**MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION**

PATIENT INFORMATION LEAFLET

FOR THE MEDICINAL PRODUCT

**VELSON®**

**Registration number:** ЛП-005391

**Trade name:** VELSON®

**International non-proprietary or generic name:** melatonin

**Pharmaceutical form:** film-coated tablets

**Composition**

One film-coated tablet contains:

*Active ingredient:* melatonin – 3 mg.

*Excipients:* calcium hydrogen phosphate dihydrate – 64.67 mg, microcrystalline cellulose – 25.00 mg, povidone K 25 – 3.33 mg, croscarmellose sodium - 2.00 mg, talc – 1.00 mg, colloidal silicon dioxide – 0.50 mg, calcium stearate – 0.50 mg.

*Film-coating composition:* white opadry (03A280002) – 3.00 mg [hypromellose (hydroxypropylmethylcellulose) – 40%, microcrystalline cellulose – 32%, titanium dioxide – 20%, macrogol (polyethylene glycol) – 8%].

**Appearance**

Round biconvex white film-coated tablets; in cross section, the core is from white to off-white with a brownish tint.

**Pharmacotherapeutic group:** adaptogenic agent.

**ATC code:** N05CH01

**Pharmacological properties**

***Pharmacodynamics***

It is a synthetic analogue of the hormone of pineal gland.

Normally, the synthesis of melatonin in the pineal gland has a certain daily rhythm. Melatonin production is synchronized with the day/night cycle, with the peak plasma concentration occurring at night, and the minimum at daytime. Information about the absence of light is perceived by the retina, from where the signal is sent through the retinohypothalamic tract to the suprachiasmatic nucleus, and then to the superior cervical ganglion. From the endings of the sympathetic nerves extending from the neurons of the superior cervical ganglion, norepinephrine is released into the parenchyma of the pineal gland, which triggers the synthesis of melatonin. Light inhibits the production of melatonin.

Impact on any link of the melatonin synthesis process can lead to a decrease in the production of this hormone and a violation of circadian rhythms. A decrease in the production of melatonin can be observed against the background of the following conditions:

• excessive exposure to artificial light sources in the dark (especially the light of the blue spectrum – TV screen, smartphone, computer);

 • disorders of the sleep-wakefulness cycle (desynchronosis), which can occur under the influence of endogenous (for example, with delayed sleep phase syndrome, sleep phase advance syndrome) and exogenous factors (for example, sleep disturbance during shift work, changing time zones);

• elderly and senile age;

• perimenopause and postmenopause in women;

• presence of bad habits (active smoking and alcohol consumption);

• simultaneous use of certain medications (non-steroidal anti-inflammatory drugs, beta-blockers, benzodiazepines).

Melatonin normalizes circadian rhythms. It has an adaptogenic, sedative and hypnotic effect. It increases the concentration of gamma-aminobutyric acid (GABA) and serotonin in the midbrain and hypothalamus, changes the activity of pyridoxal kinase, which is involved in the synthesis of GABA, dopamine and serotonin. It regulates the sleep-wakefulness cycle, daily changes in locomotor activity and body temperature, has a positive effect on the intellectual-mnestic functions of the brain and on the emotional-personal sphere.

It promotes the organization of the biological rhythm and the normalization of night sleep. It improves the quality of sleep, accelerates falling asleep, reduces the number of nighttime awakenings, improves well-being after waking up in the morning, does not cause feelings of lethargy, fatigue and fatigue upon awakening, regulates neuroendocrine functions, and reduces stress reactions. It adapts the body of meteosensitive people to changes in weather conditions.

It is not addictive.

***Pharmacokinetics***

*Absorption*

After oral administration, melatonin is rapidly absorbed in the gastrointestinal tract. In elderly patients, the rate of absorption can be reduced by 50%. The kinetics of melatonin in the range of 2-8 mg is linear. When taken orally at a dose of 3 mg, the maximum concentration (Cmax) in blood plasma and saliva is achieved after 20 minutes and 60 minutes, respectively. The time to reach the maximum concentration (TCmax) in serum is 60 minutes (normal range is 20-90 minutes). After taking 3-6 mg of melatonin, serum Cmax is usually 10 times more than endogenous melatonin serum level at night. Concomitant food intake delays the absorption of melatonin.

*Bioavailability*

The oral bioavailability of melatonin ranges from 9 to 33% (approximately 15%).

*Distribution*

In *in vitro* studies, the level of melatonin binding with plasma proteins is 60%. Basically, melatonin binds to albumin, α1-acid glycoprotein and high density lipoproteins. Its volume of distribution is about 35 liters. It is quickly distributed into saliva and passes through the blood-brain barrier; it can be determined in the placenta. Its concentration in cerebrospinal fluid is 2.5 times lower than in plasma.

*Biotransformation*

Melatonin is metabolized primarily in the liver. After ingestion, melatonin undergoes significant transformation during its primary passage through the liver, where it is hydroxylated and conjugated with sulfate and glucuronide to form 6-sulfatoxymelatonin; the level of presystemic metabolism can reach 85%. Presumably, the isoenzymes CYP1A1, CYP1A2, and CYP2C19 of the cytochrome P450 system are involved in the melatonin metabolism. The main metabolite of melatonin, 6-sulfatoxymelatonin, is inactive.

*Excretion*

Melatonin is excreted by the kidneys. The average elimination half-life (T1/2) of melatonin is 45 minutes. Excretion is carried out with the urine, about 90% in the form of sulfate and glucuronic conjugates of 6-hydroxymelatonin, and about 2-10% is excreted unchanged.

Pharmacokinetic parameters are influenced by age, caffeine intake, smoking, oral contraceptives administration. Accelerated absorption and impaired elimination are observed in critically ill patients.

*Elderly patients*

Melatonin metabolism slows down with age. At different doses of melatonin, higher values of the area under the concentration-time curve (AUC) and Cmax were obtained in elderly patients which reflects the reduced metabolism of melatonin in this group of patients.

 *Patients with impaired renal function*

No accumulation of melatonin was observed with long-term treatment. These findings are consistent with the short T1/2 of melatonin in humans.

 *Patients with impaired hepatic function*

The liver is the main organ involved in the metabolism of melatonin, therefore liver disease leads to an increase in the concentration of endogenous melatonin. In patients with liver cirrhosis, the plasma concentration of melatonin increased significantly during the daytime.

**Indications for use**

For sleep disorders, including those caused by disturbances of the "sleep-wakefulness" cycle, such as desynchronosis.

**Contraindications**

– known hypersensitivity to the components of the drug;

– autoimmune diseases;

– hepatic failure;

– acute renal failure;

– pregnancy and lactation;

– age up to 18 years (the effectiveness and safety of the drug have not been established).

**With caution**

The influence of various degrees of renal failure on the pharmacokinetics of melatonin has not been studied, therefore, VELSON® should be used with caution in patients with this pathology. VELSON® is contraindicated in patients with severe renal failure.

**Use during pregnancy and lactation**

The drug VELSON® is contraindicated for use during pregnancy and during breastfeeding.

**Dosage and Administration**

To be administered orally, followed by sufficient amount of water.

*In case of sleep disturbance, desynchronosis:* 3 mg once a day 30-40 minutes before bedtime.

*In case of use as an adaptogen when changing time zones:* 1 day before the flight and in the next 2-5 days, 3 mg 30-40 minutes before bedtime.

The maximum daily dose is 6 mg.

*In elderly patients:*

With age, there is a decrease in the metabolism of melatonin, which must be taken into account when choosing a dosage regimen for elderly patients. Taking this into account, in elderly patients, it is possible to take the drug 60-90 minutes before bedtime.

**Adverse effects**

Classification of undesirable effects by system organ classes with indication of their frequency: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000), including individual reports, frequency unknown (frequency cannot be evaluated based on available data).

*Infections and infestations:* rare – herpes zoster.

*Blood and lymphatic system disorders:* rare – leukopenia, thrombocytopenia.

*Immune system disorders:* frequency unknown – hypersensitivity reactions.

*Metabolic and nutritional disorders:* rare – hypertriglyceridemia, hypokalemia, hyponatremia.

*Mental disorders:* uncommon – irritability, nervousness, anxiety, insomnia, unusual dreams, nightmares, anxiety; rare – mood swings, aggression, agitation, tearfulness, stress symptoms, disorientation, early morning awakening, increased libido, low mood, depression.

*Nervous system disorders:* uncommon – migraine, headache, lethargy, psychomotor hyperactivity, dizziness, drowsiness; rare – fainting, memory impairment, impaired concentration, delirium, restless legs syndrome, poor sleep quality, paresthesia.

*Eye disorders:* rare – decreased visual acuity, blurred vision, increased lacrimation.

*Ear and labyrinthine disorders:* rare - vertigo, positional vertigo.

*Cardiac disorders:* rare – exertional angina, palpitations.

*Vascular disorders:* uncommon –arterial hypertension; rare – "hot flashes".

*Gastrointestinal tract disorders:* uncommon – abdominal pain, abdominal pain in the upper abdomen, dyspepsia, ulcerative stomatitis, dry mouth, nausea; rare – gastroesophageal disease, gastrointestinal distress, bullous stomatitis, ulcerative glossitis, vomiting, increased peristalsis, bloating, salivary hypersecretion, bad breath, abdominal discomfort, stomach dyskinesia, gastritis.

*Hepatic and biliary tract disorders:* uncommon – hyperbilirubinemia.

*Skin and subcutaneous tissues disorders*: uncommon – dermatitis, sweating at night, itching and generalized itching, rash, dry skin; rare – eczema, erythema, hand dermatitis, psoriasis, generalized rash, itchy rash, nail damage; the frequency is unknown – Quincke's edema, edema of the oral mucosa, edema of the tongue.

*Musculoskeletal and connective tissue disorders:* uncommon – pain in the limbs; rare – arthritis, muscle spasm, neck pain, night cramps.

*Renal and urinary tract disorders:* uncommon – glucosuria, proteinuria; rare – polyuria, hematuria, nocturia.

*Genitals and mammary glands disorders*: uncommon – menopausal symptoms; rare – priapism, prostatitis; frequency unknown – galactorrhea.

*General disorders and disorders at the administration site:* uncommon – asthenia, chest pain; rare – fatigue, pain, thirst.

*Effects on the results of laboratory and instrumental tests:* uncommon – deviation of laboratory parameters of liver function from normal limits, increase in body weight; rare – an increase in the activity of "hepatic" transaminases, deviation in the content of electrolytes in the blood from normal limits, deviation of the results of laboratory tests from normal limits.

If any of the adverse effects indicated in this leaflet are aggravated, or you notice any other adverse effects, which are not listed in the instructions, *inform your doctor.*

**Overdosage**

According to the available literature data, the use of melatonin in a daily dose of up to 300 mg did not cause clinically significant adverse reactions. Hyperemia, abdominal cramps, diarrhea, headache and scotoma were observed with the use of melatonin at the doses of 3000-6600 mg for several weeks. When very high doses of melatonin (up to 1 g) were used, loss of consciousness was observed.

*Symptoms:* in case of an overdose, daily drowsiness may develop.

*Treatment:* gastric lavage, activated charcoal, symptomatic therapy. The clearance of the active substance is assumed within 12 hours after ingestion.

**Interaction with other medicinal products**

*Pharmacokinetic interaction*

At concentrations significantly higher than therapeutic, melatonin induces the CYP3A isoenzyme *in vitro.* The clinical significance of this phenomenon is not completely understood. If signs of induction develop, consider reducing the dose of concurrently used drugs.

It is recommended to avoid combination with fluvoxamine, which increases the concentration of melatonin (increase in AUC by 17 times and Cmax by 12 times) by inhibiting its metabolism by cytochrome P450 isoenzymes (CYP): CYP1A2 and CYP2C19.

Caution should be exercised while taking the following medicines:

• 5- and 8-methoxy-psoralen, which increases the concentration of melatonin due to inhibition of its metabolism;

• cimetidine (an inhibitor of CYP2D isoenzymes), which increases the plasma melatonin content by inhibiting the latter;

• estrogens, which increase the concentration of melatonin by inhibiting its metabolism by isoenzymes CYP1A1 and CYP1A2;

• inhibitors of CYPA2 isoenzymes (e.g. quinolones), which can increase the exposure of melatonin;

• inducers of the isoenzyme CYP1A2 (for example, carbamazepine and rifampicin), which are capable of reducing the plasma concentration of melatonin.

Smoking can reduce the concentration of melatonin due to the induction of the isoenzyme CYP1A2.

There is a wealth of data published on the effect of adrenergic and opioid receptor agonists/antagonists, antidepressants, prostaglandin inhibitors, benzodiazepines, tryptophan, and alcohol on the secretion of endogenous melatonin. The study of the mutual effect of these drugs on the dynamics or kinetics of melatonin was not carried out.

*Pharmacodynamic interaction*

While taking melatonin, it is recommended to refrain from drinking alcohol, as it reduces the effectiveness of the drug.

Melatonin enhances the sedative effects of benzodiazepines and such non-benzodiazepine hypnotics as zaleplon, zolpidem, and zopiclone. Their combined use can lead to progressive disturbance of attention, memory and coordination in comparison with zolpidem monotherapy.

The use of melatonin in combination with thioridazine and imipramine may lead to increased feelings of calmness and difficulty in performing certain tasks compared with imipramine monotherapy, as well as an increase in the feeling of "cloudy head" compared to thioridazine monotherapy.

**Special precautions**

Exposure to bright light may reduce the effectiveness of VELSON®. In this regard, after taking VELSON® ’it is recommended to avoid bright lighting.

It is necessary to inform women planning pregnancy that the drug has a weak contraceptive effect.

There are no clinical data on the use of melatonin in patients with autoimmune diseases, and therefore, its use in this category of patients is not recommended.

**Effect on ability to drive and use machines**

The drug VELSON® causes drowsiness; therefore, during the period of treatment, one should refrain from driving vehicles and engaging in potentially hazardous activities that require increased concentration of attention and speed of psychomotor reactions.

**Presentation**

Film-coated tablets, 3 mg.

10 tablets in printed, lacquered polyvinyl chloride film and aluminum foil blister.

3, 6 or 9 blister strip packs with leaflet in a carton box.

**Storage conditions**

In a place protected from light at temperature below 25°С.

Keep out of the reach of children.

**Shelf life**

4 years.

Do not use after expiration date, specified on package.

**Purchasing terms**

Over the counter.

**Legal entity in whose name the marketing authorization is given:**

NPO Petrovax Pharm LLC,

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Pokrov village, Sosnovaya str, 1

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