For the use of Registered Medical Practitioner only

1. GENERIC NAME & BRAND NAME
Zolpidem Tartrate Tablets I.P. 5mg
Zolfresh® 5

Zolpidem Tartrate Tablets I.P. 10mg
Zolfresh® 10

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each film-coated tablet contains:
Zolpidem Tartrate I.P. 5 mg
Excipients q.s.
Colour: Titanium Dioxide I.P.

Each film-coated tablet contains:
Zolpidem Tartrate I.P. 10 mg
Excipients q.s.
Colour: Titanium Dioxide I.P.

3. DOSAGE FORM & STRENGTH
Refer section 1 & 2

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Zolpidem is indicated for the short-term treatment of insomnia.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Route of administration: Oral
Zolpidem has been shown to decrease sleep latency for up to 35 days in controlled clinical studies.
The clinical trials performed in support of efficacy were 4-5 weeks in duration with the final formal assessments of sleep latency performed at the end of treatment.
Use the lowest effective dose for the patient. The recommended initial dose is 5 mg for women and either 5 or 10 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. If the 5 mg dose is not effective, the dose can be increased to 10 mg. In some patients, the higher morning blood levels following use of the 10 mg dose increase the risk of next day impairment of driving and other activities that require full alertness. The total dose of zolpidem should not exceed 10 mg once daily immediately before bedtime. Zolpidem should be taken as a single dose and should not be re-administered during the same night.
The recommended initial doses for women and men are different because zolpidem clearance is lower in women.
Special Populations
Paediatric population Zolfresh is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in section Pharmacodynamic properties.
Elderly

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate therefore a 5mg dose is recommended. These recommended doses should not be exceeded.

Hepatic impairment

As clearance and metabolism of zolpidem tartrate is reduced in hepatic impairment, dosage should begin at 5mg in these patients with particular caution being exercised in elderly patients. In adults (under 65 years) dosage may be increased to 10mg only where the clinical response is inadequate and the drug is well tolerated.

4.3 CONTRAINDICATIONS

Zolpidem tartrate is contraindicated in patients with a hypersensitivity to zolpidem tartrate or any of the inactive ingredients Observed hypersensitivity reactions include anaphylaxis and angioedema, obstructive sleep apnoea, myasthenia gravis, severe hepatic insufficiency, acute and/or severe respiratory depression. In the absence of data, zolpidem tartrate should not be prescribed for children or patients with psychotic illness.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

Next-day psychomotor impairment The risk of next-day psychomotor impairment, including impaired driving ability, is increased if:

- zolpidem tartrate is taken within less than 8 hours before performing activities that require mental alertness (see section Effects on ability to drive and use machines)
- a dose higher than the recommended dose is taken
- zolpidem tartrate is co-administered with other CNS depressants or with other drugs that increase the blood levels of zolpidem tartrate, or with alcohol or illicit drugs (see section Drug Interactions).

Zolpidem tartrate should be taken in a single intake immediately at bedtime and not be re-administered during the same night.

Specific Patient groups

Respiratory Insufficiency: As hypnotics have the capacity to depress respiratory drive, precautions should be observed if Zolfresh is prescribed to patients with compromised respiratory function. Although studies with 10 mg Zolpidem tartrate did not reveal respiratory depressant effects at hypnotic doses in healthy subjects or in patients with mild-to-moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index.

Use in patients with a history of drug or alcohol abuse: Extreme caution should be exercised when prescribing for patients with a history of drug or alcohol abuse. These patients should be under careful surveillance when receiving zolpidem tartrate or any other hypnotic, since they are at risk of habituation and psychological dependence.

Psychotic illness: Hypnotics such as Zolfresh are not recommended for the primary treatment of psychotic illness.

Depression: As with other sedative/hypnotic drugs, zolpidem tartrate should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present therefore the least amount of Zolfresh 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 Zolfresh.

Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.
General information relating to effects seen following administration of benzodiazepines and other hypnotic agents which should be taken into account by the prescribing physician are described below.
Tolerance: Some loss of efficacy to the hypnotic effects of short-acting benzodiazepines and benzodiazepine-like agents like Zolfresh may develop after repeated use for a few weeks.
Dependence: Use of benzodiazepines or benzodiazepine-like agents like Zolfresh may lead to the development of physical and psychological dependence. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of psychiatric disorders and/or alcohol or drug abuse. These patients should be under careful surveillance when receiving hypnotics. Once physical dependence has developed, rapid dose decrease or 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: derealisation, depersonalisation, 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 a benzodiazepine or benzodiazepine-like agent 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 minimising anxiety over such symptoms should they occur when the medicinal product is discontinued. Since the risk of withdrawal phenomena or rebound has been shown to be greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually where clinically appropriate. There are indications that, in the case of benzodiazepines and benzodiazepine like agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.
Amnesia: Benzodiazepines or benzodiazepine-like agents such as Zolfresh may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product. In order to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 8 hours (see section Adverse Effects).

Other psychiatric and "paradoxical" reactions: Other psychiatric and paradoxical reactions like restlessness, exacerbated insomnia, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, psychosis, abnormal behaviour and other adverse behavioural effects are known to occur when using benzodiazepines or benzodiazepine like agents. Should this occur, use of the product should be discontinued. These reactions are more likely to occur in the elderly.
Somnambulism and associated behaviours: 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 Zolfresh and were not fully awake. The use of alcohol and other CNS-depressants with Zolfresh appears to increase the risk of such behaviours, as does the use of Zolfresh at doses exceeding the maximum recommended dose. Discontinuation of Zolfresh should be strongly considered for patients who report such behaviours (for example, sleep driving), due to the risk to the patient and others (See Section Drug Interactions and Adverse effects).
Severe injuries: Due to its pharmacological properties, Zolfresh can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries. Severe injuries such as hip fractures and intracranial hemorrhage have been reported.

4.5 DRUG INTERACTIONS

CNS-Active Drugs

Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression. Concomitant use of zolpidem with these drugs may increase drowsiness and psychomotor impairment, including impaired driving ability.

Imipramine, Chlorpromazine

Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance

Haloperidol

A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict the absence of an effect following chronic administration

Alcohol

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated

Sertraline

Concomitant administration of zolpidem and sertraline increases exposure to zolpidem

Fluoxetine

After multiple doses of zolpidem tartrate and fluoxetine an increase in the zolpidem half-life (17%) was observed. There was no evidence of an additive effect in psychomotor performance

Drugs That Affect Drug Metabolism Via Cytochrome P450

Some compounds known to induce or inhibit CYP3A may affect exposure to zolpidem. The effect of drugs that induce or inhibit other P450 enzymes on the exposure to zolpidem is not known.

CYP3A4 Inducers

Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem. Use of CYP3A4 inducers in combination with zolpidem may decrease the efficacy of zolpidem

CYP3A4 Inhibitors

Ketoconazole, a potent CYP3A4 inhibitor, increased the exposure to and pharmacodynamic effects of zolpidem. Consideration should be given to using a lower dose of zolpidem when a potent CYP3A4 inhibitor and zolpidem are given together

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

PREGNANCY AND LACTATION

Pregnancy for Zolpidem tartrate, no or very limited amount of data on pregnant patients are available. Although animal studies have shown no teratogenic or embryotoxic effects, safety in pregnancy has not been established. As with all drugs zolpidem tartrate should be avoided in pregnancy particularly during the first trimester. If the product 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. If, for compelling medical reasons, zolpidem tartrate is administered during the late phase of pregnancy, or during labour, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected due to the pharmacological action of the product. Cases of severe neonatal respiratory depression have been reported when zolpidem tartrate was used with other CNS depressants at the end of pregnancy. 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.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Zolfresh has major influence on the ability to drive and use machines. Vehicle drivers and machine operators should be warned that, as with other hypnotics, there may be a possible risk of drowsiness, prolonged reaction time, dizziness, sleepiness, blurred/double vision and reduced alertness and impaired driving the morning after therapy (see section Adverse Effects). In order to minimise this risk a resting period of at least 8 hours is recommended between taking zolpidem tartrate and driving, using machinery and working at heights. Driving ability impairment and behaviours such as 'sleep-driving' have occurred with zolpidem tartrate alone at therapeutic doses. Furthermore, the co-administration of zolpidem tartrate with alcohol and other CNS depressants increases the risk of such behaviours (see section warnings and precautions and Drug Interactions). Patients should be warned not to use alcohol or other psychoactive substances when taking zolpidem tartrate.

4.8 UNDESIRABLE EFFECTS

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% Not known: cannot be estimated based on available data.
There is evidence of a dose-relationship for adverse effects associated with zolpidem tartrate use, particularly for certain CNS and gastrointestinal events. As recommended in section Dosage & Administration, they should in theory be less if zolpidem tartrate is taken immediately before retiring, or in bed. They occur most frequently in elderly patients.

Immune system disorders
Not known: angioneurotic oedema

Psychiatric disorders
Common: hallucination, agitation, nightmare Uncommon: confusional state, irritability Not known: restlessness, aggression, delusion, anger, psychosis, abnormal behaviour, somnambulism (see section warnings and precautions), dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation), libido disorder, depression (see section warnings and precautions). Most of these psychiatric undesirable effects are related to paradoxical reactions
Nervous system disorders Common: somnolence, headache, dizziness, exacerbated insomnia, anterograde amnesia: (amnestic effects may be associated with inappropriate behaviour) Not known: depressed level of consciousness
Eye disorders: Uncommon: diplopia
Respiratory, thoracic and mediastinal disorders: Not Known: respiratory depression
Gastro-intestinal disorders Common: diarrhoea, nausea, vomiting, abdominal pain
Hepatobiliary disorders Not known: Liver enzymes elevated
Skin and subcutaneous tissue disorders Not known: rash, pruritus, urticaria, hyperhidrosis
Musculoskeletal and connective tissue disorders Common: back pain Not known: muscular weakness
Infections and infestations Common: upper respiratory tract infection, lower respiratory tract infection
General disorders and administration site conditions Common: fatigue Not known: gait disturbance, drug tolerance, fall (predominantly in elderly patients and when zolpidem was not taken in accordance with prescribing recommendation) (see section warnings and precautions).

4.9 OVERDOSAGE

Signs and Symptoms: In cases of overdose involving zolpidem tartrate alone or with other CNS-depressant agents (including alcohol), impairment of consciousness ranging from somnolence to 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. Flumazenil is reported to have an elimination half-life of about 40 to 80 minutes. Patients should be kept under close observation because of this short duration of action; further doses of flumazenil may be necessary. However, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions). Zolpidem is not dialyzable. The value of dialysis in the treatment of an overdose has not been determined. Dialysis in patients with renal failure receiving therapeutic doses of zolpidem have demonstrated no reduction in levels of zolpidem. In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

5. PHARMACOLOGIC PROPERTIES

5.1 Mechanism of Action:

Zolpidem is a GABAA receptor positive modulator presumed to exert its therapeutic effects in the short-term treatment of insomnia through binding to the benzodiazepine site of α1 subunit containing GABA A receptors, increasing the frequency of chloride channel opening resulting in the inhibition of neuronal excitation.

5.2 Pharmacodynamic Properties

Zolpidem binds to GABA A receptors with greater affinity for α1 subunit relative to α2 and α3 subunit containing receptors. Zolpidem has no appreciable binding affinity for α5 subunit containing GABAA receptors. This binding profile may explain the relative absence of myorelaxant effects in animal studies. Zolpidem has no appreciable binding affinity for dopaminergic D2, serotonergic 5HT2, adrenergic, histaminergic or muscarinic receptors.

5.3Pharmacokinetic Properties

Zolpidem tartrate has both a rapid absorption and onset of hypnotic action. Bioavailability is 70% following oral administration and demonstrates linear kinetics in the therapeutic dose range. Peak plasma concentration is reached at between 0.5 and 3 hours. The elimination half-life is short, with a mean of 2.4 hours (± 0.2h) and a duration of action of up to 6 hours. Protein binding amounts to 92.5% ± 0.1%. First pass metabolism by the liver amounts to approximately 35%. Repeated administration has been shown not to modify protein binding indicating a lack of competition between zolpidem tartrate and its metabolites for binding sites. The distribution volume in adults is 0.54 ± 0.02 L/kg and decreases to 0.34 ± 0.05 L/kg in the very elderly. All metabolites are pharmacologically inactive and are eliminated in the urine (56%) and in the faeces (37%). Zolpidem tartrate has been shown in trials to be non-dialysable. Plasma concentrations in elderly subjects and those with hepatic impairment are increased. In patients with renal insufficiency, whether dialysed or not, there is a moderate reduction in clearance. The other pharmacokinetic parameters are unaffected. Zolpidem tartrate is metabolised via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2. Since CYP3A4 plays an important role in zolpidem tartrate metabolism, possible interactions with drugs that are substrates or inducers of CYP3A4 should be considered.

Pre clinical safety data:

No data of therapeutic relevance.

NONCLINICAL PROPERTIES

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis:
Zolpidem was administered to mice and rats for 2 years at oral doses of 4, 18, and 80 mg base/kg/day. In mice, these doses are approximately 2.5, 10, and 50 times the MRHD of 10 mg/day (8 mg zolpidem base) based on mg/m2 body surface area and in rats, these doses are approximately 5, 20, and 100 times the MRHD based on mg/m2 body surface area. No evidence of carcinogenic potential was observed in mice. In rats, renal tumors (lipoma, liposarcoma) were seen at the mid and high doses.

Mutagenesis:
Zolpidem was negative in in vitro (bacterial reverse mutation, mouse lymphoma, and chromosomal aberration) and in vivo (mouse micronucleus) genetic toxicology assays.

Impairment of Fertility:
Zolpidem was administered to rats at 4, 20, and 100 mg base/kg/day, which are approximately 5,25, and 120 times the MRHD of 10 mg/day (8 mg zolpidem base) based on mg/m2 body surfacearea, prior to and during mating, and continuing in females through postpartum day 25.
Zolpidem caused irregular estrus cycles and prolonged precoital intervals at the highest dose tested, which is approximately 120 times the MRHD based on mg/m2 body surface area. The NOAEL for these effects is 25 times the MRHD based on a mg/m2 body surface area. There was no impairment of fertility at any dose tested.

7. DESCRIPTION

Zolpidem Tartrate Tablets 5mg -
Zolfresh 5 is supplied for oral administration, as a film coated tablet of Zolpidem Tartrate. Each film coated tablet of Zolfresh 5 contains Zolpidem Tartrate 5 mg.

Zolpidem Tartrate Tablets 10mg -
Zolfresh 10 is supplied for oral administration, as a film coated tablet of Zolpidem Tartrate. Each film coated tablet of Zolfresh 10 contains Zolpidem Tartrate 10 mg.

8. PHARMACEUTICAL PARTICULARS

8.1 INCOMPATIBILITIES

Not Applicable

8.2 SHELF LIFE

Refer pack.

8.3 PACKAGING INFORMATION

Refer pack.

8.4 STORAGE CONDITION AND HANDLING INSTRUCTIONS

Refer pack.

9. PATIENT COUNSELLING INFORMATION

Inform patients and their families about the benefits and risks of treatment with Zolfresh.Inform patients of the availability of a Medication Guide and instruct them to read the Medication Guide prior to initiating treatment with Zolfresh and with each prescription refill.

Review the Zolfresh Medication Guide with every patient prior to initiation of treatment.
Instruct patients or caregivers that Zolfresh should be taken only as prescribed.

Complex Sleep Behaviors
Instruct patients and their families that Zolfresh may cause complex sleep behaviors, including sleep-walking, sleep-driving, preparing and eating food, making phone calls, or having sex while not being fully awake. Serious injuries and death have occurred during complex sleep behaviour episodes.Tell patients to discontinue Zolfresh and notify their healthcare provider immediately if they develop any of these symptoms

CNS-Depressant Effects and Next-Day Impairment
Tell patients that Zolfresh has the potential to cause next-day impairment, and that this risk is increased if dosing instructions are not carefully followed. Tell patients to wait for at least 8 hours after dosing before driving or engaging in other activities requiring full mental alertness. Inform patients that impairment can be present despite feeling fully awake. Advise patients that increased drowsiness and decreased consciousness may increase the risk of falls in some patients.

Severe Anaphylactic and Anaphylactoid Reactions
Inform patients that severe anaphylactic and anaphylactoid reactions have occurred with zolpidem. Describe the signs/symptoms of these reactions and advise patients to seek medical attention immediately if any of them occur

Suicide
Tell patients to immediately report any suicidal thoughts.

Alcohol and other Drugs
Ask patients about alcohol consumption, medicines they are taking, and drugs they may be taking without a prescription. Advise patients not to use Zolfresh if they drank alcohol that evening or before bed.

Tolerance, Abuse, and Dependence
Tell patients not to increase the dose of Zolfresh on their own, and to inform you if they believe the drug “does not work.”

Administration Instructions
Patients should be counseled to take Zolfresh right before they get into bed and only when they are able to stay in bed a full night (7-8 hours) before being active again. Zolfresh tablets should not be taken with or immediately after a meal. Advise patients NOT to take Zolfresh if they drank alcohol that evening.

10. DETAILS OF MANUFACTURER

Refer Pack for manufacturer details.

Marketed by:
Abbott India Ltd.
Angel Space, Lifestyle, Bldg. No.D-4, Gala No. 4 to 10
& 14 to 20 Ground Floor, 107 to 110 & 117 to 120 1st floor,
207 to 210 & 217 to 220 2nd Floor, Pimplas, Dist. Thane,
Bhiwandi-421 302, Maharashtra, India.

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11. DETAILS OF PERMISSION OR LICENCE NUMBER

Refer Pack for Permission/License details

12. DATE OF REVISION
Version 3.0, dated 2-Jan-26

For Product Complaints/Adverse events or Queries please write to **webmasterindia@abbott.com**