The following information is intended for healthcare professionals only:

Eloxatin® 5 mg/ml concentrate for solution for infusion
oxaliplatin

SANOFI

GUIDE FOR THE PREPARATION OF ELOXATIN 5 mg/ml concentrate for solution for infusion

It is important that you read all of this procedure before preparing Eloxatin solution for infusion.

1. COMPOSITION

Eloxatin is a clear, colorless solution containing 5 mg/mL of oxaliplatin as a solution in water for injections.

2. PRESENTATION

Eloxatin is supplied in a single-dose vial. Each box contains 1 vial of Eloxatin (50 mg, 100 mg or 200 mg).

(Type I colorless glass) vials containing 10 mL of oxaliplatin solution (50 mg) with a bromobutyl rubber stopper.

(Type I colorless glass) vials containing 20 mL of oxaliplatin solution (100 mg) with a bromobutyl rubber stopper.

(Type I colorless glass) vials containing 40 mL of oxaliplatin solution (200 mg) with a bromobutyl rubber stopper.

Eloxatin in its original packaging:

This medicinal product must be stored in its outer packaging in order to protect from light. Do not freeze.

Solution for infusion:

After dilution of the solution in 5% glucose solution (50 mg/mL), physical and chemical stability has been demonstrated for 48 hours at a temperature of between 2 °C and 8 °C or for 24 hours at 25 °C.

However, from a microbiological point of view, the solution for infusion must be used immediately. If it is not used immediately, storage times and conditions after dilution and before use are the sole responsibility of the user, and should not exceed 24 hours at a temperature of between + 2 °C and + 8 °C, unless the dilution has been carried out under controlled and validated aseptic conditions.

Inspect the solution visually prior to use. Only clear solutions without particles should be used.

The medicinal product is for single use only. Any unused solution should be discarded.

3. RECOMMENDATIONS FOR SAFE HANDLING

As with other potentially toxic compounds, caution should be exercised when handling and preparing oxaliplatin solutions.

Instructions for handling:

The handling of this cytotoxic agent by healthcare personnel requires every precaution to guarantee the protection of the handlers and their surroundings.

The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used, under conditions that guarantee integrity of the medicinal product and the protection of the environment and in particular the protection of the personnel handling the medicines, in accordance with hospital policy. The solutions must be prepared in an area intended for this purpose. Smoking, eating and drinking are not allowed in these facilities.

Personnel must be provided with appropriate handling materials, notably long sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area, containers and collection bags for waste.

Excreta and vomit must be handled with caution.

Pregnant women must be warned and should avoid handling cytotoxic agents.

Any broken containers must be treated with the same precautions and considered as contaminated waste. Contaminated waste should be incinerated in suitably labeled rigid containers (see section "Disposal of waste" below).

If the concentrate for solution or solution for infusion should come into contact with skin, wash immediately and thoroughly with water.

If the concentrate for solution or solution for infusion should come into contact with a mucous membrane, wash immediately and thoroughly with water.

4. PREPARATION FOR INTRAVENOUS ADMINISTRATION

Special precautions for administration

NEVER use injection equipment containing aluminum. NEVER administer undiluted.

Only use 5% glucose solution (50 mg/mL) for dilution. DO NOT dilute with chloride-containing solutions or sodium chloride solution.

NEVER mix with any other medicinal products in the same infusion bag or administer simultaneously by the same infusion line.

DO NOT mix with alkaline drugs or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of other active substances. Alkaline drugs or solutions adversely affect the stability of oxaliplatin.

Instruction for use with folinic acid (as disodium folinate or calcium folinate)

The oxaliplatin 85 mg/m² intravenous infusion in 250 to 500 mL of 5% glucose solution (50 mg/mL) is administered at the same time as a folinic acid intravenous infusion in 5% glucose solution (50 mg/mL), over 2 to 6 hours, using a Y-line placed immediately before the injection site.

These two medicinal products must not be mixed in the same infusion bag. Folinic acid must not contain trometamol as an excipient and must only be diluted using isotonic 5% glucose solution (50 mg/mL), never in alkaline solutions or sodium chloride solution or chloride-containing solutions.

Instructions for use with 5-fluorouracil

Oxaliplatin should always be administered before fluoropyrimidines, i.e. 5-fluorouracil. After oxaliplatin administration, flush the line and then administer 5-fluorouracil.

For additional information about medicinal products used in combination with oxaliplatin, see the corresponding Summary of Product Characteristics of the manufacturer in question.

ONLY USE the recommended solvents (see below).

Only clear solutions without particles should be used.

4.1. Preparation of the solution for infusion

Withdraw the required amount of concentrate for solution from the vial and then dilute with 250 to 500 mL of 5% glucose solution (50 mg/mL) to obtain an oxaliplatin concentration of between 0.2 and 0.7 mg/mL. The concentration range for which physical and chemical stability of oxaliplatin has been demonstrated is 0.2 to 2.0 mg/mL.

Administer via intravenous infusion.

After dilution in 5% glucose solution (50 mg/mL), physical and chemical stability has been demonstrated for 48 hours at a temperature of between + 2 °C and + 8 °C and for 24 hours at + 25 °C.

However, from a microbiological point of view, the solution for infusion should be used immediately.

If it is not used immediately, the storage times and conditions before use are the sole responsibility of the user and generally should not exceed 24 hours at a temperature of between + 2 °C and + 8 °C, unless the dilution has been carried out under controlled and validated aseptic conditions.

Inspect the solution visually prior to use. Only clear solutions without particles should be used.

The medicinal product is for single use only. Any unused solution should be discarded (see section "Disposal of waste" below).

NEVER use chloride-containing solutions or sodium chloride solution for dilution.

The compatibility of oxaliplatin solution for infusion has been tested with standard, PVC-based administration sets.

4.2. Solution for infusion

The administration of oxaliplatin does not require prehydration.

Oxaliplatin diluted in 250 to 500 mL of 5% glucose solution (50 mg/mL) to obtain a concentration of over 0.2 mg/mL must be infused via a central venous line or a peripheral vein over 2 to 6 hours. When oxaliplatin is administered with 5-fluorouracil, the oxaliplatin infusion must precede the administration of 5-fluorouracil.

4.3. Disposal of waste

Any unused medicinal product as well as all materials used for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents in accordance with current legal requirements related to the disposal of toxic waste.

PACKAGE LEAFLET:
INFORMATION FOR THE USER

Eloxatin® 5 mg/ml concentrate for solution for infusion
oxaliplatin

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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.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Eloxatin is and what it is used for
2. What you need to know before you use Eloxatin
3. How to use Eloxatin
4. Possible side effects
5. How to store Eloxatin
6. Contents of the pack and other information

1. WHAT ELOXATIN IS AND WHAT IT IS USED FOR

The active substance of Eloxatin is oxaliplatin.

Eloxatin is used to treat cancer of the large intestine (treatment of stage III colon cancer after complete resection of the primary tumor; metastatic colorectal cancer of colon and rectum).

Eloxatin is used in combination with other anticancer medicines called 5-fluorouracil and folinic acid.

Eloxatin is an anticancer medicine that contains platinum.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE ELOXATIN

Contraindications:

Do not use Eloxatin:
- if you are allergic to oxaliplatin if you are breast-feeding,
- if you have a significantly decreased number of blood cells,
- if you have tingling and numbness in the fingers and/or toes, and have difficulty performing delicate tasks, such as buttoning clothes,
- if you have severe kidney problems.

Warnings and precautions

Talk to your doctor or pharmacist before using Eloxatin
- if you have had an allergic reaction to platinum-containing medicines, such as carboplatin or cisplatin. Allergic reactions can occur during any oxaliplatin infusion,
- if you have moderate or mild kidney problems,
- if you have liver problems or your liver function test results are not normal after receiving treatment,
- if you have or had heart disorders such as an abnormal electrical signal called prolongation of the QT interval, an irregular heartbeat, or a family history of heart problems.

Tell your doctor immediately if you have any of the following side effects. Your doctor may need to treat you for these effects. Your doctor may need to reduce the Eloxatin dose, or postpone or stop your treatment with Eloxatin.
- if you have an unpleasant feeling in your throat, particularly when swallowing, or if you have trouble breathing during treatment, talk to your doctor,
- if you have problems with the nerves in your hands or feet, such as numbness or tingling, or reduced feeling in your hands or feet, talk to your doctor,
- if you have headaches, impaired mental function, seizures or vision problems from blurry vision to blindness, talk to your doctor,
- if you are nauseous or vomiting, talk to your doctor,
- if you have severe diarrhea, talk to your doctor,
- if your lips are painful or you have mouth ulcers (inflammation of the mouth or another mucous membrane), talk to your doctor,
- if you have diarrhea or a decreased number of white blood cells or platelets, talk to your doctor. Your doctor may reduce the Eloxatin dose or postpone your treatment with Eloxatin,
- if you have unexplained respiratory symptoms such as cough or any other breathing problems, talk to your doctor. Your doctor may stop your treatment with Eloxatin.
- if you have extreme fatigue, difficulty breathing or a kidney disease resulting in the passage of little or no urine (symptoms of acute renal failure), talk to your doctor.
- If you have fever (temperature above or equal to 38 °C) or shivering, which could be signs of an infection, tell your doctor immediately. You may have sepsis (infection of the blood).
- if you have fever above 38 °C, tell your doctor. Your doctor may check whether you also have a decreased number of white blood cells
- If you have unexpected bleeding or bruising (disseminated intravascular coagulation), tell your doctor as these could be signs of blood clots in the small blood vessels of your body.
- If you faint (lose consciousness) or have an irregular heart beat while taking Eloxatin, tell your doctor immediately as this could be a sign of a serious heart condition.
- if you experience muscle pain and swelling, in combination with weakness, fever and red-brown urine, tell your doctor. These could be signs of muscle damage (rhabdomyolysis) and could lead to kidney problems or other complications.
- if you have abdominal pain, nausea, bloody vomit or vomit that looks like "coffee-grounds", or dark-colored/tarry stools, this could be a sign of an intestinal ulcer (gastrointestinal ulcers, with bleeding or possible perforation) and you should tell your doctor.
- if you have abdominal (stomach) pain, bloody diarrhea, nausea and/or vomiting, which may be caused by a reduction of blood flow to your gut wall (intestinal ischemia), tell your doctor.

Other medicines and Eloxatin

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

Pregnancy, breast-feeding and fertility

Pregnancy
- You should not plan to become pregnant during treatment with oxaliplatin; you should therefore use an effective method of contraception. Women should use a suitable method of contraception during treatment and for 4 months after the end of treatment.
- If you are pregnant or are planning a pregnancy, it is very important that you discuss this with your doctor **before** you receive any treatment.
- If you get pregnant during your treatment, you must tell your doctor immediately.

Breast-feeding
- You must not breast-feed while you are being treated with oxaliplatin.

Fertility
- Oxaliplatin may cause irreversible infertility. Male patients are therefore advised to seek advice on conservation of sperm prior to treatment.
- Male patients are also advised not to father a child during and up to 6 months after the end of treatment, and to use an appropriate method of contraception during this period.

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

Driving and using machines

Oxaliplatin treatment may result in a higher risk of dizziness, nausea and vomiting, and other neurological symptoms that affect walking and balance. If this happens, you should not drive or operate machinery. If you have vision problems while taking Eloxatin, do not drive, operate heavy machines or engage in dangerous activities.

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3. HOW TO USE ELOXATIN

Eloxatin is for adults only.

For single use only.

Dosage

The dose of Eloxatin is based on your body surface area. This is calculated from your height and weight.

The usual dose for adults, including the elderly, is 85 mg/m² of body surface area. The dose you you are given will also depend on your blood test results and whether you have previously experienced side effects with Eloxatin.

Method of administration

Eloxatin will be prescribed for you by a specialist in cancer treatment.

You will be treated by a healthcare professional who will have determined the required dose of Eloxatin.

Eloxatin is injected into one of your veins (a slow intravenous infusion over a 2 to 6 hour period).

Eloxatin will be given to you at the same time as folinic acid and before any infusion of 5-fluorouracil.

Frequency of administration

Eloxatin infusions are generally given once every 2 weeks.

Duration of treatment

Your doctor will determine the duration of treatment.

Your treatment will last a maximum of 6 months if you are receiving it after complete resection of your tumor.

If you receive more Eloxatin than you should

As this medicine is administered by a healthcare professional, it is very unlikely that you will be given too little or too much. In case of overdose, some of the side effects may be worsened. Your doctor may have to give you appropriate treatment for these side effects.

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

4. POSSIBLE SIDE EFFECTS

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

If you experience any side effects, it is important that you inform your doctor before your next treatment.

The side effects you may experience are described below.

Tell your doctor immediately if you notice any of the following side effects:
- symptoms of an allergy or an anaphylactic reaction with the sudden appearance of signs such as skin rash, itching or hives, difficulty swallowing, swelling of the face, lips, tongue or other parts of the body, difficulty breathing, noisy or labored breathing or extreme fatigue (you feel as if you might faint). In most cases these symptoms occur during or immediately after infusion; however, delayed allergic reactions have also been observed hours or even days after the infusion.
- abnormal bruising, bleeding or signs of infection such as sore throat and a high temperature,
- persistent or severe diarrhea or vomiting,
- blood or dark brown particles in your vomit,
- inflammation of the mouth or another mucous membrane (painful lips or mouth ulcers),
- breathing difficulties such as a dry or productive cough, difficulty breathing or noisy breathing, breathlessness or whistling, as these could be a sign of a serious lung disease which could be fatal,
- a group of symptoms that may or may not be associated with high blood pressure, such as headache, impaired mental function, seizures and abnormal vision (from blurry vision to vision loss) (symptoms of reversible posterior leukoencephalopathy syndrome, a rare neurological disorder),
- symptoms of stroke (including sharp, sudden headaches, confusion, vision disturbances in one or both eyes, numbness or weakness of the face, arm or leg, generally only one-sided, droopy face, difficulty walking, feeling faint, loss of balance and difficulty speaking),
- extreme fatigue with a decreased number of red blood cells and difficulty breathing (hemolytic anemia), alone or in combination with low platelet levels and abnormal bruising (thrombocytopenia) and kidney disease resulting in the passage of little or no urine (symptoms of hemolytic uremic syndrome).

The other side effects of Eloxatin are as follows:

Very common (may affect more than 1 in 10 patients)
- Eloxatin can affect the nerves (peripheral neuropathy). You may feel tingling and/or numbness in the fingers, toes, around the mouth or in the throat, sometimes with cramps. These effects are often triggered by exposure to cold (e.g. opening a refrigerator or holding a cold drink). You may also have difficulty performing delicate tasks, such as buttoning clothes. Although in the majority of cases these symptoms spontaneously resolve completely when treatment is stopped, there is a possibility of persistent symptoms of peripheral sensory neuropathy after the end of treatment. Some people have experienced tingling, shock-like sensations when lifting their arms or flexing their neck.
- Eloxatin can sometimes cause an unpleasant sensation in the throat, in particular when swallowing, and give the feeling of breathlessness. This feeling, if it happens, usually occurs during or within hours of the infusion and may be triggered by exposure to the cold. Although unpleasant, it will not last long and goes away without needing treatment. Because of this, your doctor may decide to adjust your treatment.
- Eloxatin may cause diarrhea, moderate nausea (feeling like vomiting) and vomiting. Your doctor may prescribe you medicine to prevent these symptoms before and after your treatment.
- Eloxatin causes temporary decrease in the number of blood cells. A decrease in the number of red blood cells can cause anemia, a decreased number of platelets can cause abnormal bleeding or bruising, and a decreased number of white blood cells may make you more prone to infections. Your doctor will take blood samples to check that you have enough blood cells before you start treatment and before each subsequent course.
- A feeling of discomfort at the injection site during the infusion,
- Fever, shivering, fatigue (moderate or severe), pain,
- Weight fluctuation, loss or lack of appetite, taste disorders, constipation,
- Headache, back pain,
- Muscle spasms, neck stiffness, abnormal feeling of the tongue possibly altering speech, inflammation of the mouth or of another mucous membrane (painful lips or mouth ulcers),
- Stomach pain,
- Abnormal bleeding including nose bleeds,
- Cough and difficulty breathing,
- Allergic reactions, skin rash which may be red and itchy, moderate hair loss (alopecia),
- Abnormal blood test results including liver function tests.

Common (may affect up to 1 in 10 patients)
- Infection caused by a decreased number of white blood cells,
- Serious blood infection in addition to a decrease in white blood cells (neutropenic sepsis), which can be fatal,
- Decrease in white blood cells accompanied by fever (above 38.3 °C) or a prolonged fever (above 38 °C) for more than one hour (febrile neutropenia),
- Indigestion and heart burn, hiccups, flushing, dizziness,
- Increased sweating and nail disorders, flaking skin,
- Chest pain,
- Lung disorders and runny nose,
- Joint and bone pain,
- Pain on passing urine and changes in kidney function, change in frequency of urination, dehydration,
- Blood in the urine and stools, swelling of the veins, blood clots in the lungs,
- High blood pressure,
- Depression and insomnia,
- Conjunctivitis and vision problems,
- Decreased levels of calcium in the blood,
- Falls.

Uncommon (may affect up to 1 in 100 patients)
- Serious blood infection (sepsis), which can be fatal,
- Blockage or swelling of the intestines,
- Nervousness.

Rare (may affect up to 1 in 1 000 patients)
- Loss of hearing,
- Scarring and thickening in the lungs with difficulty breathing (interstitial lung disease), sometimes fatal,
- Reversible short-term loss of vision,
- Unexpected bleeding or bruising caused by widespread blood clots throughout the small blood vessels of the body (disseminated intravascular coagulation), which can be fatal.

Very rare (may affect up to 1 in 10 000 patients)
- Blood or dark brown particles in your vomit,
- Kidney disease resulting in the passage of little or no urine (symptoms of acute renal failure),
- Problems related to blood vessels in the liver.

Frequency not known (cannot be estimated from the available data)
- Allergic vasculitis (inflammation of blood vessels),
- Auto-immune reactions leading to a decrease of all blood cell lines (autoimmune pancytopenia),
- Serious blood infection and low blood pressure (septic shock), which can be fatal,
- Seizures (uncontrolled shaking of the body),
- Throat spasms, making it difficult to breathe,
- Extreme fatigue with a decreased number of red blood cells and difficulty breathing (hemolytic anemia), alone or in combination with low platelet levels and kidney disease resulting in the passage of little or no urine (symptoms of hemolytic uremic syndrome), which can be fatal, have been reported,
- Abnormal heart rhythm (QT prolongation), that can be seen on an electrocardiogram (ECG), which can be fatal,
- Myocardial infarction (heart attack), angina pectoris (chest pain or discomfort),
- Muscle pain and swelling, in combination with weakness, fever, or red-brown urine (symptoms of muscle damage called rhabdomyolysis), which can be fatal,
- Swelling of the throat (swelling of the esophageal mucosa - the tube that joins the mouth to the stomach - which causes pain and difficulty swallowing),
- Abdominal pain, nausea, bloody vomit or vomit that looks like coffee grounds, dark-colored/tarry stools (symptoms of gastrointestinal ulcer, with potential bleeding or perforation), which can be fatal,
- Decreased blood flow to the intestine (intestinal ischemia), which can be fatal,
- Risk of new cancers, Leukemia, a type of cancer of the blood, has been reported in patients after taking Eloxatin in combination with some other medicines, Talk to your doctor about the possible increase risk of this type of cancer when taking Eloxatin in combination with some other medicines.

Reporting of side effects

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

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE ELOXATIN

KEEP THIS MEDICINE OUT OF THE SIGHT AND REACH OF CHILDREN.

Store below 30°C.

Before dilution, keep the vial in its original packaging in order to protect from light. Do not freeze.

Do not use this medicine after the expiry date which is stated on the carton and vial labels. The expiry date refers to the last day of that month.

Eloxatin must not come into contact with the eyes or skin. If this occurs, tell your doctor or nurse immediately.

As soon as the infusion has ended, Eloxatin must be disposed of carefully by the doctor or nurse.

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 Eloxatin 5 mg/mL concentrate for solution for infusion contains

The active substance is:
Oxaliplatin.....5 mg

For 1 mL of concentrate for solution for infusion.

10 mL of concentrate for solution for infusion contains 50 mg of oxaliplatin.

20 mL of concentrate for solution for infusion contains 100 mg of oxaliplatin.

40 mL of concentrate for solution for infusion contains 200 mg of oxaliplatin.

The other ingredient is: water for injections.

What Eloxatin 5 mg/mL concentrate for solution for infusion looks like and contents of the pack

Eloxatin is supplied as a concentrate for solution for infusion.

Each box contains 1 vial of 50 mg, 100 mg or 200 mg of oxaliplatin in water for injections.

Not all pack sizes may be marketed.

Marketing Authorization Holder

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