Package leaflet: Information for the patient

Vasostenoon 20 µg/ml concentrate for solution for infusion
Alprostadil

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Vasostenoon is and what it is used for

Vasostenoon contains the active ingredient alprostadil. Alprostadil is similar to the endogenous substance called prostaglandin E_1 (PGE_1) that dilates blood vessels and facilitates blood flow in limbs.

Vasostenoon is used to treat critical limb ischemia (stages III, IV according to Fontaine's classification), when there is no possibility to perform reconstructive operation due to the nature of angiographically-proven arterial lesion. Used in combination with vascular reconstructive surgeries, during the surgery and in the immediate postoperative period. Treatment of Raynaud syndrome in the case when necrotic lesions of fingers and toes have occurred as a complication of disease.

2. What you need to know before you use Vasostenoon

Do not use Vasostenoon in the following cases:
- if you are allergic to active substance or any of the other ingredients of this medicine (listed in section 6);
- if you have heart failure due to which your physical activity has been considerably restricted;
- if you have arrhythmia;

- if you have inadequately controlled coronary heart disease, arrhythmias, heart failure;
- within 6 months after suffering from myocardial infarction or stroke;
- if you have very low blood pressure;
- if you have heart valve defects;
- if you are suffering from heart failure and there is suspicion for pulmonary oedema (water in the lungs) or if you have had pulmonary oedema in past;
- severe obstructive pulmonary diseases;
- if you have pulmonary infiltration (due to pneumonia or sarcosis);
- if you have severe renal dysfunction;
- severe hepatic impairment;
- if you have bleeding tendency, for example in case of multiple injuries;
- if you have active or potential bleeding sites such as acute inflammation of the stomach with superficial defects, active gastric and/or duodenal ulcer;
- if you have bleeding in the brain (intracerebral bleeding),
- if you are planning pregnancy or if you are pregnant, breast-feeding or have just given birth;
- in children and adolescents;
- if you have general contraindication to infusion therapy (like congestive heart failure, pulmonary or cerebral oedema and increased fluid volume of the body).

Talk to your doctor if something from the above list applies to you.

Warnings and precautions
Talk to your doctor before using Vasostenoon.

This medicinal product contains 99.5 vol % ethanol (alcohol), i.e. up to 786 mg per dose, equivalent to 15.9 ml beer or 6.7 ml wine per dose. Medicinal product is harmful for those suffering from alcoholism. It also has to be taken into account in administration to patients belonging to high-risk groups, such as patients with liver disease or epilepsy.

Vasostenoon can be used for treatment only by physicians, who have sufficient experience, skills and opportunities to continuously monitor cardiovascular system of the patients. Vasostenoon should not be administrated per bolus injection. Intravenous administration is not recommended in case of state IV chronic disease.

While receiving Vasostenoon, you should be closely monitored during each dose. Monitoring is especially important when you belong to any of the risk groups as listed in section 3. Patients with propensity for cardiovascular insufficiency due to their age, also patients with ischemic heart disease, peripheral oedema and renal failure should stay at the hospital during their treatment with Vasostenoon and one day after. To avoid hyperhydration, the volume of solution for infusion in these patients should not exceed 50-100 ml per day. It is essential to assess the function of the cardiovascular system in such patients, including monitoring of blood pressure, heart rate and fluid balance. Control of body weight, blood pressure and echocardiography may be required. Patients with mild (GFR ≤ 89 ml/min/ 1,73 m^2) or moderate (GFR ≤ 59 ml/min/ 1,73 m^2) renal impairment should be closely monitored (e.g. fluid balance and renal function tests). Before discharging the patient, a stable cardiovascular condition should be established.

Concurrent use of Vasostenoon and antihypertensives, vasodilators and medicinal products for treatment of coronary heart disease should by followed by intensive cardiovascular monitoring (see section “Other medicines and Vasostenoon”).

Alprostadil should be used with caution in patients with a history of gastrointestinal disorders, including gastric mucosal inflammation with superficial defects, gastrointestinal bleeding and gastric and/or duodenal ulcers or with a history of bleeding in the brain (intracerebral haemorrhage) or other bleeding (see section 2 “Do not use Vasostenoon in the following cases”).

Caution should be taken in patients receiving concomitant medications that may increase the risk of bleeding, such as anticoagulants or platelet aggregation inhibitors. (see section 2 “Other medicines and Vasostenoon”). These patients should be closely monitored for signs and symptoms of bleeding.

Women of childbearing potential must use suitable contraception during treatment.

Children and adolescents

Alprostadil is not recommended for use in children and adolescents.

Other medicines and Vasostenoon

Tell your doctor if you are using or have recently used or might use any other medicines.
The effects of the following drugs may be increased during the treatment with Vasostenoon: antihypertensives, vasodilators, drugs used in the treatment of coronary heart disease.
Concomitant administration of Vasostenoon and anticoagulants (anticoagulants, antiplatelet agents) may cause increased the risk of bleeding. Caution should be taken when treating patients receiving concomitant anticoagulants or platelet aggregation inhibitors.
Since alprostadil may potentiate effects of antihypertensive medications (such as antihypertensives, vasodilators), intensive monitoring of blood pressure should be used in patients treated with these medications

Pregnancy, breastfeeding and fertility

Vasostenoon must not be administered to women who may become pregnant, to pregnant women or to breastfeeding mothers. Women of childbearing potential who would receive alprostadil have to use effective contraception during treatment. Pre-clinical fertility studies have been conducted and at the recommended clinical dosage of alprostadil, no effects on fertility are expected.

Driving and using machines

This medicine can affect the ability to drive and to use machines. Vasostenoon may cause decrease in blood pressure and, even if used at recommended clinical dosage, may influence your ability to concentrate to such a degree that active participation in traffic or operating machinery can be potentially dangerous.

Vasostenoon contains ethanol

This medicinal product contains 99.5 vol % ethanol (alcohol) per dose.

3. How to use Vasostenoon

Vasostenoon is dissolved in 0.9 % solution of sodium chloride and is administered as infusion into the vein or artery.

Intraarterial administration
For safety purposes intraarterial administration should be started with low dose and in the absence of side effects, the dose may be increased. To prevent thromboembolic complications, it is advised to administer heparin 15000 IU/day.

a) *Intraarterial administration within 12 hours.* Daily dose is 5-30 μg, the recommended dose is 0.1-0.6 ng/kg/min. Daily dose (5-30 μg) should be dissolved in 50 ml of 0.9% sodium chloride solution and administered using automatic syringe within 12 hours.
b) *Intraarterial administration within 1-2 hours.* Daily dose is 10-20 μg; the recommended dose during administration of 10 μg – 1.2 ng/kg/min; during administration of 20 μg – 2.4 ng/kg/min.
c) *Intraarterial administration during the surgery.* 5-40 μg of alprostadil dissolved in 50 ml of 0.9% sodium chloride solution should be administered into the distal vascular pools during the reconstructive vascular surgery.

Intravenous administration
Intravenous administration is not recommended in case of state IV chronic disease.
Daily dose is 40 μg of alprostadil twice a day or 60 μg of alprostadil once a day, the recommended dose is 4.7 ng/kg/min.
40 μg of alprostadil should be dissolved in 50-250 ml of 0.9% sodium chloride solution and administered intravenously within 2 hours in the morning and evening.
60 μg of alprostadil should be dissolved in 50-250 ml of 0.9% sodium chloride solution and administered intravenously within 3 hours once a day.

The initial daily dose should be halved in patients with impaired renal function (creatinine above 1.5 mg/dl). The initial intravenously administered dose of Vasostenoon in patients with impaired renal function should be 20 μg (1.0 ml) twice a day (administered during 2 hours). According to the patient`s clinical condition, the dose may be increased within 2-3 days to the level of the dose used in patients with normal renal function. In patients with cardiac or renal impairment it is not recommended to exceed the volume of 50-100 ml of solution for infusion per day and infusion pump should be used for administration.

Duration of the treatment
Following the 3 weeks of treatment with alprostadil it must be decided whether continuing of the therapy is clinically indicated. If by that time no therapeutic effect is achieved, the treatment should be discontinued. The duration of the therapy should not exceed 4 weeks.

Patients with renal impairment
Patients with mild (GFR ≤ 89 ml/min/ 1,73 m^2) or moderate (GFR ≤ 59 ml/min/ 1,73 m^2) renal impairment should be closely monitored (e.g. fluid balance and renal function tests).

Patients with hepatic impairment

Vasostenoon treatment is contraindicated in patients with signs of acute hepatic impairment or with known severe hepatic impairment.

Paediatric population
Alprostadil should not be used in children and adolescents below age of 18 years.

Elderly patients
Treatment of patients over 65 years is carried out according to the general dosage regimen.

If you have any further questions, ask your doctor.

If you have been given more Vasostenoon than you should
Due to its vasodilatory properties, the overdose of alprostadil can cause decrease in blood pressure and reflective tachycardia (increased heart rate).
Other symptoms may include loss of consciousness, pale skin, sweating, nausea, vomiting, myocardial ischemia and heart failure.
From local symptoms, pain, oedema and redness along the infused vein may occur.
If symptoms of overdosage should occur, the infusion should be reduced or stopped immediately. In the event of a drop in blood pressure, the legs of the lying patient should be raised. If the symptoms persist cardiac exams/tests should be performed. If required, symptomatic treatment may be initiated.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects can occur during the use of Vasostenoon:

Common: may affect 1 to 10 patients in 100
- Headache, redness of skin, swelling or feeling of warmth, pain at the site of injection;
- <u>After administration into an artery:</u> feeling of warmth, feeling swollen, localized swelling, sensitivity disorders.

Uncommon: may affect 1 to 10 patients in 1000
- Decreased blood pressure, tachycardia (increased heart rate), angina pectoris (sensation of pressure or tightness in chest), gastrointestinal disorders (nausea, vomiting, diarrhoea), allergic reactions (rash, itching, joint pain, fever, sweating, chills), confusional state, increased liver enzymes activity, reversible changes in concentration of C-reactive protein;
- <u>After administration into a vein:</u> feeling of warmth, feeling swollen, localized swelling, redness along the vein, sensitivity disorders.

Rare: may affect 1 to 10 patients in 10 000
- Reversible changes in blood composition (decreased leucocyte or thrombocyte count), convulsions, arrhythmias, biventricular heart failure, development of severe heart failure, pulmonary oedema, abnormalities in the function of liver enzymes.

Very rare: may affect less than 1 in 10 000 patients

- Anaphylactic or anaphylactoid reactions (hypersensitivity reactions), reversible tissue thickening in long bones.

Not known: cannot be estimated from the available data

- Stroke, myocardial infarction, bleeding (haemorrhage), shortness of breath, phlebitis, injection site thrombosis (blood clotting disorders at the site of the catheter tip), localized bleeding, bleeding from stomach and/or bowel.

Intraarterial and intravenous use of Vasostenoon may cause pain, redness and swelling of the corresponding limb. Such adverse reactions disappear after reducing the dose or extending time of administration. Intravenous administration can result in redness along the vein (risk of phlebitis). Phlebitis is caused by catheter inserted into a blood vessel. In this case, intact vein should be used for infusion. Haematoma or bleeding at the site of puncture may occur from moving the cannula.
Erythema occurs more often after intraarterial drug administration.
The side effects quickly disappear after discontinuation of the medication, the infusion rate should be decreased in case of fever or low blood pressure.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the www.ravimiamet.ee. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Vasostenoon

This medicine should be kept out of the sight and reach of children. This medicine should be stored and disposed by a health care provider. You will not be given Vasostenoon to store at home. Hospital pharmacist will store this medicine in a refrigerator (2°C - 8°C), in the original package, protected from light. Vasostenoon will not be given to you after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Chemical and physical in-use stability has been demonstrated for 12 hours at temperature up to 20°C, protected from light. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6. Contents of the pack and other information

What Vasostenoon contains

- The active substance is alprostadil. 1 ml (1 ampoule) of concentrate for solution for infusion contains 20 µg of alprostadil.
- Excipient is anhydrous ethanol.

What Vasostenoon looks like and contents of the pack
Vasostenoon 20 µg/ml concentrate for solution for infusion is clear, colourless solution in 1 ml glass ampoule. There are 5, 10 or 20 ampoules in a package.

Marketing Authorisation Holder and Manufacturer:
Kevelt AS
Teaduspargi 3/1
12618 Tallinn, Estonia
Tel: +372 606 6969
E-mail: kevelt@kevelt.ee

This leaflet was last revised in April 2020.