SUMMARY OF PRODUCT CHARACTERISTICS

APPROVED
By Geeta at 11:37 am, Oct 11,

1 NAME OF THE MEDICINAL PRODUCT

Zolpidem tartrate 5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg of Zolpidem tartrate

Excipient with known effect: Also contains 29.50mg of Lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film Coated Tablets

White to almost white, round, biconvex, film coated tablets with '5' embossing on one side and plain on other side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The short-term treatment of insomnia in adults in situations where the insomnia is debilitating or is causing severe distress for the patient

4.2 Posology and Method of Administration

Posology

The treatment should be taken in a single intake and not be re-administered during the same night. The recommended daily dose for adults is 10 mg to be taken immediately at bedtime. The lowest effective daily dose of zolpidem tartrate should be used and must not exceed 10 mg.

The duration of treatment should usually vary from a few days to two weeks with a maximum of four weeks including tapering off where clinically appropriate.

As with all hypnotics, long-term use is not recommended and a course of treatment should not exceed four weeks.

Special Populations

Paediatric population
Zolpidem 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 5.1.

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.

Zolpidem must not be used in patients with severe hepatic impairment as it may contribute to encephalopathy (see section 4.3)

Route of administration

Oral

4.3 Contraindications

Zolpidem tartrate is contraindicated in patients with a hypersensitivity to zolpidem tartrate or any of the inactive ingredients, 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.

Specific Patient groups

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.

Hepatic Insufficiency:

See section 4.2

Elderly:

See section 4.2 dose recommendations.

Next-day psychomotor impairment
Like other sedative/ hypnotic drugs, Zolpidem has CNS- depressant effects. 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 4.7);
• 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 4.5).

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

Risk from concomitant use of opioids:

Concomitant use of zolpidem and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as zolpidem with opioids should be reserved for patients for whom alternative treatment options are not possible.
If a decision is made to prescribe zolpidem concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

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 Zolpidem 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 drug that is feasible should be supplied to these patients to avoid because of the possibility of intentional overdose 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.

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 zolpidem may develop after repeated use for a few weeks.

Dependence

Use of benzodiazepines or benzodiazepine-like agents like zolpidem 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, 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 zolpidem 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 4.8).

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 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 (See section 4.5 Interactions with other medicinal products and other forms of interaction; and Section 4.8 Undesirable effects).

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.

Important information regarding the ingredients of this medicine
Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

- **Not recommended**:
- Concomitant intake with alcohol:

The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

- **Take into account**:
- Combination with CNS depressants.

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines. Therefore, concomitant use of zolpidem with these drugs may increase drowsiness and next-day psychomotor impairment, including impaired driving ability (see section 4.4 and section 4.7). Also, isolated cases of visual hallucinations were reported in patients taking zolpidem with antidepressants including bupropion, desipramine, fluoxetine, sertraline and venlafaxine.

Co- administration of fluvoxamine may increase blood levels of zolpidem tartrate, concurrent use is not recommended.

In the case of narcotic analgesics enhancement of euphoria may also occur leading to an increase in psychological dependence.

CYP450 inhibitors and inducers:

Co-administration of ciprofloxacin may increase blood levels of zolpidem tartrate, concurrent use is not recommended.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines and benzodiazepine-like agents.

Zolpidem tartrate is metabolised via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2. The pharmacodynamic effect of zolpidem tartrate is decreased when it is administered with a CYP3A4 inducer such as rifampicin and St. John's Wort. St. John's Wort has been shown to have a pharmacokinetic interaction with zolpidem. Mean C_{max} 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 tartrate 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 (200mg twice daily), a potent CYP3A4 inhibitor, prolonged zolpidem elimination half-life, increased total AUC, and decreased apparent oral clearance when compared to zolpidem plus placebo. The total AUC for zolpidem, when co-administered with ketoconazole, increased by 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.

Since CYP3A4 plays an important role in zolpidem tartrate metabolism, possible interactions with drugs that are substrates or inducers of CYP3A4 should be considered.

Opioids: The concomitant use of sedative medicines such as benzodiazepines or related drugs such as zolpidem with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Other drugs

When zolpidem tartrate was administered with ranitidine, no significant pharmacokinetic interactions were observed.

4.6. Fertility, 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

Zolpidem 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 4.8). In order to minimise this risk a resting period of at least 8 hours is recommended between taking zolpidem and driving, using machinery and working at heights.

Driving ability impairment and behaviours such as ‘sleep-driving’ have occurred with zolpidem alone at therapeutic doses.

Furthermore, the co-administration of zolpidem with alcohol and other CNS depressants increases the risk of such behaviours (see section 4.4 and 4.5). Patients should be warned not to use alcohol or other psychoactive substances when taking zolpidem.

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 4.2, 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, depression (see section 4.4)
Uncommon: confusional state, irritability, restlessness, aggression, somnambulism (see section 4.4), euphoric mood
Rare: Libido disorder
Very rare: Delusion, dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation)
Not known: anger, psychosis, abnormal behaviour,
Most of these psychiatric undesirable effects are related to paradoxical reactions.

Nervous system disorders:
Common: somnolence, headache, dizziness, exacerbated insomnia, cognitive defects such as anterograde amnesia: (amnestic effects may be associated with inappropriate behaviour)
Uncommon: paraesthesia, tremor, disturbance in attention, speech disorder
Rare: depressed level of consciousness

Respiratory, thoracic and mediastinal disorders
Very rare: respiratory depression (see section 4.4)

Eye disorders:
Uncommon: diplopia, vision blurred
Very rare: Visual impairment

Gastro-intestinal Disorders:
Common: diarrhoea, nausea, vomiting, abdominal pain

Hepatobiliary disorders:
Uncommon: Liver enzymes elevated
Rare: hepatocellular, cholestatic or mixed liver injury (see sections 4.2, 4.3 and 4.4)

Skin and subcutaneous **tissue** *disorders:*
Uncommon: rash, pruritus, hyperhidrosis
Rare: urticaria

Musculoskeletal and connective tissue disorders:
Common: back pain
Uncommon: Myalgia, muscle spasms, Muscular weakness

Infections and infestations
Common: upper respiratory tract infection, lower respiratory tract infection

General disorders and administration site conditions:
Common: fatigue
Rare: gait disturbance, fall (predominantly in elderly patients and when zolpidem was not taken in accordance with prescribing recommendation) (see section 4.4).
Not known: drug tolerance

Metabolism and nutrition disorders
Uncommon: appetite disorder

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme website: www.mhra.gov.uk/yellow card or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9. Overdose

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 has 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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Benzodiazepine related drugs

ATC Code : N05CF02

(GABA-A receptor modulator selective for omega-1 receptor subtype hypnotic agent).

Zolpidem tartrate is an imidazopyridine which preferentially binds the omega-1 receptor subtype (also known as the benzodiazepine-1 subtype) which corresponds to GABA-A receptors containing the alpha-1 sub-unit, whereas benzodiazepines non-selectively bind both omega-1 and omega-2 subtypes. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem tartrate. These effects are reversed by the benzodiazepine antagonist flumazenil.

In animals: The selective binding of zolpidem tartrate to omega-1 receptors may explain the virtual absence at hypnotic doses of myorelaxant and anti-

convulsant effects in animals which are normally exhibited by benzodiazepines which are not selective for omega-1 sites.

In man: zolpidem tartrate decreases sleep latency and the number of awakenings, and increases sleep duration and sleep quality. These effects are associated with a characteristic EEG profile, different from that of the benzodiazepines. In studies that measured the percentage of time spent in each sleep stage, zolpidem tartrate has generally been shown to preserve sleep stages. At the recommended dose, zolpidem tartrate has no influence on the paradoxical sleep duration (REM). The preservation of deep sleep (stages 3 and 4 - slow-wave sleep) may be explained by the selective omega-1 binding by zolpidem tartrate. All identified effects of zolpidem tartrate are reversed by the benzodiazepine antagonist flumazenil.

The randomized trials only showed convincing evidence of efficacy of 10mg zolpidem.

In a randomized double-blind trial in 462 non-elderly healthy volunteers with transient insomnia, zolpidem 10mg decreased the mean time to fall asleep by 10 minutes compared to placebo, while for 5mg zolpidem this was 3 minutes.

In a randomized double-blind trial in 114 non-elderly patients with chronic insomnia, zolpidem 10mg decreased the mean time to fall asleep by 30 minutes compared to placebo, while for 5mg zolpidem this was 15 minutes.

In some patients, a lower dose of 5mg could be effective.
Paediatric population: Safety and efficacy of zolpidem have not been established in children aged less than 18 years. A randomized placebo-controlled study in 201 children aged 6-17 years with insomnia associated with Attention Deficit Hyperactivity Disorder (ADHD) failed to demonstrate efficacy of zolpidem tartrate 0.25 mg/kg/day (with a maximum of 10 mg/day) as compared to placebo. Psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem tartrate versus placebo and included dizziness (23.5% versus 1.5%), headache (12.5% versus 9.2%), and hallucinations (7.4% versus 0%) (See sections 4.2 and 4.3).

5.2 Pharmacokinetic 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 (± 0.2 h) 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.

5.3. Preclinical Safety Data

No data of therapeutic relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Pregelatinised starch
Sodium starch glycollate
Silica colloidal anhydrous
Magnesium stearate.

Film coating:
Hypromellose
Titanium dioxide (E171)
Talc
Macrogol 6000.

6.2 Incompatibilities

None known

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 25ºC.

Store in the original package.

6.5 Nature and contents of container

Cartons of 7, 14, 28, 56 or 84 tablets containing PVC/Aluminium foil blister strips of 7 or 14 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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