PATIENT INFORMATION LEAFLET

Bevacizumab 100mg & 400mg concentrate for solution for infusion

1. Composition

Each mL contains 25 mg of Bevacizumab

4 mL vial: Each single-use vial contains 100 mg of Bevacizumab

16 mL vial: Each single-use vial contains 400 mg of Bevacizumab

2. Product description

Bevacizumab is a type of protein called a “monoclonal antibody”. Bevacizumab binds selectively to a protein called human vascular endothelial growth factor (VEGF), which is found on the lining of blood and lymph vessels in the body. The VEGF protein causes blood vessels to grow within tumours, these blood vessels provide the tumour with nutrients and oxygen. Once Bevacizumab is bound to VEGF, tumour growth is prevented by blocking the growth of the blood vessels which provide the nutrients and oxygen to the tumour.

3. Presentation

Bevacizumab is 4/16 ml injection clear glass vial, supplied as a concentrate for solution for infusion.

- 4 mL vial is available as a pack of 1 vial
- 16 mL vial is available as a pack of 1 vial

4. What it is used for indication

Bevacizumab is used to treat Metastatic Colorectal Cancer (mCRC), Non-Squamous Non–Small Cell Lung Cancer (NSCLC), Glioblastoma, Metastatic Renal Cell Carcinoma (mRCC), Persistent, Recurrent, or Metastatic Carcinoma of the Cervix and Metastatic breast cancer (mBC).

5. How to use: method of administration, route of administration, dosage

Dosage and frequency of administration

The dose of Bevacizumab needed depends on your body weight and the kind of cancer to be treated. The recommended dose is 5 mg, 7.5 mg, 10 mg or 15 mg per kilogram of your body weight. Your doctor will prescribe a dose of Bevacizumab that is right for you. You will be treated with Bevacizumab once every 2 or 3 weeks. The number of infusions that you receive will depend on how you are responding to treatment; you should continue to receive this medicine until Bevacizumab fails to stop your tumour growing. Your doctor will discuss this with you.

Method and route of administration

Bevacizumab is a concentrate for solution for infusion. Depending on the dose prescribed for you, some or all of the contents of the Bevacizumab vial will be diluted with sodium chloride solution before use. A doctor or nurse will give you this diluted Bevacizumab solution by intravenous infusion (a drip into your

vein). The first infusion will be given to you over 90 minutes. If this is well-tolerated the second infusion may be given over 60 minutes. Later infusions may be given to you over 30 minutes.

6. When do not take this drug: contraindication

Do not take Bevacizumab if:

- You are allergic (hypersensitive) to bevacizumab or to any of the other ingredients of this medicine.
- You are allergic (hypersensitive) to Chinese hamster ovary (CHO) cell products or to other recombinant human or humanised antibodies.
- You are pregnant.

7. Adverse reaction

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

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

The side effects listed below were seen when Bevacizumab was given together with chemotherapy. This does not necessarily mean that these side effects were strictly caused by Bevacizumab.

Allergic reactions

If you have an allergic reaction, tell your doctor or a member of the medical staff straight away. The signs may include: difficulty in breathing or chest pain. You could also experience redness or flushing of the skin or a rash, chills and shivering, feeling sick (nausea) or being sick (vomiting).

You should seek help immediately if you suffer from any of the below mentioned side effects.

Severe side effects, which may be very common (affects more than 1 user in 10), include:

- high blood pressure,
- feeling of numbness or tingling in hands or feet,
- decreased number of cells in the blood, including white cells that help to fight against infections (this may be accompanied by fever), and cells that help the blood to clot,
- feeling weak and having no energy,
- tiredness,
- diarrhoea, nausea, vomiting and abdominal pain.

Severe side effects, which may be **common** (affects 1 to 10 users in 100), include:

- perforation of the gut,
- bleeding, including bleeding in the lungs in patients with non-small cell lung cancer,
- blocking of the arteries by a blood clot,

- blocking of the veins by a blood clot,
- blocking of the blood vessels of the lungs by a blood clot,
- blocking of the veins of the legs by a blood clot,
- heart failure,
- problems with wound healing after surgery,
- redness, peeling, tenderness, pain, or blistering on the fingers or feet,
- decreased number of red cells in the blood,
- lack of energy,
- stomach and intestinal disorder,
- muscle and joint pain, muscular weakness,
- dry mouth in combination with thirst and/or reduced or darkened urine,
- inflammation of the moist lining of mouth and gut, lungs and air passages, reproductive, and urinary tracts,
- sores in the mouth and the tube from the mouth to the stomach, which may be painful and cause difficulty swallowing,
- pain, including headache, back pain and pain in the pelvis and anal regions,
- localised pus collection,
- infection, and in particular infection in the blood or bladder,
- reduced blood supply to the brain or stroke,
- sleepiness,
- nose bleed,
- increase in heart rate (pulse),
- blockage in the gut or bowel,
- abnormal urine test (protein in the urine),
- shortness of breath or low levels of oxygen in the blood,
- infections of the skin or deeper layers under the skin,
- fistula: abnormal tube-like connection between internal organs and skin or other tissues that are not normally connected, including connections between vagina and the gut in patients with cervical cancer.

Severe side effects of **unknown** frequency (frequency cannot be estimated from the available data), include:

- serious infections of the skin or deeper layers under the skin, especially if you had holes in the gut wall or problems with wound healing,
- allergic reactions (the signs may include difficulty breathing, facial redness, rash, low blood pressure or high blood pressure, low oxygen in your blood, chest pain, or nausea/vomiting),

- a negative effect on a woman's ability to have children (see the paragraphs below the list of side effects for further recommendations),
- a brain condition with symptoms including seizures (fits), headache, confusion, and changes in vision (Posterior Reversible Encephalopathy Syndrome or PRES),
- symptoms that suggest changes in normal brain function (headaches, vision changes, confusion, or seizures), and high blood pressure,
- clogging of a very small blood vessel(s) in the kidney,
- abnormally high blood pressure in the blood vessels of the lungs which makes the right side of the heart work harder than normal,
- a hole in the cartilage wall separating the nostrils of the nose,
- a hole in the stomach or intestines,
- an open sore or hole in the lining of the stomach or small intestine (the signs may include abdominal pain, feeling bloated, black tarry stools or blood in your stools (faeces) or blood in your vomit),
- bleeding from the lower part of the large bowel,
- lesions in the gums with an exposed jaw bone that does not heal and may be associated with pain and inflammation of the surrounding tissue (see the paragraphs below the list of side effects for further recommendations),
- hole in the gall bladder (symptoms and signs may include abdominal pain, fever, and nausea/vomiting).

You should seek help as soon as possible if you suffer from any of the below mentioned side effects.

Very common (affects more than 1 user in 10) side effects, which were not severe, include:

- constipation,
- loss of appetite,
- fever,
- problems with the eyes (including increased production of tears),
- changes in speech,
- change in the sense of taste,
- runny nose,
- dry skin, flaking and inflammation of the skin, change in skin colour,
- loss of body weight,
- nose bleeds.

Common (affects 1 to 10 users in 100) side effects, which were not severe, include:

- voice changes and hoarseness.

Patients older than 65 years have an increased risk of experiencing the following side effects:

- blood clot in the arteries which can lead to a stroke or a heart attack,
- reduction in the number of white cells in the blood, and cells that help the blood clot,
- diarrhoea,
- sickness,
- headache,
- fatigue,
- high blood pressure.

Bevacizumab may also cause changes in laboratory tests carried out by your doctor. These include a decreased number of white cells in the blood, in particular neutrophils (one type of white blood cell which helps protect against infections) in the blood; presence of protein in the urine; decreased blood potassium, sodium or phosphorous (a mineral); increased blood sugar; increased blood alkaline phosphatase (an enzyme); increased serum creatinine (a protein measured by a blood test to see how well your kidneys are working); decreased haemoglobin (found in red blood cells, which carry oxygen), which may be severe.

Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs and symptoms of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience any of them.

Pre-menopausal women (women who have a menstrual cycle) may notice that their periods become irregular or are missed and may experience impaired fertility. If you are considering having children you should discuss this with your doctor before your treatment starts.

Bevacizumab has been developed and made to treat cancer by injecting it into the bloodstream. It has not been developed or made for injection into the eye. It is therefore not authorised to be used in this way. When Bevacizumab is injected directly into the eye (unapproved use), the following side effects may occur:

- Infection or inflammation of the eye globe,
- 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,
- Bleeding in the eye.

Reporting of side effects

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

8. What you should avoid to use with this drug: interaction with other medicines and food

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Combinations of Bevacizumab with another medicine called sunitinib malate (prescribed for renal and gastrointestinal cancer) may cause severe side effects. Discuss with your doctor to make sure that you do not combine these medicine.

Tell your doctor if you are using platinum- or taxane-based therapies for lung or metastatic breast cancer. These therapies in combination with Bevacizumab may increase the risk of severe side effects.

Please tell your doctor if you have recently received, or are receiving, radiotherapy.

9. What to do if missing a dose

your doctor will decide when you should be given your next dose of Bevacizumab. You should discuss this with your doctor.

10. Storage condition: temperature

Keep this medicine out of the sight and reach of children. Store in a refrigerator (2 °C – 8 °C). Keep the container in the outer carton in order to protect from light.

11. Overdosage handling: signs and symptoms of overdose, what should you do if you overdose

you may develop a severe migraine. If this happens you should talk to your doctor, pharmacist or nurse immediately.

12. Warning and precaution

Talk to your doctor, pharmacist or nurse before using Bevacizumab:

- It is possible that Bevacizumab may increase the risk of developing holes in the gut wall. If you have conditions causing inflammation inside the abdomen (e.g. diverticulitis, stomach ulcers, colitis associated with chemotherapy), please discuss this with your doctor.

- Bevacizumab may increase the risk of developing an abnormal connection or passageway between two organs or vessels. The risk of developing connections between the vagina and any parts of the gut can increase if you have persistent, recurrent or metastatic cervical cancer.
- This medicine can increase the risk of bleeding or increase the risk of problems with wound healing after surgery. If you are going to have an operation, if you have had major surgery within the last 28 days or if you still have an unhealed wound following surgery, you should not receive this medicine.
- Bevacizumab may increase the risk of developing serious infections of the skin or deeper layers under the skin, especially if you had holes in the gut wall or problems with wound healing.
- Bevacizumab can increase the incidence of high blood pressure. If you have high blood pressure which is not well controlled with blood pressure medicines, please consult your doctor as it is important to make sure that your blood pressure is under control before starting Bevacizumab treatment.
- This medicine increases the risk of having protein in your urine especially if you already have high blood pressure.
- The risk of developing blood clots in your arteries (a type of blood vessel) can increase if you are over 65 years old, if you have diabetes, or if you have had previous blood clots in your arteries. Please talk to your doctor since blood clots can lead to heart attack and stroke.
- Bevacizumab can also increase the risk of developing blood clots in your veins (a type of blood vessel).
- This medicine may cause bleeding, especially tumour-related bleeding. Please consult your doctor if you or your family tend to suffer from bleeding problems or you are taking medicines to thin the blood for any reason.
- It is possible that Bevacizumab may cause bleeding in and around your brain. Please discuss this with your doctor if you have metastatic cancer affecting your brain.
- It is possible that Bevacizumab can increase the risk of bleeding in your lungs, including coughing or spitting blood. Please discuss with your doctor if you noticed this previously.
- Bevacizumab can increase the risk of developing a weak heart. It is important that your doctor knows if you have ever received anthracyclines (for example doxorubicin, a specific type of chemotherapy used to treat some cancers) or had radiotherapy to your chest, or if you have heart disease.
- This medicine may cause infections and a decreased number of your neutrophils (a type of blood cell important for your protection against bacteria).
- It is possible that Bevacizumab can cause hypersensitivity and/or infusion reactions (reactions related to your injection of the medicine). Please let your doctor, pharmacist or nurse know if you

have previously experienced problems after injections, such as dizziness/feeling of fainting, breathlessness, swelling or skin rash.

- A rare neurological side effect named posterior reversible encephalopathy syndrome (PRES) has been associated with Bevacizumab treatment. If you have headache, vision changes, confusion or seizure with or without high blood pressure, please contact your doctor.

Please consult your doctor, even if these above statements were only applicable to you in the past.

Before you are given Bevacizumab or while you are being treated with Bevacizumab:

- if you have or have had pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth tell your doctor and dentist immediately.
- if you need to undergo an invasive dental treatment or dental surgery, tell your dentist that you are being treated with Bevacizumab, in particular when you are also receiving or have received an injection of bisphosphonate into your blood.

You may be advised to have a dental check-up before you start treatment with Bevacizumab.

Children and adolescents

Bevacizumab use is not recommended in children and adolescents under the age of 18 years because the safety and benefit have not been established in these patient populations.

Death of bone tissue (osteonecrosis) in bones other than the jaw have been reported in patients under 18 years old when treated with Bevacizumab.

Pregnancy, breast feeding and fertility

You must not use this medicine if you are pregnant. Bevacizumab may cause damage to your unborn baby as it may stop the formation of new blood vessels. Your doctor should advise you about using contraception during treatment with Bevacizumab and for at least 6 months after the last dose of Bevacizumab.

Tell your doctor straightaway if you are pregnant, become pregnant during treatment with this medicine, or plan to become pregnant in the near future.

You must not breast-feed your baby during treatment with Bevacizumab and for at least 6 months after the last dose of Bevacizumab, as this medicine may interfere with the growth and development of your baby.

Bevacizumab may impair female fertility. Please consult your doctor for more information.

Ask your doctor, pharmacist or nurse for advice before taking any medicine.

13. When to consult a physician, pharmacist

Consult your physician or pharmacist, in case of any problems with the product.

14. Shelf-life

24 Months

15. Name, address, logo (if have) of manufacture

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