Hypnotic
Japanese Pharmacopeia **Zolpidem Tartrate Tablet**
NIKP-Zolpidem tablet 10 mg

This package insert is continually updated: please read carefully before using a new pack. In case of any question, please contact your physician or pharmacist.

[WARNINGS]

1. **Use of this drug may induce twilight states or parasomnias (e.g., sleepwalking) and complex sleep-related behaviours. In addition, the user may not remember activities they do before they fall asleep or during nocturnal awakenings.**
2. **Due to the lactose content, this drug is contraindicated in the event of congenital galactosaemia, glucose or galactose malabsorption syndrome or lactase deficiency.**

[CONTRAINDICATIONS (This product is contraindicated in the following patients.)]

1. Patients with a history of hypersensitivity to any of the ingredients of this drug.
2. Patients with severe liver disorder [The blood concentration would rise due to impaired metabolic function, which could strengthen the effects of the drug.]
3. Patients with myasthenia gravis [The muscle relaxing effects of the drug could exacerbate symptoms.]
4. Patients with acute narrow-angle glaucoma [The drug could increase intraocular pressure and exacerbate symptoms.]

[RELATIVE CONTRAINDICATIONS (This drug is generally contraindicated in the following patients, but may be administered with caution if indispensable.]

Patients with acute pulmonary heart disease, pulmonary emphysema, bronchial asthma, and cerebrovascular disease whose respiratory function is highly compromised [Such patients are prone to carbon dioxide narcosis from respiratory depression.]

[DESCRIPTION]

1. Composition

Each tablet contains 10 mg of zolpidem tartrate.
Excipients: lactose, cellulose, sodium starch glycolate, hypromellose, talc, magnesium stearate, macrogol, titanium oxide, yellow ferric oxide, ferric oxide, carnauba wax.

2. Product description

This drug is scored, light orange, film-coated tablets.

Brand name	Appearance Weight (mg)	Diameter (mm)	Thickness (mm)	Identification code (on tablet)	Identification code (on package)
NIKP-Zolpidem tablet 10 mg	 124	 7.1	 3.2	ℼ 175	ⓝ 175

[INDICATIONS]

Short-term treatment of insomnia (excluding insomnia associated with schizophrenia and manic depression)

<Precautions>

This drug should be administered only after the primary disease causing insomnia has been diagnosed. They are not effective for treating insomnia associated with schizophrenia or manic depression.

[DOSAGE AND ADMINISTRATION]

(1) The recommended initial dose is 5mg for women and either 5 or 10mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening.
(2) If the 5mg dose is not effective, the dose can be increased to 10mg. In some patients, the higher morning blood levels following use of 10mg dose increase the risk of next day impairment of driving and other activities that require full alertness.
(3) Use the lowest effective dose for the patient.
(4) The total dose of zolpidem should not exceed 10mg once daily immediately before bedtime.
(5) The recommended dose of zolpidem in elderly patients is 5mg once daily immediately before bedtime.
(6) The recommended dose of zolpidem in patients with hepatic insufficiency is 5mg once daily immediately before bedtime.

[PRECAUTIONS]

1. Careful administration (This product should be administered with care in the following patients.)

(1) Debilitated patients [Drug effects are strong and thus adverse reactions are more likely.]
(2) Elderly patients (Refer to "Elderly")
(3) Patients with cardiac disorder [Blood pressure may decrease, which could exacerbate symptoms in patients with cardiac disorder.]
(4) Patients with liver disorder (Refer to “CONTRAINDICATIONS”)
(5) Patients with kidney disorder [Delayed excretion could strengthen the effects of the drug.]
(6) Patients with organic brain disorder [The effects of the drug could be strengthened.]

2. Important Precautions

(1) Continuous administration of this drug should be avoided; it should only be administered for a short period of time. If continuous administration is absolutely necessary, it should be done carefully while closely monitoring the patient for any abnormalities in their condition or symptoms on a regular basis.
(2) The effects of this drug may extend past the following morning and result in sleepiness and decreased alertness, concentration, and reflexive motor skills.It is recommended not to drive or perform activities that require mental alertness until 8 hours after taking zolpidem.
(3) Worsening of depression and suicidal thoughts and actions (including completed suicides) reported primarily depressed patients; prescribe the lowest feasible number of tablets at a time.

3. Drug Interactions

This drug is mainly metabolized by the liver drug metabolizing enzyme CYP3A4 and partially metabolized by CYP2C9 and CYP1A2. Zolpidem should not be taken together with alcohol, other medicines that have an effect on mental function and/or the central nervous system.

Precautions for coadministration (This drug should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Narcotics	Use with caution as respiratory depression may occur.	Respiration may be depressed in an additive manner.
Central nervous system depressants Phenothiazine derivatives Barbiturate derivatives, etc.	Use with caution as drug interactions may lead to further depression of the central nervous system.	Both this drug and central nervous system depressants depress the central nervous system.
Alcohol consumption	Use of this drug with alcohol may further decrease mental function, perception, and motor function, and thus should be avoided to the greatest extent possible.	Alcohol depresses the central nervous system by acting on GABAA receptors, so interactions between alcohol and this drug may lead to further depression of the central nervous system.
Rifampicin	Decreases the blood concentration of this drug and may weaken its effect.	Induces the drug metabolizing enzyme CYP3A4 and promotes metabolism of this drug.

4. Adverse Reactions

Surveys or studies that demonstrate frequency of adverse reaction have not been conducted.

(1) **Clinically significant adverse reactions** (Frequency unknown)

1) **Dependence and withdrawal symptoms**
Drug dependence may occur with use, so this drug should be administered with caution while carefully monitoring patients. Furthermore, a rapid reduction in dose or discontinuation during use may lead to withdrawal symptoms such as rebound insomnia or irritability. If administration is to be discontinued, it should be done carefully by gradually decreasing the dose.

2) **Psychiatric symptoms and disturbances of consciousness**
Psychiatric symptoms and disturbances of consciousness (e.g., delirium, confusion, somnambulism, hallucinations, excitation, disinhibition, depressed level of consciousness) may occur. Patients, hence, should be carefully monitored. If any abnormal findings are observed, administration of this drug should be discontinued and appropriate therapeutic measures should be taken.

3) **Transient anterograde amnesia and twilight states**
Sleep walking and other associated behaviours such as “sleep driving”, preparing and eating food, making phone calls or having sex, with amnesia for the event, have been reported in patients who had taken zolpidem and were not fully awake. The use of alcohol and other CNS-depressants with zolpidem appears to increase the risk of such behaviours, as does the use of zolpidem at doses exceeding the maximum recommended dose. Discontinuation of zolpidem should be strongly considered for patients who report such behaviours (for example, sleep driving), due to the risk to the patient and others.

4) **Respiratory depression**
Respiratory depression may occur. Furthermore, carbon dioxide narcosis may occur if this drug are administered to a patient with highly compromised respiratory function. Therefore, in such circumstances, appropriate therapeutic measures such as airway management and ventilation should be taken.

5) **Hepatic function disorder, jaundice**

Hepatic function disorder and jaundice accompanied by increased AST (GOT), increased ALT (GPT), increased γ-GTP, and increased Al-P may occur. Patients, hence, should be carefully monitored. If any abnormal findings are observed, administration of this drug should be discontinued and appropriate therapeutic measures should be taken.

(2) **Other adverse reactions**

		Frequency unknown
*	**Psychoneurologic**	Light-headedness, sleepiness, headache, feeling of residual sleepiness, dull headache, dizziness, anxiety, nightmares, exhilaration, optical illusions, numbness
	Hematologic	Leukocytosis, leukopenia
	Hepatic	Increased ALT (GPT), increased γ-GTP, increased AST (GOT), increased LDH
	Renal	Proteinuria
*	**Gastrointestinal**	Nausea, vomiting, anorexia, abdominal pain, diarrhea, oral paresthesia
	Cardiovascular	Palpitations
	Hypersensitivity Note 1)	Rash, itching, angioedema, severe allergic reactions
	Musculoskeletal	Malaise, fatigue, lower limb weakness
*	**Ophthalmologic**	Diplopia, visual impairment, blurred vision
*	**Other**	Dry mouth, discomfort, dysgeusia, fall Note 2), back pain

Note 1: If these occur, administration should be discontinued.

*Note 2: Fractures from falls have been reported in elderly patients.

5. Elderly

Ataxia is common. Furthermore, as elderly patients are prone to adverse reactions, a low dose (5 mg/dose) should be administered at first and no more than 10 mg should be taken at one time.

6. Pregnancy, Delivery or Lactation

(1) **Pregnant women, etc.**

This drug should only be administered to pregnant women or women suspected of being pregnant, if the expected therapeutic benefits are evaluated to exceed the possible risks of treatment. [The safety of zolpidem in pregnant women has not been established. Children born to mothers who took a zolpidem tartrate formulation during late pregnancy may develop withdrawal symptoms such as respiratory depression, convulsions, tremors, irritability, and nursing difficulties. These symptoms have presented as birth asphyxia in some cases.]

(2) **Nursing mothers**

It is desirable to avoid the administration of this drug to nursing mothers. However, if the administration is indispensable, nursing should be discontinued. [Transfer to breast milk has been reported and may lead to lethargy in newborns.]

7. Children

The safety of this drug in low birth weight infants, newborns, nursing infants, and children has not been established. (No clinical experience.)

8. Overdosage

(1) **Symptoms**

Disturbances of consciousness ranging from somnolence to coma have been reported after overdose of zolpidem tartrate in monotherapy. Furthermore, severe symptoms such as central nervous system depression, hypotension, respiratory depression, and apnea may develop.

(2) **Treatment**

Respiration, pulse, and blood pressure should be monitored and appropriate therapeutic measures (e.g., induction of emesis, gastric lavage, administration of adsorbents or laxatives, transfusion, airway management) should be taken. Furthermore, if overdose of this drug is confirmed or suspected and flumazenil (a benzodiazepine receptor antagonist) is to be used as a treatment, precautions for using flumazenil (e.g., contraindications, careful administration, and drug interactions) must be read in advance. It should be noted this drug is not dialyzable.

9. Precautions Concerning Usage

Precautions for dispensing： Patients should be instructed to remove the tablets from the blister package prior to use. (It has been reported that, if the blister is swallowed, its sharp corners may puncture the esophageal mucosa, and resulting in serious complications such as mediastinitis.)

10. Other Precautions

If this drug is administered again in a patient who received flumazenil (a benzodiazepine receptor antagonist) before the drug taken was identified, the sedative and anticonvulsive effects of this drug may change or persist for a longer period of time.

[PHARMACOKINETICS]

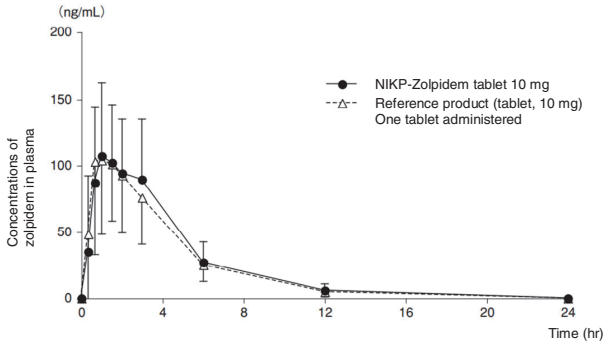
1. Bioequivalence Study

When a single oral dose of one tablet of NIKP-Zolpidem tablet 10 mg or one tablet of the reference product (both tablets contain 10 mg of zolpidem tartrate) was given to healthy male adults during fasting with a cross-over method, the plasma concentrations of zolpidem were measured. In a statistical analysis for the obtained pharmacokinetic parameters (AUC and Cmax), calculation results of 90% confidence intervals for the parameters were within a range between log (0.8) and log (1.25), demonstrating the bioequivalence of the two formulations.

<NIKP-Zolpidem tablet 10 mg>

	Pharmacokinetic parameters		Reference parameters	
	$AUC_{0\rightarrow24}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
NIKP-Zolpidem tablet 10 mg	560.8± 273.7	127.1± 49.9	1.40± 0.94	2.28± 0.40
Reference product (Tablet, 10 mg)	521.7± 253.0	121.5± 58.2	1.25± 0.82	2.21± 0.52

(Administered one tablet, Mean ± S.D., n = 10)



Plasma concentration and pharmacokinetic parameters such as AUC and C_{max} may vary depending on study conditions including selection of subjects, body fluid sampling frequency/sampling time, etc.

2. Dissolution profile

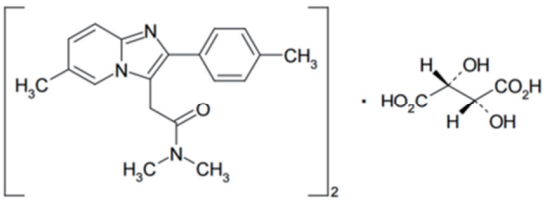
This drug has been shown to meet the dissolution specification for zolpidem tartrate tablets set forth in the Official Monographs of the Japanese Pharmacopoeia.

[PHYSICOCHEMISTRY]

Nonproprietary name: Zolpidem Tartrate

Chemical name:

N,N,6-Trimethyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-acetamide hemi-(2*R*,3*R*)-tartrate



Molecular formula: $(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$

Molecular weight: 764.87

Description: Zolpidem Tartrate occurs as a white crystalline powder.

It is freely soluble in acetic acid (100), soluble in N,N-dimethylformamide and in methanol, sparingly soluble in water, and slightly soluble in ethanol (99.5) and in acetic anhydride.

It dissolves in 0.1 mol/L hydrochloric acid test solution.

It gradually changes to yellow in color on exposure to light.

[PRECAUTIONS FOR HANDLING]

1. Shelf-life

2 years

2. Storage

Store below 25ºC

Do not use after expiry date indicated on the outer carton box.

[PACKAGING]

20 tablets (10 tablets 2 blisters)
100 tablets (10 tablets 10 blisters)
Not all pack sizes may be marketed.

[NAME OF MANUFACTURER]

Nichi-Iko Pharmaceutical Co., Ltd. Toyama Plant 1

[DATE OF ISSUE]

November 2015

[COUNTRY]

Hong Kong