APPROVED
Order of the Ministry of Defense
health of Ukraine
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Registration certificate
No. UA/18680/01/01

INSTRUCTION
for medical use of the medicinal product
DONOVIT-VS®
(DONOVIT-VS)

Composition:
active substance: liquid extract of the root of the wrestler;
1 tablet of 10 mcg contains 0.02 ml of liquid root extract (*Aconite radices extractum fluidum*) (1:4) (extractant ethanol 40%) (with the content of acetylbenzoylaconine not less than 480 mcg/ml and not more than 520 mcg/ml) excipients: lactose, monohydrate; magnesium stearate.
Medicinal form. Tablets.
Main physicochemical properties: biconvex tablets of grayish-white or yellowish-white color. Splashes of dark color are allowed.
Pharmacotherapeutic group.
Alkaloids of plant origin and other preparations of natural origin.
ATX code L01C X**.**
Pharmacological properties.
Pharmacodynamics.
DONOVIT-VS® is a medicinal product of plant origin, which includes a liquid extract of the root of the wrestler. Wrestler is a perennial herbaceous plant from the ranunculaceae family *(Ranunculaceae Juss)*, the root of which *(Aconiti radix)* contains alkaloids of the deterpene group. The main component of the medicinal product DONOVIT-VS® is the alkaloid aconitine (acetylbenzoylaconine), which exhibits antitumor and antimetastatic activity against solid tumors with angiogenesis-dependent growth.
DONOVIT-VS® exhibits antitumor activity, which was recorded in experimental models of solid tumors: Lewis lung carcinoma LLC/R9, Ehrlich carcinoma and S180 sarcoma. Antitumor activity was manifested in more than 65% ($p < 0.05$) inhibition of the growth of the primary tumor (Ehrlich's carcinoma, sarcoma S180), which was maintained for at least 8 days after the end of the use of the drug. The antimetastatic effect of the drug on Lewis lung carcinoma LLC/R9 was manifested in a significant inhibition of both the number and volume of metastases: a decrease in the average number of lung metastases by 92.2% ($p < 0.01$), the volume of metastatic lesions by 78 .0% ($p < 0.05$). The antitumor activity of the DONOVIT-VS® drug is completely absent in relation to ascites forms of experimental tumors.
In the course of preclinical studies, it was proven that the antitumor and antimetastatic effects are due to two mechanisms: antiangiogenic and antivascular.
The research results showed the ability of the drug DONOVIT-VS® to significantly affect the vascular system. Thus, microscopic studies of tumors (LLC, LLC/R9, glioma 101-8) and internal organs (lungs, liver, kidneys, and heart) of intact mice and rats revealed a significant damaging effect of the extract on blood vessels after a single administration of the drug in lethal and sublethal doses vessels, which was manifested in their expansion, increased permeability, or in some cases, the occurrence of ruptures in the vessel walls. Ruptures of the blood vessel walls, especially in the tumor tissue, were accompanied by the release of erythrocytes into the perivascular space. In the control group of animals, such blood vessel damage was not observed either in tumor tissue or in normal organs.
The anti-vascular and anti-angiogenic effect of the drug DONOVIT-VS® was also confirmed by the results of studies of the effect on the vascularization of the horionallantoic membrane (HAM), which was determined on chicken embryos.

Inhibition of vascularization of HAM by aconitine-containing extract was dose-dependent. At the same time, the proportion of vessels whose diameter exceeded 0.6 mm progressively decreased with an increase in the dose of the drug, and at a dose of 0.4 μg per embryo, such vessels were completely absent.
A significant effect of the medicinal product DONOVIT-VS® on the electrokinetic characteristics of endothelial and tumor cells was revealed. The effect of the drug on the electrokinetic characteristics of MAEC endothelial cells (modeling of angiogenesis in vitro using 3D-cultures of endothelial cells) was significantly different from that on tumor cells. An increase in the concentration of the drug DONOVIT-VS® caused a 30% ($p < 0.05$) decrease in the surface charge density of LLC/R9 cells, but did not affect its sign. A decrease in surface charge density by 50% while maintaining its sign was also recorded when the drug acted on endothelial cells at a concentration of $IC_{50}/10$. However, at lower concentrations ($IS_{50}/20$), DONOVIT-VS® induced a significant negative surface charge in most endothelial cells. Since the positive surface charge of endothelial cells plays an important role in the morphogenesis of blood vessels, the drug-induced change in the charge to a negative one can inhibit the growth of new vessels (antiangiogenic effect of the drug) and disrupt the structure of blood vessels, increasing their permeability (direct antivascular effect).
Chemotherapy drugs, such as cisplatin, showed higher efficiency when combined with the drug DONOVIT-VS®.
In the course of clinical studies, DONOVIT-VS® was prescribed to patients with colorectal cancer and breast cancer as an accompanying drug during a course of chemotherapy. In patients with colorectal cancer and breast cancer, who took DONOVIT-VS®, along with antimetastatic and antitumor effects, a decrease in the severity of complications of chemotherapy, such as leukopenia, anemia, neutropenia, and thrombocytopenia, was found, compared to the group of patients who received only chemotherapy, as well as reducing the severity and frequency of nausea and vomiting.
The drug DONOVIT-VS®, which is prescribed against the background of chemotherapy, is an effective tool in the treatment of patients with glioblastoma (malignant glial tumors of the brain).
Based on the analysis of the data of the clinical study, it was proven that the treatment of glioblastoma was more effective in the group of patients who received the study drug DONOVIT-VS® against the background of antitumor chemotherapy compared to the group of patients who received only chemotherapy. The results of the study showed that in patients who received the drug DONOVIT-VS® in combination with chemotherapy, a significant increase in one-year recurrence-free survival (without progression) and overall survival was achieved.
On the basis of the above, the drug DONOVIT-VS® can be recommended for medical use in patients with malignant glial tumors of the brain as an accompanying drug during a course of chemotherapy, as well as for continuous use after basic therapy.
Pharmacokinetics.
Not studied.
Clinical characteristics.
Indication.
To be used for the prevention of adverse reactions of adjuvant chemotherapy in patients with colorectal cancer and breast cancer after operations, in the adjuvant treatment of malignant glial tumors of the brain.
Contraindication.
Hypersensitivity to the active substance or to any other component of the medicinal product. Severe liver failure, severe renal failure.
Interaction with other medicinal products and other types of interactions.
When interacting with other drugs, no side effects were detected.
Features of application.
DONOVIT-VS® contains lactose, so if the patient has an intolerance to some sugars, you should consult a doctor before taking this medicine.
It is recommended to use DONOVIT-VS® with caution in patients with impaired renal function, as it is excreted mainly by the kidneys.
Use during pregnancy or breastfeeding.

The drug is not used during pregnancy and breastfeeding, no studies were conducted.

The ability to influence the speed of reaction when driving vehicles or other mechanisms.

Studies on the effect of the drug on the ability to drive vehicles or work with other mechanisms have not been conducted.

Method of application and dosage.

Dosage requires an individual approach depending on the patient's clinical condition. The maximum single dose is 1 tablet. The maximum daily dose is 3 tablets (1 tablet 3 times a day).

Use 1 tablet 3 times a day for 3 months, or longer depending on the condition.

It is advisable to take the tablets 15–20 minutes before a meal, or 1.5–2 hours after a meal, drinking ½ cup of warm boiled water.

The duration of use depends on the severity and course of the disease and is determined by the doctor, taking into account CT, MRI, PET data.

Patients with impaired kidney function

For patients with mild and moderate degrees of impaired renal function, it is recommended to carefully titrate the dose, especially at the beginning of therapy. Treatment should be started with 1 tablet per day; the dose may be increased to a maximum of 2 tablets per day for patients with moderate renal impairment (glomerular filtration rate (GFR) > 30 mL/min but < 60 mL/min) if clinically indicated.

Children.

The medicine is not used for children.

Overdose.

Symptoms: nausea, shortness of breath, headache, hyperemia of the face, numbness of the tip of the tongue and lips, sometimes a feeling of numbness of the scalp.

Treatment. In case of overdose, you should stop using the medicine and consult a doctor.

Adverse reactions.

Allergic reactions to the active substance or any other component of the drug are possible when using the medicinal product DONOVIT-VS®.

Expiration date.

2 years.

Do not use the medicine after the expiration date indicated on the package.

Storage conditions.

Store in the original packaging at a temperature not higher than 25°C.

Keep out of the reach of children.

Packaging.

30 tablets in a blister, 3 blisters in a box.

Release category.

By prescription.

Producer.

"ASTRAPHARM" LLC, Ukraine.

The location of the manufacturer and the address of the place of its activity.

08132, Kyiv region, Kyiv-Svyatoshynsky district, Vyshneve city, st. Kyivska, 6.

The applicant

NVF AXOMED LTD LLC, Ukraine.

Location of the applicant.

04210, Kyiv, Heroiv Stalingrad Avenue, 6, building 4.

Date last viewed.

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