cerebrovascular disease, confusion, difficulty driving a car, disorientated, lethargy, lightheadedness, motor retardation, sleep disorder, vertigo , hepatic encephalopathy

Ophthalmic Effects: visual disturbance, abnormal vision, diplopia

Cardiovascular Effects: chest pain, tachycardia hypertension, palpitations

Immunologic Effects: anaphylaxis (rare)

Psychiatric Effects: complex mannerisms - behavior, depression, worsening, suicidal thoughts, anxiety, dream disorder, euphoria, hallucinations, memory impairment

Dermatologic Effects: rash

Hepatic Effects: abnormal liver function, ALT/SGPT level raised

Musculoskeletal Effects: arthralgia, backache, myalgia

Renal Effects: urinary tract infection

Respiratory Effects: hiccoughs, pharyngitis, sinusitis, upper respiratory infection

Withdrawal sign or symptom: Withdrawal symptoms, including convulsions, tremor, abdominal and muscle cramps, vomiting, sweating, mild dysphoria, and insomnia have been reported with abrupt discontinuation of sedative/hypnotics. Other withdrawal effects reported include fatigue,

nausea, flushing, lightheadedness, uncontrolled crying, emesis, panic attack, nervousness, and abdominal discomfort

Other: angioedema (rare), influenza-like illness, fatigue

Overdose and Treatment

Symptoms

Mild to moderate poisoning: Somnolence, slurred speech, confusion, and ataxia may occur.
Severe poisoning: Severe effects are very rare but may occur after co-ingestion with other sedatives and may include coma and respiratory depression. Death is extremely rare but may be caused by respiratory depression. Patients that present with coma are at risk for aspiration pneumonia, rhabdomyolysis, and renal failure.

Treatment

Majority of patients develop mild to moderate toxicity, and only require supportive care.
Severe toxicity generally occurs if other sedating agents are also ingested. Administer activated charcoal if the ingestion is recent and the patient is alert or the airway is protected. Orotracheal intubation for airway protection should be performed if the patient is increasingly drowsy or comatose.

Storage Conditions

[eg Store below….°C]

Dosage Forms and Packaging Available

[Packaging type & pack size]

Name and Address of Manufacturer

[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder

[Name & full address of marketing authorization holder]

Date of Revision of Package Insert

[day/month/year]