Package leaflet: Information for the user

Kadcyla 100 mg powder for concentrate for solution for infusion
Kadcyla 160 mg powder for concentrate for solution for infusion
trastuzumab emtansine

Read all of this leaflet carefully before you start being given 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 Kadcyla is and what it is used for

What Kadcyla is
Kadcyla contains the active substance trastuzumab emtansine, which is made up of two parts that are linked together:
- trastuzumab - a monoclonal antibody that binds selectively to an antigen (a target protein) called human epidermal growth factor receptor 2 (HER2). HER2 is found in large amounts on the surface of some cancer cells where it stimulates their growth. When trastuzumab binds to HER2 it can stop the cancer cells growth and cause them to die.
- DM1 – an anti-cancer substance that becomes active once Kadcyla enters the cancer cell.

What Kadcyla is used for
Kadcyla is used to treat breast cancer in adults when:
- the cancer cells have many HER2 proteins on them - your doctor will test your cancer cells for this.
- you have already received the medicine trastuzumab and a medicine known as a taxane.
- the cancer has spread to areas near the breast or to other parts of your body (metastasized)
- the cancer has not spread to other parts of the body and treatment is going to be given after surgery (treatment after surgery is called adjuvant therapy).

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

You must not be given Kadcyla
- if you are allergic to trastuzumab emtansine or any of the other ingredients of this medicine (listed in section 6).

You should not be given Kadcyla if the above applies to you. If you are not sure, talk to your doctor or nurse before you are given Kadcyla.

Warnings and precautions
Talk to your doctor or nurse before you are given Kadcyla if:

- you have ever had a serious infusion-related reaction from using trastuzumab characterised by symptoms such as flushing, chills, fever, shortness of breath, difficulty breathing, rapid heartbeat or a drop in blood pressure.
- you are receiving treatment with blood thinning medicines (e.g. warfarin, heparin).
- you have any history of liver problems. Your doctor will check your blood to test your liver function before and regularly during treatment

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before you are given Kadcyla.

Look out for side effects
Kadcyla can make some existing conditions worse, or cause side effects. See section 4 for more details about what side effects to look out for.

Tell your doctor or nurse straight away if you notice any of the following serious side effects while you are given Kadcyla:

- **Breathing problems:** Kadcyla can cause serious breathing problems such as shortness of breath (either at rest or while performing any type of activity) and cough. These may be signs of inflammation of your lung, which may be serious, and even fatal. If you develop lung disease your doctor may stop treatment with this medicine.

- **Liver problems:** Kadcyla can cause inflammation or damage to cells in the liver that can stop the liver from functioning normally. Inflamed or injured liver cells may leak higher than normal amounts of certain substances (liver enzymes) into the bloodstream, resulting in elevated liver enzymes in blood tests. In most cases you will not have any symptoms. Some symptoms could be yellowing of your skin and whites of your eyes (jaundice). Your doctor will check your blood to test your liver function before and regularly during treatment.

  Another rare abnormality that can occur in the liver is a condition known as nodular regenerative hyperplasia (NRH). This abnormality causes the structure of the liver to change and can change how the liver functions. Over time, this may lead to symptoms such as a bloated sensation or swelling of the abdomen due to fluid accumulation or bleeding from abnormal blood vessels in the gullet or rectum.

- **Heart problems:** Kadcyla can weaken the heart muscle. When the heart muscle is weak, patients may develop symptoms such as shortness of breath at rest or when sleeping, chest pain, swollen legs or arms, and a sensation of rapid or irregular heartbeats. Your doctor will check your heart function before and regularly during treatment. You should tell your doctor immediately if you notice any of the above symptoms.

- **Infusion-related reactions or allergic reactions**: Kadcyla can cause flushing, shivering fits, fever, trouble breathing, low blood pressure, rapid heartbeat, sudden swelling of your face, tongue, or trouble swallowing during the infusion or after the infusion on the first day of treatment. Your doctor or nurse will check to see whether you are having any of these side effects. If you develop a reaction, they will slow down or stop the infusion and may give you treatment to counteract the side effects. The infusion may be continued after the symptoms improve.

- **Bleeding problems:** Kadcyla can lower the number of platelets in your blood. Platelets help your blood to clot so you might get unexpected bruising or bleeding (such as nose bleeds, bleeding from gums). Your doctor will check your blood regularly for decreased platelets. You should tell your doctor immediately if you notice any unexpected bruising or bleeding.

- **Neurological problems:** Kadcyla can damage nerves. You may experience tingling, pain, numbness, itching, crawling sensation, pins and needles in your hands and feet. Your doctor will monitor you for signs and symptoms of neurological problems.

- **Injection site reaction:** If you get a burning sensation, feel pain or tenderness at the infusion site during the infusion, this could indicate that Kadcyla has leaked outside the blood vessel. Tell your doctor or nurse immediately. If Kadcyla has leaked outside the blood vessel, increased pain, discoloration, blistering and sloughing of your skin (skin necrosis) can occur within days or weeks after the infusion.

Tell your doctor or nurse straight away if you notice any of the side effects above.

Children and adolescents
Kadcyla is not recommended for anyone under the age of 18 years. This is because there is no information on how well it works in this age group.

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

In particular, tell your doctor or pharmacist if you are taking:
- any medicines to thin your blood such as warfarin or decrease the ability to form blood clot such as aspirin
- medicines for fungal infections called ketoconazole, itraconazole or voriconazole
- antibiotics for infections called clarithromycin or telithromycin
- medicines for HIV called atazanavir, indinavir, nelfinavir, ritonavir or saquinavir.
- medicine for depression called nefazodone

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before you are given Kadcyla.

Pregnancy
Kadcyla is not recommended if you are pregnant because this medicine may cause harm to the unborn baby.
- Tell your doctor before using Kadcyla if you are pregnant, think you may be pregnant or are planning to have a baby.
- Use effective contraception to avoid becoming pregnant while you are being treated with Kadcyla. Talk to your doctor about the best contraception for you.
- You should continue to take your contraception for at least 7 months after your last dose of Kadcyla. Talk to your doctor before stopping your contraception.
- Male patients or their female partners should also use effective contraception.
- If you do become pregnant during treatment with Kadcyla, tell your doctor straight away.

Breast-feeding
You should not breast-feed during treatment with Kadcyla. Also you should not breast-feed for 7 months after your last infusion of Kadcyla. It is not known whether the ingredients in Kadcyla pass into breast-milk. Talk to your doctor about this.

Driving and using machines
It is not expected that Kadcyla will affect your ability to drive, cycle, use tools or machines. If you experience flushing, shivering fits, fever, trouble breathing, low blood pressure or a rapid heartbeat (infusion-related reaction), blurred vision, tiredness, headache, or dizziness, do not drive, cycle, use tools or machines until these reactions stop.

Important information about some of the ingredients of Kadcyla
This medicine contains less than 1 mmol sodium (23 mg) per dose. It is essentially ‘sodium- free’.

3. How you are given Kadcyla

Kadcyla will be given to you by a doctor or nurse in a hospital or clinic:
- It is given by a drip into a vein (intravenous infusion).
- You will be given one infusion every 3 weeks.

How much you will be given
- You will be given 3.6 mg of Kadcyla for every kilogram of your body weight. Your doctor will calculate the correct dose for you.
- The first infusion will be given to you over 90 minutes. You will be observed by a doctor or nurse while it is being given and for at least 90 minutes following the initial dose, in case you have any side effects.
- If the first infusion is well tolerated, the infusion on your next visit may be given over 30 minutes. You will be observed by a doctor or nurse while it is being given and for at least 30 minutes following the dose, in case you have any side effects.
- The total number of infusions that you will be given depends on how you respond to the treatment and which indication is treated.
- If you experience side effects, your doctor may decide to continue your treatment but lower your dose, delay the next dose or stop the treatment.

If you miss a Kadcyla treatment
If you forget or miss your Kadcyla appointment, make another appointment as soon as possible. Do not wait until your next planned visit.

If you stop Kadcyla treatment
Do not stop treatment with this medicine without talking to your doctor first.

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

4. Possible side effects

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

Tell your doctor or nurse straight away if you notice any of following serious side effects.

Very common (may affect more than 1 in 10 people):
- Kadcyla may cause inflammation or damage to cells in the liver, resulting in elevated liver enzymes in blood tests. However, in most cases during Kadcyla treatment, liver enzyme levels are elevated mildly and temporarily, do not cause any symptoms, and do not affect liver function.
- Unexpected bruising and bleeding (such as nose bleeds).
- Tingling, pain, numbness, itching, crawling sensation, pins and needles in your hands and feet. These symptoms may indicate nerve damage.

Common (may affect up to 1 in 10 people):
- Flushing, shivering fits, fever, trouble breathing, low blood pressure or a rapid heartbeat during the infusion or up to 24 hours after the infusion – these are so-called infusion-related reactions.
- Heart problems can occur. Most patients will not have symptoms from the heart problems. If symptoms do occur, cough shortness of breath at rest or when sleeping flat, chest pain and swollen ankles or arms, a sensation of rapid or irregular heartbeats may be observed.

Uncommon (may affect up to 1 in 100 people):
- Inflammation of your lungs can cause breathing problems such as shortness of breath (either at rest or while performing any type of activity), coughing or coughing spells with a dry cough – these are signs of inflammation of your lung tissue.
- Your skin and whites of your eyes get yellow (jaundice) – these could be signs of severe liver damage.

- Allergic reactions can occur and most patients will have mild symptoms such as itching or tightness in the chest. In more severe cases, swelling of your face or tongue, trouble swallowing or difficulty breathing may occur.

Frequency not known:
- If Kadcyla infusion solution leaks into the area around the infusion site you may develop pain, discoloration, blistering and sloughing of your skin (skin necrosis) at the infusion site. Contact your doctor or nurse immediately.

Tell your doctor or nurse straight away if you notice any of the serious side effects above.

Other side effects include

Very common:
- decreased red blood cells (shown in a blood test)
- being sick (vomiting)
- diarrhoea
- dry mouth
- urinary tract infection
- constipation
- stomach ache
- cough
- shortness of breath
- inflammation of the mouth
- difficulty sleeping
- muscle or joint pain
- fever
- headache
- feeling tired
- weakness

Common:
- chills or flu like symptoms
- decrease in your potassium levels (shown in a blood test)
- skin rashes
- decreased white blood cells (shown in a blood test)
- dry eyes, watery eyes or blurred vision
- eye redness or infection
- indigestion
- swelling of legs and/or arms
- bleeding from the gums
- increase in blood pressure
- feeling dizzy
- taste disturbances
- itching
- difficulty in remembering
- hair loss
- hand-and-foot skin reaction (Palmar-plantar erythrodysaesthesia syndrome)
- nail disorder

Uncommon:
- Another abnormality that can be caused by Kadcyla is a condition known as nodular regenerative hyperplasia of the liver. This abnormality causes the structure of the liver to change. Patients develop multiple nodules in the liver that can change how the liver functions.

Over time, this may lead to symptoms such as a bloated sensation or swelling of the abdomen due to fluid accumulation or bleeding from abnormal blood vessels in the gullet or rectum.
- If the Kadcyla infusion solution leaks into the area around the infusion site you may develop tenderness or redness of your skin, or swelling at the infusion site.

If you get any of the side effects after your treatment with Kadcyla has stopped, talk to your doctor or nurse and tell them that you have been treated with Kadcyla.

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

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kadcyla

Kadcyla will be stored by the healthcare professionals at the hospital or clinic.

- 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 vial after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze.
- When prepared as a solution for infusion Kadcyla is stable for up to 24 hours at 2°C to 8°C, and must be discarded thereafter.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Kadcyla contains
- The active substance is trastuzumab emtansine.
- Kadcyla 100mg: One vial of powder for concentrate for solution for infusion contains 100 mg of trastuzumab emtansine. After reconstitution one vial of 5 mL solution contains 20 mg/mL of trastuzumab emtansine.
- Kadcyla 160mg: One vial of powder for concentrate for solution for infusion contains 160 mg of trastuzumab emtansine. After reconstitution one vial of 8 mL solution contains 20 mg/mL of trastuzumab emtansine.
- The other ingredients are succinic acid, sodium hydroxide (see section 2 under ‘Important information about some of the ingredients of Kadcyla’), sucrose, and polysorbate 20.

What Kadcyla looks like and contents of the pack
- Kadcyla is a white to off-white lyophilised powder for concentrate for solution for infusion supplied in glass vials.
- Kadcyla is available in packs containing 1 vial.

Marketing Authorisation Holder: F. Hoffmann-La Roche Ltd Grenzacherstrasse, 124 Basel, CH-4070, Switzerland

Manufacturer: F. Hoffmann-La Roche Ltd. 4303 Kaiseraugst for F. Hoffmann-La Roche Ltd., Grenzacherstrasse, 124, CH-4070, Basel, Switzerland

The following information is intended for medical or healthcare professionals only:

In order to prevent medicinal product errors it is important to check the vial labels to ensure that the medicinal product being prepared is Kadcyla (trastuzumab emtansine) and not Herceptin (trastuzumab).

Kadcyla must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. It must not be administered as an intravenous push or bolus.

Always keep this medicine in the closed original pack at a temperature of 2ºC – 8 ºC in a refrigerator. A vial of Kadcyla reconstituted with water for injections (not supplied) is stable for 24 hours at 2ºC – 8 ºC after reconstitution and must not be frozen.

Appropriate aseptic technique should be used. Appropriate procedures for the preparation of chemotherapeutic medicinal products should be used.

The reconstituted Kadcyla solution should be diluted in polyvinyl chloride (PVC) or latex-free PVC-free polyolefin infusion bags.

The use of 0.20 or 0.22 micron in-line polyethersulfone (PES) filter is required for the infusion when the concentrate for infusion is diluted with sodium chloride 9 mg/mL (0.9%) solution for infusion.

Instructions for reconstitution

- Kadcyla 100mg: using a sterile syringe, slowly inject 5 mL of sterile water for injection into the 100 mg trastuzumab emtansine vial.
- Kadcyla 160mg: using a sterile syringe, slowly inject 8 mL of sterile water for injection into the 160 mg trastuzumab emtansine vial.
- Swirl the vial gently until completely dissolved. Do not shake.

Reconstituted solution should be inspected visually for particulate matter and discolouration prior to administration. The reconstituted solution should be free of visible particulates, clear to slightly opalescent. The colour of the reconstituted solution should be colourless to pale brown. Do not use if reconstituted solution is cloudy or discoloured.

Discard any unused portion. The reconstituted product contains no preservative and is intended for single use only.

Instructions for dilution

Determine the volume of the reconstituted solution required based on a dose of 3.6 mg trastuzumab emtansine/kg body weight:

$$\textbf{Volume}\ (\text{mL}) = \frac{\textit{Total dose to be administered} = (\textbf{body weight}\ (\text{kg}) \times \textbf{dose}\ (\text{mg/kg}))}{\textbf{20}\ (\text{mg/mL, concentration of reconstituted solution})}$$

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of sodium chloride 4.5 mg/mL (0.45%) solution for infusion or sodium chloride 9 mg/mL (0.9%) solution for infusion. Glucose (5%) solution should not be used. Sodium chloride 4.5 mg/mL (0.45%) solution for infusion may be used without a polyethersulfone (PES) 0.20 or 0.22-µm in-line filter. If sodium chloride 9 mg/mL (0.9%) solution for infusion is used for infusion, a 0.20 or 0.22 micron in-line polyethersulfone (PES) filter is required. Once the infusion is prepared it should be administered immediately. Do not freeze or shake the infusion during storage. If diluted aseptically, it may be stored for up to 24 hours at 2°C to 8°C.