Stivant

Bevacizumab

Package leaflet: Information for the patient
Stivant 100 mg in 4 mL and 400 mg in 16 mL (25mg/mL)
Concentrate for solution for infusion
Bevacizumab

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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this Leaflet?

1. What Stivant is and what is it used for

Stivant contains the active substance called Bevacizumab with protein structure. It belongs to a class of medicines known as anti-neoplastic (anti-cancer) agents. Different types of anti-neoplastic agents exist but Stivant belongs to anti-angiogenic group. This group of medicines will block the process of blood vessels formation in the body which is known as angiogenesis.
Stivant which is a protein (monoclonal antibody) will bind to another protein called Vascular Endothelial Growth Factor (VEGF); that is found on the cells lining blood vessels. The role of VEGF is to stimulate growth of blood vessels and the role of blood vessels is to provide nutrients and oxygen to the cells. Tumors usually make high amounts of VEGF, therefore more blood vessels are produced and hence, tumors will get more nutrients and oxygen, giving them chance to grow more. When Stivant blocks VEGF, it will disturb the supply of blood to the cells, therefore disturbs the supply of oxygen and nutrients and the growth of tumors will be stopped or slowed.

Stivant is used for

- Treatment of adults with metastatic (spreading) cancer of colon or rectum, in combination with other chemotherapy regimens such as fluorouracil or fluoropyrimidine-based chemotherapies.
- As a single agent in treatment of progressive glioblastoma (a type of tumor that occurs in brain and spinal cord).
- Treatment of different types of lung cancer in adults when combined with other chemotherapy agents.
- In combination with interferon therapy for treatment of advanced and/or metastatic cancer of the kidney.
- Treatment of cancer of the ovaries and fallopian tubes, in combination with other chemotherapy medicines.
- Treatment of persistent, recurrent, or metastatic cervical cancer, in combination with other chemotherapy agents such as paclitaxel and either cisplatin or topotecan.
- In combination with other chemotherapy medicines such as paclitaxel or capecitabine for treatment of adults with metastatic breast cancer. (Off-label)

2. What you need to know before you use Stivant

Do not use Stivant if

- You have ever had an allergic reaction to Bevacizumab, proteins of hamster origin, or any of the other ingredients of this medicine. (Listed in section 6).
- You are pregnant. (Details given in sections below).
- You have untreated central nervous system (CNS) metastases.

Warnings and Precautions

Talk to your doctor or pharmacist before using Stivant.

- If you ever had or have a fistula (a permanent abnormal tube-like connection between two organs in the body or between an organ and the exterior part of the body) or perforation (a hole in an organ of your body) tell your doctor or pharmacist. This is because; patients treated with Stivant are at increased risk of developing fistulas or perforations in different parts of the body, especially in the gastrointestinal tract (stomach), between vagina and any part of the gut (GI-vaginal fistula). Tell your doctor if you have ever undergone radiation therapy, because this may increase the risk of development of gastrointestinal perforations.
- You need to tell your doctor if you have had a surgery within the last 28 days, because Stivant may delay the process of wound healing. Therefore, it is needed for you not to start Stivant until your wound is completely healed.
- If you are having hypertension (high blood pressure) and are taking antihypertensive medicines such as Furosemide you will need to tell your doctor before starting Stivant. Stivant may increase the risk or worsen the existing hypertension.
- Contact your doctor immediately if you ever develop symptoms such as headache, confusion, seizure, lack of energy or feeling of tiredness, problem with your eyesight or neurological disturbances which may occur after 16 hours to 1 year of starting treatment with Stivant. These may be due to a condition known as Posterior Reversible Encephalopathy Syndrome (PRES).
- If you ever develop symptoms such as foamy urine, reduced appetite, weight gain not associated with increased eating or if you have hypertension, tell your doctor. These may be signs of presence of high levels of protein in your urine which may be caused by Stivant.
- Stivant is associated with an increased risk of blood clot formation, which can lead to heart attack or stroke when used in combination with chemotherapy agents. History of blood clot in your blood vessels, diabetes, 65 years of age or more; may present an even greater risk. You need to tell your doctor if you have a history of such problems.
- Tell your doctor immediately if you ever develop symptoms such as sudden shortness of breath, fast heartbeat, sudden and sharp chest pain which gets worse with coughing or breathing, sweating, coughing up blood or a pink mucus or fainting. These may be due to a blockage of a blood vessel in your lungs.
- Risk of bleeding increases with Stivant. If you ever have bleeding from your nose, cough up blood, vomit blood, see blood in your stool, abnormal vaginal bleeding or severe headache; contact your doctor immediately. Tell your doctor if you have cancerous brain tumor (brain metastases) which is not treated and if you are using anticoagulant medicines such as Aspirin.
- Stivant increases the risk of heart disease. Tell your doctor if you have or had a history of heart disease, if you ever used anthracyclines (a group of anti-neoplastic medicines) or had radiotherapy to your chest.
- If you have low levels of white blood cells or if you ever develop signs of infection such as fever, sore mouth, skin abscess, contact your doctor immediately.
- If anytime during infusion with Stivant you develop shortness of breath, fast heartbeat or itching on your body inform the nurse or the doctor immediately. These may be signs of allergic reaction to Stivant.
- A condition called Osteonecrosis of the Jaw (ONJ) that is a bone damage in the jaw, may happen with Stivant. You need to take some precautions in order to prevent ONJ and your doctor may ask you to have a dental checkup before starting Stivant. You need to always keep a good oral hygiene while on Stivant and you may need to tell your dentist that you are taking this medicine. If you use dentures, make sure they are completely fitted on your mouth. Immediately inform your doctor if you ever get a problem in your mouth such as; pain, loose teeth, swelling, discharge or sores which do not heal, as these may be signs of ONJ. This condition may happen more in patients who have used or are using a group of medicine called bisphosphonates. Tell your doctor if you have ever used bisphosphonates.
- Stivant has been made to treat different types of cancers by injecting it into the bloodstream. It has not been made for injection into the eye. It is therefore not authorized to be used in this way. When Stivant is injected directly into the eye (unapproved use), different side effects such as; infection or inflammation of interior of the eye, redness of the eye, small particles or spots in your vision (floaters), eye pain, seeing flashes of light with floaters progressing to a loss of some of your vision, increased eye pressure and bleeding in the eye, may occur.

Children and Adolescents

It is not recommended to use Stivant in less than 18 years of age. The safety and effectiveness of Stivant has not been studied in children and adolescents.

Other medicines and Stivant

- Tell your doctor, pharmacist or nurse if you are using or have recently used any other medicine including herbal medicines, non-prescription medicines or vitamins.
- Tell your doctor if you are undergoing radiotherapy.
- Some medicines may interact with Bevacizumab if used together. The following is a list of these medicines:
  - Sunitinib maleate (a medicine for gastrointestinal and kidney cancer): it should be avoided because it increases the risk of different types of anemia.
  - Combination with platinum or taxane-based therapies: increases risk of infection.
  - Anthracyclines: combination with Bevacizumab may increase the risk of heart disease.
  - Sorafenib (a drug used for treatment of kidney, liver and a type of thyroid cancer): combination with Bevacizumab may increase the incidence of hand-foot syndrome (a condition of reddening, swelling and peeling of the skin of palms and/or soles).

Pregnancy, breast-feeding and fertility

Pregnancy

Stivant should be avoided during pregnancy. If you are pregnant or are planning to get pregnant tell your doctor before starting the treatment. You will need to use effective birth control methods while using Stivant and for at least 6 months after you stop it. If you get pregnant while using Stivant or less than 6 months after stopping it, contact your doctor.

Breast-feeding

It is not known if Bevacizumab is excreted in breast milk. It is not recommended to breast-feed while using Stivant and after 6 months of stopping it. If you are breast-feeding, you need to stop and consult your doctor regarding the best solution to this issue.

Fertility

Studies have shown that Bevacizumab affects the fertility of female. Fertility problems may happen with Stivant. Consult your doctor regarding this issue.

Effects on ability to drive or use machines

Stivant does not have any significant effect on using machines or ability to drive. However, if you

experience symptoms that affect your vision or concentration try avoiding driving or using machinery until the symptoms are gone.

3. How to use Stivant

Use in adults

Stivant is only available on prescription. Stivant should be prepared and administered by a physician who is having experience in use of antineoplastic medicines.
The dose of Stivant is calculated according to your body weight and depends on the type of cancer for which you are being treated.
The recommended dose for different types of cancers is as follows:

Metastatic cancer of colon or rectum

Either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg of body weight given once every 3 weeks.

Progressive Glioblastoma

10 mg/kg of body weight given once every 2 weeks as monotherapy.

Non-Small Cell Lung Cancer (NSCLC)

15 mg/kg every 3 weeks (in combination with platinum-based chemotherapy) for 6 cycles followed by Stivant alone as monotherapy until disease progression or unacceptable toxicity.

Advanced and/or metastatic cancer of the kidney

10 mg/kg of body weight given once every 2 weeks.

Ovarian, fallopian tube and primary peritoneal cancer

- Treatment of choice:
  Stivant administered in addition to carboplatin and paclitaxel for up to 6 cycles followed by continued use of Stivant alone until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs first. The recommended dose of Stivant is 15 mg/kg given once every 3 weeks.
- Treatment of platinum-sensitive recurrent disease: in combination with either carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of Stivant alone until disease progression. The recommended dose of Stivant is 15 mg/kg given once every 3 weeks.
- Treatment of platinum-resistant recurrent disease: the recommended dose of Stivant is 10 mg/kg given once every 2 weeks (in combination with weekly paclitaxel, every 4 week doxorubicin [liposomal], or days 1, 8, and 15 topotecan), or when given in combination with every 3 weeks topotecan, 15 mg/kg given once every 3 weeks.

Cervical cancer

15 mg/kg every 3 weeks (in combination with paclitaxel and either cisplatin or topotecan).

Metastatic breast cancer (off-label)

10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks.

Use in children and adolescents

Stivant is not recommended for use in anyone under the age of 18 years.

Route and method of administration

Stivant is administered as an intravenous infusion.
The first dose will be given to you over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, next infusions may be administered over 30 minutes.

If you take more Stivant than you should

If you have been given too much Stivant you may develop a severe migraine. If this happens tell your doctor or nurse immediately.

If you forget to use Stivant

Always try to remember the schedule of your injections. If you ever forget to go to hospital for your infusion, consult your physician for rescheduling the next dose of Stivant. Your doctor will decide for this matter.

If you stop taking Stivant

Never stop using your medicine before consulting your physician. In order to take the complete benefit from your medicine, always complete the treatment course recommended by your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The following side effects were seen when Stivant was combined with other chemotherapy drugs, and it does not mean that they were caused only by Stivant alone.

Serious side effects

The below mentioned side effects may not happen commonly but if they do, they can be life-threatening. If you ever experience any of the following, contact your doctor immediately:

- Patients treated with Bevacizumab are at increased risk of developing perforations in different parts of the body, especially in the gastrointestinal tract (stomach). If you ever experience symptoms such as very bad stomach pain, nausea, vomiting or chills contact your doctor immediately as these may be due to gastrointestinal perforation.
- Bleeding, including bleeding in the lungs with symptom of coughing up blood is more common in lung cancer patients.
- Bevacizumab is associated with an increased risk of blood clots in your blood vessels. If you ever experience feeling of numbness or coldness in your hand or feet, absence of pulse or movement in the arm or leg, contact your doctor.

The following additional side effects have been observed with Bevacizumab and are listed in order of decreasing frequency

Very common side effects (may affect more than 1 in 10 people)

- High blood pressure (hypertension)
- Fatigue
- Headache
- Slurred speech
- Feeling of bad taste in the mouth
- Tingling sensation or feeling of numbness at fingers or toes (peripheral sensory neuropathy)
- Wound healing complications
- Dry skin, skin discoloration
- Reduced white blood cells that fight infections and cells that help blood to clot
- Severe weight loss (anorexia)
- Low blood Magnesium levels
- Low blood Sodium levels
- Ovarian failure
- Abdominal pain
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Bleeding from rectum
- Presence of protein in the urine (proteinuria)
- Pain in the joints (arthralgia)
- Muscular pain (myalgia)
- Difficulty in breathing (dyspnea)
- Runny nose
- Bleeding from the nose
- Cough
- Increased lacrimation

Common side effects (may affect up to 1 in 10 people)

- Heart failure
- Increase heartbeat
- Stroke
- Syncope
- Drowsiness (somnolence)
- Hand-foot syndrome with symptoms of redness, swelling and pain in the palm or soles
- Dehydration
- Recto-vaginal fistula
- Pain in the pelvis
- Anemia
- Low levels of lymphocytes in blood (lymphopenia)
- Hypersensitivity
- Allergic reaction at the infusion site
- Back pain
- Muscular weakness
- Urinary tract infection
- Infection
- Abscess
- Cellulitis

Rare side effects (may affect up to 1 in 1000 people)

- Flesh-eating disease (necrotizing fasciitis)
- A brain condition with symptoms of confusion, headache, seizure or visual loss (Posterior Reversible Encephalopathy Syndrome (PRES)

Not known (frequency cannot be estimated from the available data)

- Stomach ulcer
- Gallbladder perforation
- Osteonecrosis of the jaw
- Fetal abnormalities
- Blood clot in the kidney (Renal thrombotic microangiopathy)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This may include any possible side effects not listed in this leaflet.
You can also report side effects directly via the national reporting system fda.gov.ir or by +98-21-22382641. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Stivant

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and outer carton after "EXP". The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C).
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not shake excessively.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Content of the pack and other information

What Stivant contains

The active substance is Bevacizumab.
Each milliliter of concentrate contains 25 mg of Bevacizumab.
Each 4 ml vial contains 100 mg of Bevacizumab.
Each 16 ml vial contains 400 mg of Bevacizumab.
The other ingredients are Trehalose dihydrate, Sodium Phosphate, Polysorbate 20 and Water for Injections.

What Stivant looks like and contents of the pack

Stivant is a concentrate for solution for infusion.
The concentrate is a clear to slightly opalescent, colorless to pale brown liquid in vial.
Each small box of Stivant 100 mg contains one 4 ml vial and a patient information leaflet.
Each small box of Stivant 400 mg contains one 16 ml vial and a patient information leaflet.

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