SUMMARY OF PRODUCT CHARACTERISTICS

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SOLPEDEM

Zolpidem Tartrate Tablets 5 mg and 10 mg

R_x Only

NAME OF DRUG PRODUCT : Zolpidem Tartrate Tablets 5 mg
Zolpidem Tartrate Tablets 10 mg

(TRADE) NAME OF PRODUCT : SOLPEDEM 5
SOLPEDEM 10

STRENGTH : 5 mg and 10 mg.

PHARMACEUTICAL DOSAGE FORM: Tablet.

QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

Zolpidem Tartrate Tablets 5 mg

Each film-coated tablet contains Zolpidem Tartrate Ph.Eur. 5 mg.

Zolpidem Tartrate Tablets 10 mg

Each film-coated tablet contains Zolpidem Tartrate Ph.Eur. 10 mg.

PHARMACEUTICAL FORM:

Zolpidem Tartrate Tablets 5 mg: White to off-white, circular, biconvex, film-coated tablets, debossed with “E” on one side and “78” on the other side.

Zolpidem Tartrate Tablets 10 mg: White to off-white, oval shaped, biconvex, film-coated tablets, debossed with “E” on one side and debossed with “80” with a score line between “8” and “0” on the other side.

CLINICAL PARTICULARS:

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.

Posology and method of administration Route of administration: Oral

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.

Treatment should be as short as possible. It should not exceed four weeks including the period of tapering off. In certain cases extension beyond the maximum treatment period may be necessary; if so, 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.

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.

Elderly

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate therefore a 5 mg 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 5 mg in these patients with particular caution being exercised in elderly patients. In adults (under 65 years) dosage may be increased to 10 mg 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

Contraindications

Zolpidem tartrate is contraindicated in patients with a hypersensitivity to zolpidem tartrate, obstructive sleep apnoea, myasthenia gravis, severe hepatic insufficiency, acute and/or severe respiratory depression. Zolpidem tartrate should not be prescribed for children or patients with psychotic illness.

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

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;

• 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.

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 Zolpidem is prescribed to patients with compromised respiratory function.

Hepatic insufficiency:

See posology and method of administration.

Elderly:

See posology and method of administration for dose recommendations.

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.

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.

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.

Suicidal ideation, suicide attempt, suicide and depression:

Some epidemiological studies suggest an increased incidence of suicidal ideation, suicide attempt and suicide in patients with or without depression, and treated with benzodiazepines and other hypnotics, including zolpidem. However, a causal relationship has not been established.

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 Zolpidem that is feasible should be supplied to these patients to avoid 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 may develop after repeated use for a few weeks.

Dependence

Use of zolpidem may lead to the development of physical and psychological dependence. The risk of dependence increases with dose and duration of treatment. The risk of abuse and dependence is also greater in patients with a history of psychiatric disorders and/or alcohol, substance or drug abuse. Zolpidem should be used with extreme caution in patients with current or a history of alcohol, substance or drug abuse or dependence.

If 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 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 8 hours.

Other Psychiatric and "paradoxical" reactions

Other psychiatric and paradoxical reactions like restlessness, aggravated insomnia, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate 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.

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.

Interaction with other medicinal products and other forms of interaction

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.

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. 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.

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

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 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 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 (200 mg 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 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.

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

Other drugs:

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

Pregnancy and lactation.

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.

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.

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

Effects on 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 the morning after therapy. In order to minimise this risk a resting period of 7 to 8 hours is recommended between taking zolpidem tartrate and driving.

Undesirable effects

Adverse effects like CNS and gastrointestinal events may occur associated with zolpidem tartrate use. They occur most frequently in elderly patients.

Immune system disorders

Not known: angioneurotic oedema

Psychiatric disorders

Common: hallucination, agitation, nightmare, depression

Uncommon: confusional state, irritability, restlessness, aggression, somnambulism, 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 disorders 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

Eye disorders

Uncommon: diplopia, vision blurred

Very rare: visual impairment

Respiratory, thoracic and mediastinal disorders

Very rare: respiratory depression

Gastrointestinal disorders

Common: diarrhea, nausea, vomiting, abdominal pain

Hepatobiliary disorders

Uncommon: liver enzymes elevated

Rare: hepatocellular, cholestatic or mixed liver injury

Metabolism and nutrition disorders

Uncommon: appetite disorder

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritus, hyperhidrosis

Rare: urticarial

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).

Not known: drug tolerance

Overdose

Overdose with zolpidem tartrate alone, impairment of consciousness has ranged from somnolence to coma.

Overdose cases involving zolpidem tartrate among multiple CNS-depressant agents (including alcohol), have resulted in more severe symptomatology, including fatal outcomes.

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.

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

(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.

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. 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.

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%).

Plasma concentrations in elderly 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.

PHARMACEUTICAL PARTICULARS

List of excipients

Lactose monohydrate, Cellulose, microcrystalline, Sodium starch glycolate, Magnesium Stearate, Hypromellose, Macrogol 400, Titanium dioxide and Purified water.

Incompatibilities

None known.

Shelf life

Please refer to outer package.

Special precautions for storage

Store in a dry place below 30°C.

Nature and contents of container

Blister pack

Zolpidem Tartrate Tablets 5 mg: 1 x 14's Tablets

Zolpidem Tartrate Tablets 10 mg: 1 x 14's Tablets

MANUFACTURED BY:

Aurobindo Pharma Ltd., Unit-III,

Survey No. 313 & 314, Bachupally, Bachupally Mandal,

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MARKETING AUTHORISATION HOLDER

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DATE OF PREPARATION OF LEAFLET

October 2019