**FRONT SIDE** / PLEASE, INCLUDE YOUR DESIGN ON THIS KEYLINE

**Alymsys® 25 mg/mL**
**concentrate for solution for infusion**
bevacizumab

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Package leaflet: Information for the user

# Alymsys® 25 mg/mL

**concentrate for solution for infusion**

bevacizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**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 Alymsys is and what it is used for

Alymsys contains the active substance bevacizumab, which is a humanised monoclonal antibody (a type of protein that is normally made by the immune system to help defend the body from infection and cancer). 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.

Alymsys is a medicine used for the treatment of adult patients with advanced cancer in the large bowel, i.e., in the colon or rectum. Alymsys will be administered in combination with chemotherapy treatment containing a fluoropyrimidine medicine.

Alymsys is also used for the treatment of adult patients with metastatic breast cancer. When used for patients with breast cancer, it will be administered with a chemotherapy medicinal product called paclitaxel or capecitabine.

Alymsys is also used for the treatment of adult patients with advanced non-small cell lung cancer. Alymsys will be administered together with a chemotherapy regimen containing platinum.

Alymsys is also used for the treatment of adult patients with advanced non-small cell lung cancer when cancer cells have specific mutations of a protein called epidermal growth factor receptor (EGFR). Alymsys will be administered in combination with erlotinib.

Alymsys is also used for treatment of adult patients with advanced kidney cancer. When used for patients with kidney cancer, it will be administered with another type of medicine called interferon.

Alymsys is also used for the treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. When used for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, it will be administered in combination with carboplatin and paclitaxel.

When used for those adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease has come back at least 6 months after the last time they were treated with a chemotherapy regimen containing a platinum agent, Alymsys will be administered in combination with carboplatin and gemcitabine or with carboplatin and paclitaxel.

When used for those adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease has come back before 6 months after the last time they were treated with a chemotherapy regimen containing a platinum agent, Alymsys will be administered in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin.

Alymsys is also used for the treatment of adult patients with persistent, recurrent or metastatic cervical cancer. Alymsys will be administered in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy.

## 2. What you need to know before you use Alymsys

**Do not use Alymsys if:**
- you are allergic to bevacizumab or any of the other ingredients of this medicine (listed in section 6).
- you are allergic to Chinese hamster ovary (CHO) cell products or to other recombinant human or humanised antibodies.
- you are pregnant.

**Warnings and precautions**
Talk to your doctor, pharmacist or nurse before using Alymsys:

- Alymsys 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.

- Alymsys 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.

- Alymsys 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.

- Alymsys 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.

- Alymsys 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 Alymsys treatment.

- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.

- Alymsys 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.

- Alymsys can also increase the risk of developing blood clots in your veins (a type of blood vessel).

- Alymsys 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.

- Alymsys may cause bleeding in and around your brain. Please discuss this with your doctor if you have metastatic cancer affecting your brain.

- Alymsys can increase the risk of bleeding in your lungs, including coughing or spitting blood. Please discuss with your doctor if you noticed this previously.

- Alymsys 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.

- Alymsys may cause infections and a decreased number of your neutrophils (a type of blood cell important for your protection against bacteria).

- Alymsys can cause hypersensitivity (including anaphylactic shock) 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 Alymsys treatment. If you have headache, vision changes, confusion or seizure with or without high blood pressure, please contact your doctor.

- Death of bone tissue (osteonecrosis) in bones other than the jaw has been reported in patients under 18 years old when treated with Alymsys. 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 could be signs and symptoms of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience any of them.

Please consult your doctor, even if these above statements were only applicable to you in the past.
Before you are given Alymsys or while you are being treated with Alymsys:
- 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 Alymsys, 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 Alymsys.

Alymsys 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 Alymsys 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.

**Children and adolescents**
Alymsys 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.

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

Combinations of Alymsys 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 medicines.

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

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

**Pregnancy, breast-feeding and fertility**
You must not use this medicine if you are pregnant. Alymsys 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 Alymsys and for at least 6 months after the last dose of Alymsys.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

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

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

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.

**Driving and using machines**
Alymsys has not been shown to reduce your ability to drive or to use any tools or machines. However, sleepiness and fainting have been reported with Alymsys use. If you experience symptoms that affect your vision or concentration, or your ability to react, do not drive and use machines until symptoms disappear.

**Alymsys contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

## 3. How to use Alymsys

**Dosage and frequency of administration**
The dose of Alymsys 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 Alymsys that is right for you. You will be treated with Alymsys 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 Alymsys fails to stop your tumour growing. Your doctor will discuss this with you.

**Method and route of administration**
Do not shake the vial. Alymsys is a concentrate for solution for infusion. Depending on the dose prescribed for you, some or all of the contents of the Alymsys vial will be diluted with sodium chloride solution before use. A doctor or nurse will give you this diluted Alymsys 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.

**The administration of Alymsys should be temporarily discontinued**
- if you develop severe high blood pressure requiring treatment with blood pressure medicines,
- if you have problems with wound healing following surgery,
- if you undergo surgery.

**The administration of Alymsys should be permanently discontinued if you develop**
- severe high blood pressure which cannot be controlled by blood pressure medicines; or a sudden severe rise in blood pressure,
- presence of protein in your urine accompanied by swelling of your body,
- a hole in your gut wall,
- an abnormal tube-like connection or passage between the windpipe and the gullet, between internal organs and skin, between the vagina and any parts of the gut or between other tissues that are not normally connected (fistula), and are judged by your doctor to be severe,
- serious infections of the skin or deeper layers under the skin,
- a blood clot in your arteries,
- a blood clot in the blood vessels of your lungs,
- any severe bleeding.

**If too much of Alymsys is given**
- you may develop a severe migraine. If this happens you should talk to your doctor, pharmacist or nurse immediately.

**If a dose of Alymsys is missed**
- your doctor will decide when you should be given your next dose of Alymsys. You should discuss this with your doctor.

**If you stop treatment with Alymsys**
Stopping your treatment with Alymsys may stop the effect on tumour growth. Do not stop treatment with Alymsys unless you have discussed this with 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 side effects listed below were seen when Alymsys was given together with chemotherapy. This does not necessarily mean that these side effects were strictly caused by Alymsys.

**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) , swelling, lightheadedness, fast heartbeat and loss of consciousness.

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

Severe side effects, which may be **very common** (may affect more than 1 in 10 people), 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.

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Severe side effects, which may be **common** (may affect up to 1 in 10 people), include:
- allergic reactions (the signs may include breathing difficulty, facial redness, rash, low blood pressure or high blood pressure, low oxygen in your blood, chest pain, or nausea/vomiting),
- 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, which may be **rare** (may affect up to 1 in 1,000 people), include:
- sudden, severe allergic reaction with breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating and loss of consciousness (anaphylactic shock).

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,
- 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,
- an enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections),
- 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** (may affect more than 1 in 10 people) 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** (may affect up to 1 in 10 people) 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.

Alymsys 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.

**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 via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Alymsys

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 outer carton and on the vial label after the abbreviation 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.

Infusion solutions should be used immediately after dilution. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless the infusion solutions have been prepared in a sterile environment. When dilution has taken place in a sterile environment, Alymsys is stable for a period of up to 30 days at 2°C to 8°C after dilution and a period of up to 48 hours at temperatures not exceeding 30°C.

Do not use Alymsys if you notice any particulate matter or discolouration prior to administration.

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 protect the environment.

## 6. Contents of the pack and other information

**What Alymsys contains**
- The active substance is bevacizumab. Each mL of concentrate contains 25 mg of bevacizumab, corresponding to 1.4 to 16.5 mg/mL when diluted as recommended.
  Each 4 mL vial contains 100 mg of bevacizumab, corresponding to 1.4 mg/mL when diluted as recommended.
  Each 16 mL vial contains 400 mg of bevacizumab, corresponding to 16.5 mg/mL when diluted as recommended
- The other ingredients are trehalose dihydrate, monobasic sodium phosphate monohydrate, disodium phosphate, polysorbate 20 and water for injections (see section 2 "Alymsys contains sodium").

**What Alymsys looks like and contents of the pack**
Alymsys is a concentrate for solution for infusion (sterile concentrate). The concentrate is a colourless to yellowish or brownish liquid with opalescence in a glass vial with a rubber stopper. Each vial contains 100 mg bevacizumab in 4 mL of solution or 400 mg bevacizumab in 16 mL of solution. Each pack of Alymsys contains one vial.

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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