SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zolpidem Vitabalans 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of zolpidem tartrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White capsule shaped convex tablet with score. Length 10 mm, width 5 mm.

The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
The treatment period should be as short as possible. It varies normally between a few days up to 2 weeks, with a maximum of 4 weeks including phasing out.
As with all hypnotics, long-term use is not recommended and course of treatment should not exceed four weeks.
In certain cases, it may be necessary to extend the treatment period beyond the maximum treatment period. However, before continuing with the treatment the patient's status should be re-evaluated.

Adults
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 should be used and must not exceed 10 mg.

Elderly
In elderly or debilitated patients, which may be especially sensitive to the effects of zolpidem, a 5 mg daily dose is recommended. The dose should only be exceeded in certain cases.

Impaired hepatic function
In patients with mild or moderate liver insufficiency, in whom zolpidem elimination is slower than in patients with normal hepatic function, a 5 mg starting dose is recommended 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 is contraindicated in patients with severe liver insufficiency (see section 4.3).

The maximum daily dose for all patient groups is 10 mg.

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.

Method of administration
For oral use.
The tablet should be taken with fluid just before going to bed.

4.3 Contraindications

- Myasthenia gravis
- Hypersensitivity to zolpidem or to any excipient
- Sleep apnoea syndrome
- Acute respiratory and/or severe respiratory insufficiency
- Severe liver insufficiency.

4.4 Special warnings and precautions for use

The cause of insomnia should if possible be determined. Underlying causes should be treated before prescribing a hypnotic. If the insomnia remains after 7-14 days of treatment, it may be caused by a primary psychological or physical disturbance that should be investigated.

Next-day psychomotor impairment
The risk of next-day psychomotor impairment, including impaired driving ability, is increased if:
- zolpidem 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 is co-administered with other CNS depressants or with other drugs that increase the blood levels of zolpidem, or with alcohol or illicit drugs (see section 4.5).

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

Amnesia
Benzodiazepines or benzodiazepine similar agents may induce anterograde amnesia. The condition occurs most often several hours after ingesting the medicine. 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).

Tolerance
Some loss of efficacy to the hypnotic effects of benzodiazepines or benzodiazepine similar agents may develop after repeated use for a few weeks.

Dependence
Use of benzodiazepines or benzodiazepine similar agents 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 benzodiazepines or benzodiazepine similar agents.
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 effect: A transient syndrome whereby the symptoms that led to treatment with benzodiazepines or benzodiazepine similar 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.

Since the risks for reactions in connection with discontinuation of therapy/rebound effect is greater when the drug is abruptly discontinued and therefore it is recommended that dose is gradually decreased.
Symptoms of abstinence may occur between doses for short-acting benzodiazepine related hypnotics.

Treatment duration
The treatment period should be as short as possible (see section 4.2) and should not exceed 4 weeks including phasing out. Treatment period should not be extended without re-evaluation of the situation.
It may be of importance to inform the patient that the treatment period is limited and explain exactly how the dose is gradually decreased. Furthermore the patient should be cautioned of the possibility of rebound insomnia so that the symptoms should not increase anxiety, should they occur when the treatment is discontinued.
In case of hypnotics with a short duration of action there are indications that withdrawal phenomena may occur within the dosage interval, especially when the dosage is high.

Other psychiatric and paradoxical effects
Other psychiatric and paradoxical reactions such as restlessness, aggravated insomnia, agitation, irritability, aggression, delusions, anger, nightmares, hallucinations, psychoses, abnormal behaviour, and other adverse behavioural effects may occur when using benzodiazepines or benzodiazepine similar agents.
Should these reactions occur, use of the product should be discontinued. These reactions are more likely to occur in children and 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 and 4.8).

Use in patients with psychotic illness: benzodiazepines and benzodiazapine-like agents are not recommended for the primary treatment.

Depression
Benzodiazepine and benzodiazepine-like agents should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients). Zolpidem should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present. Due to the possibility of intentional overdose by the patient, the lowest amount of the drug that is feasible should be supplied to these patients. 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.

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.

Risk from concomitant use of opioids
Concomitant use of Zolpidem Vitabalans 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 Vitabalans 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 caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Special patient groups
Elderly: See dose recommendations.

As benzodiazepines or benzodiazepine similar agents may worsen the respiratory insufficiency, zolpidem should be given with particular caution to patients with chronic respiratory insufficiency.
Benzodiazepines or benzodiazepine similar agents are not indicated for patients with liver insufficiency since they may cause encephalopathy.
Benzodiazepines or benzodiazepine similar agents should be given with utmost caution in patients with previous alcohol or drug abuse.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol
Zolpidem is not recommended to be taken together with alcohol, since concomitant use may enhance the sedative effect and affect the ability to drive and 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 (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, concurrent use is not recommended.

The depressant effect on the central nervous system may be enhanced, if zolpidem is used concomitantly with muscle relaxants. Concomitant use of zolpidem and narcotic analgesics may also enhance the euphoria leading to an increase in psychological dependence.

Opioids
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Zolpidem Vitabalans 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).

CYP450 inhibitors and inducers
Zolpidem is metabolized via several CYP-450-isoforms with CYP3A4 being the predominant one, and CYP1A2 contributing to a lesser extent. Drugs that inhibit the activity of CYP450-isoforms (especially CYP3A4) may increase the plasma concentrations and enhance the effects of zolpidem.
Co- administration ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

Approximately 60% reduction of the maximum plasma concentration of zolpidem when administered with rifampicine has been observed. The pharmacodynamic effect of zolpidem is decreased when it is administered with rifampicin (a CYP3A4 inducer).
However when zolpidem was administered with itraconazole (a CYP3A4 inhibitor) it´s pharmacokinetics and pharmacodynamics were not significantly modified. The clinical relevance of these results is unknown.

When zolpidem was administered with ketoconazole, a potent CYP3A4 inhibitor, zolpidem's elimination half-life was prolonged, total exposure to zolpidem (AUC) was increased by 83%, and the apparent oral clearance of zolpidem was decreased. 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.

Other drugs
When zolpidem was administered with warfarin, haloperidol, chlorpromazine, digoxin, or ranitidine, no significant pharmacokinetic interactions were observed.

4.6 Fertility, pregnancy and lactation

There are insufficient data to permit an assessment of the safety of zolpidem during pregnancy and lactation. Although animal studies have shown no teratogenic or embryotoxic effects, safety in pregnancy has not been established in humans. Therefore zolpidem should not be used during pregnancy especially in the first trimester.

If zolpidem is prescribed to a woman of childbearing potential, she should be encouraged to contact her physician regarding discontinuance of the product if she intends to become or suspect that she is pregnant.

If, for compelling medical reason, zolpidem 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 develop withdrawal symptoms in the postnatal period as a result of physical dependence.

Zolpidem passes into breast milk in small amounts. Zolpidem should therefore not be used by breast-feeding mothers since effects on the infant are not studied.

4.7 Effects on ability to drive and use machines

Zolpidem Vitabalans 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 adverse drug reactions are stated in the table below using the following convention:
Very common (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000; <1/100); rare (≥1/10,000; <1/1,000); very rare (<1/10,000); not known (cannot be estimated from available data).

There is evidence for a dose connection for reactions associated with use of zolpidem, especially certain CNS-reactions. Theoretically they should be less if zolpidem is taken immediately before bedtime. They occur most frequently in elderly patients.

System Organ Class	Frequency			
	Common	**Uncommon**	**Rare**	**Not known**
Immune system disorders				Angioneurotic oedema
Psychiatric disorders	Hallucination, agitation, nightmare, Numbed emotions,	Confusional state, irritability		Restlessness, aggression, delusion, anger, psychosis, abnormal behaviour, sleep walking (see section 4.4), dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation), libido disorder, depression (see section 4.4)
Nervous System Disorders	Somnolence, headache, dizziness, increased insomnia, anterograde amnesia: (amnestic effects may be associated with inappropriate behaviour) drowsiness during the following day, reduced alertness	Ataxia		Depressed level of consciousness
Eye disorders	Double vision			
Ear and labyrinth disorders	Vertigo			
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain			
Hepatobiliary disorders				Elevated liver enzymes
Skin and Subcutaneous tissue disorders				Rash, pruritus, urticaria, hyperhidrosis
Musculoskeletal, connective tissue and bone disorders	Back pain	Muscle weakness		
General Disorders	Fatigue		Paradoxical reactions	Gait disturbance, drug tolerance, fall (predominantly in elderly patients and when zolpidem was not taken in accordance with prescribing recommendation) (see section 4.4)

These phenomena occur predominantly at the start of the therapy or in elderly patients and usually disappear with repeated administration.

Amnesia
Anterograde amnesia may occur during therapeutic dosages, the risk increasing at higher dosages. In order to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 8 hours. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

Depression
Pre-existing depression may become manifest during use of benzodiazepines or benzodiazepine-like agents (see section 4.4).

Psychiatric and “paradoxical” reactions
Reactions like restlessness, agitation, irritability, aggressiveness, delusions, rage, nightmares, increased insomnia, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects may occur when using benzodiazepines and benzodiazepine-like agents. Such reactions are more likely to occur in the elderly (see section 4.4).

Dependence
Use (even at therapeutic dosages) may lead to physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4).

Psychic dependence may occur. Abuse has been reported in polydrug abusers.

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 the national reporting system listed in Appendix V*.

4.9 Overdose

In reports of overdose with zolpidem alone or with other CNS-depressant agents (including alcohol), impairment of consciousness has ranged from somnolence to coma and fatal outcomes have been reported.

Individuals have fully recovered from overdoses up to 400 mg of zolpidem, 40 times the recommended dose.

General symptomatic and supportive measures should be used. Immediate gastric lavage should be used where appropriate. Intravenous fluids should be administered as needed. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Monitoring of respiratory and cardiovascular functions should be considered. Sedating medicinal products should be withheld even if excitation occurs.

Use of flumazenil may be considered when serious symptoms are observed. Flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

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

Due to the high distribution volume and protein binding of zolpidem, haemodialysis and forced diuresis are not effective measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives, benzodiazepine related drugs

ATC code: N05CF02.

Zolpidem, an imidazopiridine, is a hypnotic agent similar to benzodiazepines. It has been shown in experimental studies that it has sedative effects at lower dosages than those required to exercise anticonvulsive, muscle relaxant or anxiolytic effects. These effects are associated with a specific agonistic action on the central receptors belonging to the GABA-omega (BZ1 and BZ2) macromolecular receptor complex that modulates the aperture of the chlorine ion channel. Zolpidem acts primarily on the omega receptor subtypes (BZ1). The clinical relevance is unknown.

The randomized trials only showed convincing evidence of efficacy of 10 mg zolpidem.
In a randomized double-blind trial in 462 non-elderly healthy volunteers with transient insomnia, zolpidem 10 mg decreased the mean time to fall asleep by 10 minutes compared to placebo, while for 5 mg zolpidem this was 3 minutes.
In a randomized double-blind trial in 114 non-elderly patients with chronic insomnia, zolpidem 10 mg decreased the mean time to fall asleep by 30 minutes compared to placebo, while for 5 mg zolpidem this was 15 minutes.
In some patients, a lower dose of 5 mg 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 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 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

Administration
The pharmacokinetics are linear within the therapeutic dose range. The therapeutic plasma level is between 80 and 200 ng/ml.
After oral administration, the bioavailability of zolpidem is around 70%, reaching peak plasma concentration between 0.5 and 3 hours after ingestion. Interindividual variability is high (CV% of AUC is 60-70 % and for C_{max} 40-50%).

Distribution
Around 92% is plasma protein bound. The distribution volume in adults is 0.54 l/kg and decreases to 0.34 l/kg in the elderly. 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 and its metabolites for binding sites.

Elimination
Zolpidem is excreted in the form of inactive metabolites (liver metabolism), primarily in urine (48-67%) and faeces (29-42%). The plasma elimination half-life is approximately 2.4 hours (0.7-3.5 hours). Clearance is approximately 300 ml/min. Reduced clearance, approximately 100 ml/min, has been observed in elderly. The maximal plasma concentration is increased by approximately 80% without a significant increase of the half life (around 3 hours) in a patient group aged 81-95 years.
In patients with renal failure, whether dialysed or not, there is a moderate reduction of clearance.

Renal impairment
In patients with renal failure, whether dialysed or not, there is a moderate reduction of clearance.

Hepatic impairment
In patients with liver failure, the bioavailability of zolpidem is increased by 80% and the elimination half-life is prolonged from 2.4 h in healthy subjects to 9.9 h in hepatic impaired subjects. In patients with liver cirrhosis, there is a five-fold increase of the exposure and a three-fold increase in the elimination half-life.

5.3 Preclinical safety data

Preclinical effects were only observed at dosages well above the maximum human exposure levels and are therefore of little significance for clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Calcium hydrogen phosphate dihydrate
Silica, colloidal anhydrous
Sodium starch glycolate (type A)
Magnesium stearate

Tablet coating:
Polydextrose
Hypromellose
Titanium dioxide (E171)
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10, 20, 30, 60, 90, 100 film-coated tablets in PVC/Al blister surrounded by carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Vitabalans Oy
Varastokatu 8
13500 Hämeenlinna
FINLAND

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2011-03-16 / 2016-03-16

10. DATE OF REVISION OF THE TEXT

2023-12-07