ANPRO-ZOLPIDEM TABLETS 10MG

NAME AND STRENGTH OF ACTIVE INGREDIENT(S):
Each tablet contains:
Zolpidem Tartrate……10mg

PRODUCT DESCRIPTION:
A yellow, oblong tablet of size 10 x 4mm.

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 (stage 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 occuring 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:
Dose
The treatment should be taken as a single dose and not be re-administered during the same night.
The recommended daily dose for adults is 10mg to be taken immediately at bedtime.
Treatment should be started at the lowest effective dose and the maximum dose must not exceed 10mg.

Elderly or debilitated subjects
As elderly or debilitated patients are especially sensitive to the effects of zolpidem, the recommended dose in this population is 5mg (i.e. ½ a tablet).

Liver failure
As the clearance and metabolism of zolpidem are reduced in liver failure, treatment should begin at 5mg per day in these patients, with particular caution being exercised in elderly patients.
Under no circumstance should the daily dose exceed 10mg.
Zolpidem may be prescribed for use continuously or as required, depending on the signs and symptoms.

Pediatric population
The safety and efficacy of zolpidem in children and adolescents under 18 years of age have not been demonstrated. Therefore, use of zolpidem is not recommended in this population. The available evidence from placebo-controlled clinical trials is presented in section Pharmacodynamic properties.

Duration
As with all hypnotics, long-term use of zolpidem is not recommended. Treatment should be as short as possible, and should not exceed four weeks, including the tapering-off period (see section Special warnings and special precautions for use).
The duration of treatment must be explained to the patient:
-2 to 5 days for transient insomnia (when traveling, for example),
-2 to 3 weeks for short-term insomnia (following a serious event, for example).
Very short-term treatment do not require a tapering-off period.
Extension beyond the maximum treatment period 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.

ROUTE OF ADMINISTRATION:
Oral.

CONTRAINDICATIONS:
- Hypersensitivity to the active substance or any of the ingredients in the product.
- Severe respiratory insufficency.
- Sleep apnoea syndrome.
- Severe, acute or chronic hepatic insufficiency (risk of encephalopathy).
- Myasthenia.
- Due to 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 hypnotic is 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 common place: 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 sleep of 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 episode since 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.

<u>Risk from Concomitant Use with Opioids</u>
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Anpro-Zolpidem Tablets 10mg with opioids. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.
If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Anpro-Zolpidem Tablets 10mg is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of opioids (See Drug Interations).

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 on 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

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

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.

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

Opioids

Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions).

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

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, occuring 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.

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.

SIDE 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

SYMPTOMS & TREATMENT OF OVERDOSE:

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.

EFFECT ON ABILITY TO DRIVE AND USE MACHINE.

Activities such as driving or operating machinery should be avoided. Drivers and machine operators should be advised that there is a risk of drowsiness with zolpidem tartrate.

PRECLINICAL SAFETY DATA

Not applicable.

INSTRUCTION FOR USE

The tablet should always be taken immediately before bedtime.

STORAGE CONDITIONS

Store below 30ºC in well-closed container. Protect from light, heat and moisture.
Keep the medicine out of reach of children/Jauhi dari kanak-kanak.

DOSAGE FORMS AND PACKAGING AVAILABLE:

Dosage Form: Tablet
Packing Size: Blister pack: 10x10’s, 100x10’s

NAME AND ADDRESS OF MANUFACTURER/PRODUCT REGISTRATION HOLDER:

MALAYSIAN PHARMACEUTICAL INDUSTRIES SDN BHD
Plot 14, Lebuhraya Kampung Jawa, 11900 Bayan Lepas,
Pulau Pinang, Malaysia.

DATE OF REVISION:

16/06/2021