PACKAGE LEAFLET : INFORMATION FOR THE USER

ZALTRAP™ 25 mg/ml

concentration for solution for infusion

aflibercept

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again, or provide it to future healthcare providers.
- 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.

What is in this leaflet:

1. What ZALTRAP is and what it is used for

Pharmacotherapeutic group
What ZALTRAP is and how it works
ZALTRAP contains the active substance aflibercept, a protein that works by blocking the growth of new blood vessels within the tumour. The tumour needs nutrients and oxygen from blood in order to grow. By blocking the growth of blood vessels, ZALTRAP helps to stop or slow down the growth of the tumour.

Therapeutic indications
What ZALTRAP is used for
ZALTRAP is a medicine used to treat advanced cancers of the colon or rectum (parts of the large intestine) in adults. It will be given with other medicines called 'chemotherapy', including '5-fluorouracil', 'folinic acid', and 'irinotecan'.

2. What you need to know before you are given ZALTRAP

Contraindications
Do not use ZALTRAP:
- if you are allergic to aflibercept or any of the other ingredients of this medicine (listed in section 6);
- in your eye, since it may severely damage it.

Please also read the package leaflets for the other medicines ('chemotherapy') that are part of your treatment, to see if they are suitable for you. If you are unsure, ask your doctor, pharmacist or nurse if there are any reasons why you cannot use these medicines.

Appropriate precautions for use; special warnings
Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given ZALTRAP and during your treatment if:
- you have any bleeding problems or if you notice any bleeding after treatment (see section 4) or if you feel extreme tiredness, weakness, dizziness, or have changes in the colour of your stool. If the bleeding is severe, your doctor will stop your treatment with ZALTRAP. This is because ZALTRAP may increase the risk of bleeding;
- you have illnesses where your gut is inflamed, such as an infected section of the bowel wall (also called 'diverticulitis'), stomach ulcers or colitis. This is because ZALTRAP may increase the risk of developing holes in the gut wall. If this should happen to you, your doctor will stop your treatment with ZALTRAP;
- you have had any abnormal tube-like connections or passageways inside the body between internal organs and skin or other tissues (also called 'fistula'). If you develop such a connection or passageway during treatment, your doctor will stop your treatment with ZALTRAP;
- you have high blood pressure. Zaltrap may increase blood pressure (see section 4) and your doctor will need to monitor your blood pressure and may adjust your blood pressure medicines or your dose of ZALTRAP. It is therefore also important to tell your doctor, pharmacist or nurse if you have other heart problems since high blood pressure could make these worse;
- you experience signs of a blood clot (see section 4). The signs of a blood clot may vary depending on where it appears (e.g. lungs, leg, heart or brain) but may include symptoms such as chest pain, coughing, being short of breath or having difficulty breathing. Other signs may include swelling in one or both legs, pain or tenderness in one or both legs, discolouration and warmth of the skin on the affected leg or visible veins. It may also present itself as a sudden numb or weak feeling in the face, arms, or legs. Other signs include feeling confused, problems with sight, walking, coordination or balance, problems in saying words or slurring of speech. If you experience any of these symptoms, talk to your doctor immediatley since your doctor may want to treat your symptoms and stop your treatment with ZALTRAP;
- you have kidney problems (protein in the urine), since your doctor will monitor your kidney function and may need to adjust your dose of ZALTRAP;
- your number of white blood cells is too low. Zaltrap may reduce the number of white cells in your blood and your doctor will monitor your white blood cell count and may give you additional medicines to increase it. If your white blood cells are low, your doctor may need to delay your treatment;
- you have severe or long-lasting diarrhoea, feel sick (nausea) or are being sick (vomiting) – these could cause severe loss of body fluids (called 'dehydration'). Your doctor may need to treat you with other medicines and/or fluids given intravenously;
- you have ever had any allergies – serious allergic reactions can happen during treatment with ZALTRAP (see section 4). Your doctor may need to treat the allergic reaction or stop your treatment with ZALTRAP;
- you have had a tooth removed or any form of surgery in the last 4 weeks, or you are going to have an operation or a dental or medical procedure, or you have a wound after surgery that has not healed. Your doctor will temporarily stop the treatment before and after surgery;
- you experience fits (seizures). If you experience changes in your vision or confusion, your doctor may stop your treatment with ZALTRAP;
- you are 65 years of age or older and experience diarrhoea, dizziness, weakness, weight loss, or severe loss of body fluids (called 'dehydration'). Your doctor should monitor you carefully;
- your level of everyday activities is limited or worsens on treatment. Your doctor should monitor you carefully.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before you are given ZALTRAP and during your treatment.
During treatment, your doctor will perform a number of tests to monitor the function of your body and how the medicine is working. Tests may include blood and urine tests, x-ray or other scanning techniques and/or other tests.
ZALTRAP is given by a drip (infusion) into one of your veins ('intra-venous') to treat advanced cancers of the colon or rectum. ZALTRAP must not be injected into the eye, since it may severely damage it.

Children and adolescents
Do not give this medicine to children or adolescents under the age of 18 years because the safety and benefit of using ZALTRAP in children and adolescents have not been shown.

Other medicines and ZALTRAP
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This may include medicines obtained without a prescription or herbal medicines.

Pregnancy, breast-feeding and fertility
You should not use ZALTRAP during pregnancy unless you and your doctor decide that the benefit for you is greater than any possible risk to you or your unborn baby.
If you are a woman that could become pregnant you should use effective contraception (see "Contraception" section below for details on male and female contraception). This medicine may harm your unborn baby since it may stop new blood vessels from forming.
Talk to your doctor before being given this medicine if you are breast-feeding. This is because it is not known if the medicine passes into breast milk.
ZALTRAP may affect male and female fertility. Talk to your doctor for advice if you plan to have or father a child.

Contraception
Men and women who can father or have children should use effective contraception:
- during treatment with ZALTRAP and
- for at least 6 months after the last dose of treatment.

Driving and using machines
You may have side effects that affect your sight, concentration or ability to react. If this happens, do not drive or use any tools or machines.

3. How ZALTRAP is given

ZALTRAP will be given to you by a doctor or a nurse that is experienced in the use of 'chemotherapy'. It is given by a drip (infusion) into one of your veins ('intra-venous'). ZALTRAP must not be injected into the eye, since it may severely damage it.
The medicine must be diluted before it is given. Practical information for handling and administration of ZALTRAP for doctors, nurses and pharmacists when using this medicine, is provided with this leaflet.

How much and how often you will receive treatment
- The drip (infusion) lasts for about 1 hour.
- You will usually be given an infusion once every 2 weeks.
- The recommended dose is 4 mg for each kilogram of your body weight. Your doctor will decide the correct dose for you.
- Your doctor will decide how often you will be given the medicine and if you need a change in the dose.

ZALTRAP will be given with other chemotherapy medicines including '5-fluorouracil', 'folinic acid', and 'irinotecan'. Your doctor will decide the appropriate doses for these other chemotherapy medicines.
Treatment will continue as long as your doctor thinks the treatment is of benefit to you, and the side effects are acceptable.
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 ZALTRAP was given together with chemotherapy.

Serious side effects
Talk to your doctor straight away, if you notice any of the following serious side effects – you may need urgent medical treatment:
- **Bleeding: Very common** (may affect more than 1 in 10 people) – this includes bleeding from the nose, but may also include severe bleeding in your gut and other parts of the body, which may lead to death. Signs may include feeling very tired, weak, and/or dizzy, or having changes in the colour of your stool.
- **Holes in the gut** (also called 'gastro-intestinal perforation'): **Uncommon** (may affect up to 1 in 100 people) – this is a hole in the stomach, food pipe, gut or bowel. This can lead to death. Signs may include stomach pain, being sick (vomiting), fever or chills.
- **Connections or passageways inside the body between internal organs and skin or other tissues** (also called 'fistula'): **Common** (may affect up to 1 in 10 people) – these abnormal tube-like connections or passageways can form for example, between the gut and your skin. Sometimes, depending on where this happens, you may get an unusual discharge at that place. If you are uncertain contact your doctor.
- **High blood pressure** (also called 'hypertension'): **Very common** (may affect more than 1 in 10 people) – this may develop or get worse. If blood pressure is not controlled, it may cause stroke, heart and kidney problems. Your doctor should check your blood pressure throughout your treatment.
- **Blocking of the arteries by a blood clot** (also called 'arterial thrombo-embolic events'): **Common** (may affect up to 1 in 10 people) – this may lead to a stroke or heart attack. Signs may include chest pain or heaviness in the chest, sudden numb or weak feeling in the face, arms, or legs. Other signs include feeling confused; problems with sight, walking, coordination or balance; or problems in saying words or slurring of speech.
- **Blocking of the veins by a blood clot** (also called 'venous thrombo-embolic events'): **Common** (may affect up to 1 in 10 people) – this may include a blood clot in the lungs or legs. Signs may include chest pain, coughing, being short of breath, difficulty breathing or coughing up blood. Other signs include swelling in one or both legs, pain or tenderness in one or both legs while standing or walking, warmth of the skin on the affected leg, red or discoloured skin in the affected leg or visible veins.
- **Protein in the urine** (also called 'proteinuria'): **Very common** (may affect more than 1 in 10 people) – this is very commonly seen in tests. This may include swelling of the feet or whole body and may be related to kidney disease.
- **Low white blood cell count** (also called 'neutropenia'): **Very common** (may affect more than 1 in 10 people) – this can cause serious infections. Your doctor will do blood tests regularly to check your white blood cell counts throughout your treatment. They may also prescribe a medicine called 'G-CSF' to help prevent complications if your white blood cell count is too low. Signs of infection may include fever, chills, cough, burning on passing water or muscle ache. You should take your temperature often during treatment with this medicine.
- **Diarrhoea and dehydration: Very common** (may affect more than 1 in 10 people) for diarrhoea and **Common** (may affect up to 1 in 10 people) for dehydration – severe diarrhoea and being sick (vomiting) can cause you to lose too much body fluid (called 'dehydration') and body salts (electrolytes). Signs may include dizziness especially when going from sitting to standing. You may need to go to the hospital for treatment. Your doctor may give you medicines to stop or treat diarrhoea and being sick (vomiting).
- **Allergic reactions: Common** (may affect up to 1 in 10 people) – these may happen within a few minutes after your infusion. Signs of allergic reaction may include rash or itching, skin redness, feeling dizzy or faint, being short of breath, tight chest or throat, or swelling of the face. Tell your doctor or nurse straight away if you have any of these signs during or soon after an infusion of ZALTRAP.
- **Wounds which heal slowly or not at all: Uncommon** (may affect up to 1 in 100 people) – this is when a scar has trouble healing or staying closed, or if a healed wound re-opens. Your doctor will stop this medicine for at least 4 weeks before planned surgery and until the wound is fully healed.
- **A side effect which affects your nervous system** (called 'posterior reversible encephalopathy syndrome' or PRES): **Uncommon** (may affect up to 1 in 100 people) – signs may include headache, sight changes, feeling confused or fits with or without high blood pressure.

Talk to your doctor straight away, if you notice any of the side effects above.

Other side effects include:
Very common (may affect more than 1 in 10 people)
- drop in the number of white blood cells (leucopenia),
- drop in the number of certain cells in the blood that help it to clot (thrombocytopenia),
- decreased appetite,
- headache,
- nose bleeds,
- change of the voice, e.g. developing a hoarse voice,
- difficulty when breathing,
- painful sores in the mouth,
- stomach pain,
- swelling and numbness of the hands and feet that happens with chemotherapy (called 'Palmar-Plantar Erythrodysaesthesia syndrome'),
- feeling tired or weak,
- weight loss ,
- kidney problem with an increase in creatinine (a marker of kidney function),
- liver problem with an increase in liver enzymes.

Common (may affect up to 1 in 10 people)
- urinary tract infection,
- inflammation inside the nose and upper part of the throat,
- pain in the mouth or throat,
- runny nose,
- haemorrhoids, bleeding or pain in the back passage,
- inflammation inside the mouth,
- toothache,
- changes in the colour of the skin.

Uncommon (may affect up to 1 in 100 people)
- an increase in protein in the urine, an increase in cholesterol in the blood, and swelling from excess fluid (oedema) (also called 'nephrotic syndrome'),
- blood clot in very small blood vessels (also called 'thrombotic microangiopathy').

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

5. How to store ZALTRAP

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 label of the vial after EXP. The expiry date refers to the last day of that month.
Store in a refrigerator (2°C – 8°C).
Store in the original package in order to protect from light.
Information about storage and the time to use ZALTRAP, after it has been diluted and is ready to use, is described in the 'Practical information for healthcare professionals on preparation and handling of ZALTRAP 25 mg/ml concentrate for solution for infusion' at the end of this leaflet.
Do not use ZALTRAP if you notice particles or discolouration of the medicine in the vial or infusion bag.
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 ZALTRAP contains
- The active substance is aflibercept. One ml of concentrate contains 25 mg aflibercept. One 4 ml vial of concentrate contains 100 mg aflibercept. One 8 ml vial of concentrate contains 200 mg aflibercept.
- The other ingredients are: sucrose, sodium chloride, sodium citrate dihydrate, citric acid monohydrate, polysorbate 20, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, sodium hydroxide and/or hydrochloric acid and water for injections.

What ZALTRAP looks like and contents of the pack
ZALTRAP is a concentrate for solution for infusion (sterile concentrate). The concentrate is a clear, colourless to pale yellow solution.
- 4 ml of concentrate in a 5 ml clear borosilicate glass vial (type I), sealed by a flanged stopper with flip-off cap and inserted coated sealing disc. Pack size of 1 vial.
- 8 ml of concentrate in a 10 ml clear borosilicate glass vial (type I), sealed by a flanged stopper with flip-off cap and inserted coated sealing disc. Pack size of 1 vial.

Not all pack sizes may be marketed.

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The following information is intended for healthcare professionals only:

PRACTICAL INFORMATION FOR HEALTHCARE PROFESSIONALS
ON PREPARATION AND HANDLING OF ZALTRAP 25 mg/ml CONCENTRATE FOR SOLUTION FOR INFUSION
This information supplements the sections 3 and 5 for the user.
It is important that you read the entire content of this procedure prior to the preparation of infusion solution.
ZALTRAP is a sterile, preservative-free and non-pyrogenic concentrate, therefore the solution for infusion should be prepared by a healthcare professional using safe-handling procedures and aseptic technique.
Caution should be exercised when handling ZALTRAP, taking into account the use of containment devices, personal protective equipment (e.g. gloves), and preparation procedures.

Preparation of the infusion solution
- Inspect the ZALTRAP vial visually prior to use. The concentrate solution must be clear and without particles.
- Based on the required dose for the patient, withdraw the necessary volume of ZALTRAP concentrate from the vial. More than one vial could be needed for the preparation of the infusion solution.
- Dilute it to the required administration volume with sodium chloride 9 mg/ml (0.9 %) solution or 5% glucose solution for infusion. The concentration of the final ZALTRAP solution for intravenous infusion should be kept within the range of 0.6 mg/ml to 8 mg/ml of aflibercept.
- PVC containing DEHP infusion bags or polyolefin infusion bags should be used.
- The diluted solution should be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution should be discarded.
- ZALTRAP is a single-use vial. Do not re-enter the vial after the initial puncture. Any unused concentrate should be discarded.

Shelf-life after dilution in the infusion bag
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C and for 8 hours at 25°C.
From a microbiological point of view, the solution for infusion should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

Method of administration
ZALTRAP is to be administered only as an intravenous infusion over 1 hour. Due to hyperosmolality (1000 mOsmol/kg) of the ZALTRAP concentrate, undiluted ZALTRAP concentrate must not be administered as an intravenous push or bolus.
ZALTRAP must not be administered as an intravitreal injection (see section 2 of the package leaflet).
Each vial of concentrate for solution for infusion is for single use (single-dose) only.
Diluted solutions of ZALTRAP should be administered using infusion sets containing a 0.2 micron polyethersulfone filter.
The infusion sets should be made of one of the following materials:
- polyvinyl chloride (PVC) containing bis(2-ethylhexyl) phthalate (DEHP)
- DEHP free PVC containing trioctyl-trimellitate (TOTM)
- polypropylene
- polyethylene lined PVC
- polyurethane

Filters made of polyvinylidene fluoride (PVDF) or nylon must not be used.

Disposal
Any unused medicine or waste material should be disposed of in accordance with local requirements.