For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack.

Zolpidem Tartrate Prolonged Release Tablets IP
STILNOCT®
STILNOCT 6.25mg
Each film coated bi-layered tablet contains:
Zolpidem tartrate I.P …… 6.25 mg
Excipients.....q.s
Colour: Titanium Dioxide IP, Red Iron Oxide

STILNOCT 12.5mg
Each film coated bi-layered tablet contains:
Zolpidem tartrate I.P …… 12.5 mg
Excipients……q.s
Colour: Titanium Dioxide IP, Yellow Iron Oxide, Indigotine Aluminium Lake

DESCRIPTION
STILNOCT® contains zolpidem tartrate, a gamma-aminobutyric acid (GABA) A agonist of the imidazopyridine class. STILNOCT® (Zolpidem tartrate prolonged release tablets IP) is available in 6.25 mg and 12.5 mg strength tablets for oral administration.

Chemically, zolpidem tartrate is N, N, 6-trimethyl-2-p-tolylimidazo [1, 2-a] pyridine-3-acetamide L-(+)-tartrate (2:1).

STILNOCT® consists of a coated two-layer tablet: one layer that releases its drug content immediately and another layer that allows a slower release of additional drug content.

INDICATIONS
STILNOCT® (zolpidem tartrate prolonged release tablets IP) is indicated for the short term treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

DOSAGE AND ADMINISTRATION
General
STILNOCT® acts rapidly and therefore should be taken immediately before retiring or in bed. STILNOCT® should be taken in a single intake and not be readministered during the same night. 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. **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** (see Section Precautions)**.**
The recommended daily dose for adults is 12.5mg. The lowest effective daily dose of zolpidem should be used and must not exceed 12.5 mg.

The tablets are to be swallowed whole and should not be crushed, chewed or divided.

Special Population

Children
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 (*see Precautions: paediatric patients).*

Elderly
Since elderly or debilitated patients may be especially sensitive to the effects of zolpidem, in these subjects a 6.25 mg dose is recommended.

Hepatic impairment
As clearance and metabolism of zolpidem is reduced in hepatic impairment, caution should be exercised in these patients; dosage should begin at 6.25mg in subjects with hepatic impairment with particular caution being exercised in elderly patients.

Administration
For oral use only.

CONTRAINDICATIONS
Zolpidem is contraindicated in patients with :
- a hypersensitivity to zolpidem or any of the inactive ingredients,
- severe hepatic insufficiency,
- acute and / or severe respiratory insufficiency.

WARNINGS
Zolpidem should be used with caution in patients with sleep apnea syndrome, and myasthenia gravis.

- ***Respiratory insufficiency***
  As hypnotics have the capacity to depress respiratory drive, precautions should be observed if zolpidem is prescribed to patients with compromised respiratory function (see *Adverse Reactions*).

- ***Risks from concomitant use with opioids***
  Concomitant use **of opioids with** benzodiazepines or other sedative-hypnotic drugs, including zolpidem, may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

  If a decision is made to prescribe zolpidem concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation (see Section Interactions)

- ***Hepatic insufficiency***
  Zolpidem must not be used in patients with severe hepatic impairment as it may contribute to encephalopathy (See Sections Dosage & Administration, Contraindications, Adverse Reactions).

PRECAUTIONS

The cause of insomnia should be identified wherever possible and the underlying factors treated before a hypnotic is prescribed. The failure of insomnia to remit after a 7-14 day course of treatment may indicate the presence of a primary psychiatric or physical disorder, and the patient should be carefully re – evaluated at regular intervals.

- ***Paediatric Patients***

Safety and effectiveness of zolpidem have not been established in patients below the age of 18 years. In an 8-week study in paediatric patients (aged 6-17 years) with insomnia associated with attention – deficit /hyperactivity disorder (ADHD), psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs.0%) (*See Dosage And Administration: Special population: children*).

- ***Elderly***

See dose recommendations.

- ***Psychotic illness***

Hypnotics such as zolpidem are not recommended for the primary treatment of psychotic illness.

- ***Amnesia***

Sedative/hypnotic agents such as zolpidem may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours.

- ***Suicidality and Depression:***

Several epidemiological studies show an increased incidence of suicide and suicide attempt in patients with or without depression, treated with benzodiazepines and other hypnotics, including zolpidem. A causal relationship has not been established. As with other sedative/hypnotic drugs, zolpidem should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present, therefore the least amount of zolpidem that is feasible should be supplied to these patients to avoid the possibility of intentional overdosage by the patient. Pre–existing depression may be unmasked during use of zolpidem. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists

- ***Other psychiatric and "paradoxical" reactions***

Other psychiatric and "paradoxical" reactions like restlessness, insomnia exacerbated, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, abnormal behavior and other adverse behavioral effects are known to occur when using sedative / hypnotic agents like zolpidem. Should this occur, use of zolpidem should be discontinued. These reactions are more likely to occur in the elderly.

- ***Somnambulism and associated behaviors***

Sleep walking and other associated behaviors 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 behaviors, 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 behaviors (for example, sleep driving), due to the risk to the patient and others (*See interactions and Adverse Reactions*).

- ***Psychomotor impairment***

Like other sedative/hypnotic drugs, zolpidem has CNS-depressant effects.

The risk of psychomotor impairment, including impaired driving ability, is increased if:
zolpidem is taken within less than 7-8 hours before performing activities that require mental alertness, a dose higher than the recommended dose is taken, or zolpidem is co-administered with other CNS depressants, alcohol, or with other drugs that increase the blood levels of zolpidem.(See Section interactions and Driving a Vehicle or performing other hazardous tasks).

- ***Tolerance***

Some loss of efficacy to the hypnotic effects of sedative /hypnotic agents like zolpidem may develop after repeated use for a few weeks.

- ***Dependence***

Use of zolpidem may lead to the development of **abuse and/or** physical and psychological dependence. The risk of dependence increases with dose and duration of treatment. **Cases of dependence have been reported more frequently in patients treated with Stilnoct for longer than 4 weeks. The risk of abuse and dependence** is also greater in patients with a history of psychiatric disorders and/or alcohol or drug abuse. **Stilnoct should be used with extreme caution in patients with current or a history of alcohol or drug abuse.**

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety and tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

- ***Rebound insomnia***

A transient syndrome whereby the symptoms that led to treatment with sedative/hypnotic agents recur in an enhanced form, may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness. It is important that the patient should be aware of the possibility of rebound phenomena, thereby minimizing anxiety over such symptoms should they occur when the medicinal product is discontinued.

In the case of sedative / hypnotic agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval.

- ***Severe injuries***

Due to its pharmacological properties, zolpidem can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries.

- ***Patients with Long QT syndrome***

An in vitro cardiac electrophysiological study showed that under experimental conditions using very high concentration and pluripotent stem cells zolpidem may reduce the hERG related potassium currents. The potential consequence in patients with congenital long QT syndrome is unknown. As a precaution, the benefit/risk ratio of zolpidem treatment in patients with known congenital long QT syndrome should be carefully considered.

INTERACTIONS

- **Alcohol**

Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

- **CNS Depressants**

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytic/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistaminics. Concomitant use of zolpidem with these drugs may increase drowsiness and psychomotor impairment, including impaired driving ability. In the case of narcotic analgesics enhancement of euphoria may also occur leading to an increase in psychological dependence.

- **Opioids**

The concomitant use of benzodiazepines and other sedative-hypnotic drugs, including zolpidem, and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see Section Warnings)

- **CYP450 inhibitors and inducers:**

Compounds that inhibit cytochrome P450 may enhance the activity of some hypnotics like zolpidem. Zolpidem is metabolized via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2. The pharmacodynamic effect of zolpidem is decreased when it is administered with a CYP3A4 inducer such as rifampicin (a CYP3A4 inducer) and St John's Wort. St. Johns Wort has been shown to have a pharmacokinetic interaction with zolpidem. Mean Cmax and AUC were decreased (33.7 and 30.0% lower, respectively) for zolpidem administered with St. John's Wort compared to zolpidem administered alone. Co-administration of St. John's Wort may decrease blood levels of zolpidem, concurrent use is not recommended**.**

However when zolpidem was administered with itraconazole (a CYP3A4 inhibitor) its pharmacokinetics and pharmacodynamics were not significantly modified. The clinical relevance of these results is unknown.

Co-administration of zolpidem with ketoconazole (200 mg twice daily), a potent CYP3A4 inhibitor, prolonged zolpidem elimination half-life increased total AUC, and decreased apparent oral clearance when compared with zolpidem plus placebo. The total AUC for zolpidem, when co-administered with ketoconazole, increased by a factor of 1.83 when compared to zolpidem alone. A routine dosage adjustment of zolpidem is not considered necessary, but patients should be advised that use of zolpidem with ketoconazole may enhance the sedative effects.

Fluvoxamine is a strong inhibitor of CYP1A2 and a moderate to weak inhibitor of CYP2C9 and CYP3A4. Co- administration of fluvoxamine may increase blood levels of zolpidem, concurrent use is not recommended.

Ciprofloxacin has been shown to be a moderate inhibitor of CYP1A2 and CYP3A4. Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

Other Drugs
When zolpidem was administered with warfarin, digoxin, ranitidine or cimetidine, no significant pharmacokinetic interactions were observed.

PREGNANCY
The use of zolpidem is not recommended during pregnancy..

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Zolpidem crosses the placenta.

A large amount of data collected from cohort studies has not demonstrated evidence of the occurrence of malformations following exposure to benzodiazepines during the first trimester of pregnancy. However, in certain epidemiological case-control studies, an increased incidence of cleft lip and palate was observed with benzodiazepines.

Cases of reduced fetal movement and fetal heart rate variability have been described after administration of benzodiazepines during the second and/or third trimester of pregnancy.

Administration of zolpidem during the late phase of pregnancy or during labor, has been associated with effects on the neonate, such as hypothermia, hypotonia feeding difficulties (which may result in poor weight gain)and respiratory depression, due to the pharmacological action of the product. Cases of severe neonatal respiratory depression have been reported.

Moreover, infants born to mothers who took sedative/hypnotic 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. Appropriate monitoring of the newborn in the postnatal period is recommended.

If STILNOCT® is prescribed to a woman of childbearing potential, she should be warned to contact her physician about stopping the product if she intends to become or suspects that she is pregnant.

LACTATION
Small quantities of zolpidem appear in breast milk.
The use of zolpidem in nursing mothers is, therefore, not recommended

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
Vehicle drivers and machine operators should be warned that, as with other hypnotics, there may be a possible risk of adverse reactions including drowsiness, prolonged reaction time, dizziness,

sleepiness, blurred/double vision, reduced alertness and impaired driving the morning after therapy. In order to minimize this risk a full night of sleep (7-8h) is recommended.

Furthermore, the co-administration of zolpidem with alcohol and other CNS depressants increases the risk of such effects. Patients should be warned not to use alcohol or other psychoactive substances when taking zolpidem.

ADVERSE EVENTS
The following CIOMS frequency rating is used, when applicable:
Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and < 1% ; Rare ≥ 0.01 and < 0.1% ; Very rare < 0.01% Unknown (cannot be estimated from available data).
Not known: Cannot be estimated based on available data

There is evidence of a dose – relationship for adverse effects associated with zolpidem use, particularly for certain CNS events. As recommended in section on dosage and administration, they should in theory, be less if zolpidem is taken immediately before retiring, or in bed. They occur most frequently in elderly patients.

The adverse drug reactions reported in the zolpidem extended release tablets group with an incidence greater than in the placebo group in clinical trials are listed below.

Infections and infestations
Common: influenza
Uncommon: gastroenteritis, labyrinthitis, lower respiratory tract infection, otitis externa, upper respiratory tract infection

Immune system disorders
Not Known: angioneurotic oedema

Metabolism and nutrition disorders
Uncommon: appetite disorder

Psychiatric disorders
Common: anxiety, psychomotor retardation, disorientation
Uncommon: restlessness, aggression, somnambulism (see Section Precautions) depression, hallucination, including visual and hypnagogic hallucination ,apathy, binge eating, confusional state, depersonalization, depressed mood, disinhibition, euphoric mood, mood swings, nightmare, stress symptoms
Rare: libido disorder
Very rare: delusion, dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation)
Not Known: anger, abnormal behavior,.
Most of these psychiatric undesirable effects are related to paradoxical reactions.

Nervous system disorders
Very common: headache, somnolence
Common: dizziness, cognitive disorders such as memory disorders (memory impairment, amnesia, anterograde amnesia), disturbance in attention

Uncommon: balance disorder, hypoaesthesia, paraesthesia, ataxia, burning sensation, dizziness postural, dysgeusia, muscle contractions involuntary, tremor
Rare: depressed level of consciousness, speech disorder

Eye disorders
Common: visual disturbance
Uncommon: eye redness, vision blurred, altered visual depth perception, asthenopia

Ear and labyrinth disorders
Uncommon: vertigo, tinnitus

Cardiac disorders
Uncommon: palpitations

Respiratory, thoracic and mediastinal disorders
Uncommon: cough, dry throat, throat irritation
Very rare**:** respiratory depression (see Warnings)

Gastrointestinal disorders
Common: nausea, constipation
Uncommon: vomiting, abdominal discomfort, flatulence, frequent bowel movements, gastroesophageal reflux disease

Hepatobiliary disorders
Rare: hepatocellular, cholestatic or mixed liver injury (see sections Dosage and Administration, Contraindications, Warnings)

Skin and subcutaneous tissue disorders
Uncommon: rash, urticarial, dermatitis contact, skin wrinkling

Musculoskeletal and connective tissue disorders
Common: Myalgia, muscle cramp, neck pain, back pain
Uncommon: arthralgia, muscular weakness

Renal and urinary disorders
Uncommon: dysuria

Reproductive system and breast disorders
Uncommon: dysmenorrhoea , menorrhagia, vulvovaginal dryness

General disorders and administration site conditions
Common: fatigue
Uncommon: asthenia, chest discomfort, feeling drunk, influenza like illness, lethargy , pain, pyrexia
Rare: gait disturbance, fall (predominantly in elderly patients and when zolpidem was not taken in accordance with prescribing recommendation) (See precautions).

Investigations:
Uncommon: blood pressure increased, body temperature increased, heart rate increased

Injury, poisoning and procedural complications
Uncommon: contusion, neck injury

Surgical and medical procedures
Uncommon: tooth repair.

Social circumstances
Uncommon: exposure to poisonous plant

OVERDOSE
Signs and Symptoms
In cases of overdose involving zolpidem alone or with other CNS-depressant agents (including alcohol), impairment of consciousness upto coma, and more severe symptomatology, including fatal outcomes have been reported.

Management
General symptomatic and supportive measures should be used. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Sedating drugs should be withheld even if excitation occurs. Use of flumazenil may be considered where serious symptoms are observed. However, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

Zolpidem is not dialyzable.

Storage: Store protected from light and moisture at a temperature not exceeding 30ºC

Shelf life: See Outer Carton

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