Grandaxin®

International Non-Proprietary Name (INN): Tofisopam

Dosage Form: tablets

Structure: 1 tablet contains:
Active ingredient: Tofisopam 50mg.
Excipients: stearic acid; magnesium stearate; gelatine; talc; potato starch; lactose monohydrate; microcrystalline cellulose.

Description: round, flat tablets of white or greyish-white colour in the form of a disc, with a facet and a break line on one side and engraving "GRANDAX" - on the other, without or with almost no smell.

Pharmacological Classification: anxiolytic, tranquilizer

ATX Code: N05BA23

Pharmacological Action: anxiolytic

Pharmacodynamics:
The medicine belongs to the group of benzodiazepine derivatives (an atypical benzodiazepine derivative). It has an anxiolytic effect. It has almost no sedative, myorelaxing or anticonvulsant action. It is a psycho-vegetative regulator; it eliminates various forms of vegetative disorders. Has a moderate stimulating effect.
Since there is no muscle relaxant effect, the medicine can be used for patients with myopathy and myasthenia. Due to the atypical chemical structure, unlike classical benzodiazepine derivative, in therapeutic doses Grandaxin® almost does not cause physical, psychological dependence and withdrawal syndrome.
Grandaxin® is a daytime anxiolytic.

Pharmacokinetics:
The medicine is quickly and almost completely absorbed from the gastro-intestinal tract. The maximum concentration in the blood is reached within 2 hours, after that the concentration in the plasma decreases monoexponentially. Tofisopam is not accumulated in the body. Its metabolites do not have pharmacological activity. It is excreted mainly in urine (60-80%) in the form of conjugates with glucuronic acid and to a lesser extent (about 30%) in feces. The half-life is 6-8 hours.

Intended Uses:
- Neuroses and neurosis-like states (states accompanied by emotional stress, vegetative disorders, moderately expressed anxiety, apathy, decreased activity, compulsive emotions);
- Reactive depression with mild psychopathological symptoms;
- Mental disorder (post-traumatic stress disorder);
- Climacteric syndrome (as an independent medicine, or in combination with hormonal drugs);
- Premenstrual syndrome;
- Cardialgia (in the form of monotherapy or in combination with other drugs);
- Alcohol withdrawal syndrome;
- Myasthenia, myopathies, neurogenic muscular atrophies and other pathological conditions with secondary neurotic symptoms, when anxiolytics with a pronounced myorelaxing effect are contraindicated.

Contraindications:
- Hypersensitivity to the active or any other ingredient of the medicine or to any other benzodiazepines;
- Conditions accompanied by severe psychomotor agitation, aggressiveness or severe depression;
- Decompensated respiratory failure;
- 1 trimester of pregnancy and breastfeeding;
- Sleep apnea (in the anamnesis);
- Simultaneous taking of tacrolimus, sirolimus, cyclosporin;

- Intolerance to galactose, congenital lactase insufficiency or glucose and galactose malabsorption syndrome (the medicine contains lactose monohydrate).

With caution: Decompensated chronic respiratory distress, the acute respiratory failure in the anamnesis, angle-closure glaucoma, epilepsy, organic brain lesions (such as atherosclerosis).

Dosage and Administration:

Per os. The dosage is set individually taking into account the patient's condition, clinical form of the disease and individual sensitivity to the medicine.

For adults: 50-100 mg (1-2 tablets) 1-3 times a day. In case of occasional administration, 1-2 tablets can be taken. The maximum daily dose is 300 mg.

For elderly patients and patients with renal insufficiency, the daily dose is reduced approximately 2-fold.

To prevent sleep disorders, the drug should be taken no later than 3-4 pm.

With alcohol withdrawal syndrome as well as for the prevention and treatment of delirium, a short course of therapy is indicated (from several days to 3-6 weeks).

Side Effects:

The digestive tract: decreased appetite, constipation, increased flatus, nausea, dry mouth. In some cases, obstructive jaundice.

The central nervous system: headache, insomnia, increased irritability, agitation, confusion, convulsions may occur in patients with epilepsy.

Allergic reactions: exanthema, scarlatiniform exanthema, itching.

The locomotor system: muscle tension, muscle pain.

The respiratory system: respiratory depression.

Overdose:

Symptoms: effects of the central nervous system (CNS) suppression manifest themselves only after high doses (50-120 mg/kg). Such doses can cause vomiting, confusion, coma, respiratory depression and/or epileptic seizures.

Treatment: in case of pronounced suppression of the CNS functions induction of vomiting is not recommended. Lavage of the stomach can be carried out. The activated charcoal helps to reduce the absorption of the medicine. It is necessary to monitor the basic physiological indicators on a constant basis and apply appropriate symptomatic therapy. In case of respiratory depression, the artificial lung ventilation (ALV) can be carried out. Administration of the CNS stimulants is not recommended. Hypotension can be eliminated by intravenous administration of fluids and by bringing the patient to Trendelenburg position. If these measures do not restore normal arterial pressure, dopamine or norepinephrine can be administered. Dialysis and induced diuresis are ineffective.

Flumazenil can be administered as an antagonist, but its use in case of Tofisopam overdose has not been clinically tested.

Interaction with Other Drugs:

The simultaneous use of tacrolimus, sirolimus, cyclosporine and Tofisopam is contraindicated. Medicines, which are metabolized by CYP3A4, can increase their concentration in blood plasma in case of simultaneous admission with Tofisopam.

The use of Tofisopam with medicines suppressing the CNS function (analgesics, general anesthesia medicines, antidepressants, H1-antihistamines, sedatives, hypnotics, antipsychotics), enforces their effects (e.g., sedative effect or respiratory depression).

Liver enzymes inductors (barbiturates, alcohol, nicotine, antiepileptic medicines) may increase Tofisopam metabolism, which may lead to the lowering of its concentration in the blood plasma and to the weakening of the therapeutic effect.

Some antifungal medicines (ketoconazole, itraconazole) can slow the hepatic metabolism of Tofisopam, which leads to an increase of its concentration in the blood plasma.

Some antihypertensive medicines (clonidine, calcium channels antagonists) can enhance the effects of Tofisopam. Beta-adrenoceptor blocking agents can slow the medicine metabolism, but this effect has no clinical significance.
Tofisopam can increase the level of digoxin in the blood plasma.
Benzodiazepines can affect the anticoagulant effect of warfarin.
The long-term use of disulfiram can inhibit Tofisopam metabolism.
Antacids can affect the absorption of Tofisopam. Cimetidine and omeprazole inhibit Tofisopam metabolism.
Oral contraceptives can reduce the intensity of Tofisopam metabolism.
Tofisopam weakens the depressant effect of alcohol on the CNS.

Pregnancy and Lactation:
Contraindicated in the 1st trimester of pregnancy. Breastfeeding should be discontinued while medication.

Influence on the Ability to Drive Vehicles and Mechanisms:
Grandaxin® does not significantly reduce attention and ability to concentrate.
The possibility of driving vehicles should be addressed only after assessing the individual response of the patient to the drug.

Special Precautions:
It should be noted that in patients with mental retardation, in elderly patients, and in those with impaired renal and/or liver function, side effects may be more likely than in other patients.
It is not recommended to apply Tofisopam in case of chronic psychosis, phobia or obsessive conditions. In these cases, the risk of suicidal attempts and aggressive behaviour increases. Therefore, Tofisopam is not recommended as a monotherapy for depression or depression accompanied by anxiety.
Care must be taken when treating patients with depersonalization, and with organic brain damage (e.g., atherosclerosis).
In patients with epilepsy, Tofisopam may increase the threshold of convulsive readiness.

Each Grandaxin® tablet contains 92 mg of lactose, which should be taken into account by patients suffering from lactose intolerance (see "Contraindications").

Terms Of Release From Pharmacy: on prescription

Storage Conditions: at a temperature of 15-25°C. Keep out of the reach of children.

Shelf Life: 5 years. Do not use beyond the expiration date.

Country of Manufacture: Hungary