Package leaflet: Information for the user

Ontruzant® 150 mg powder for concentrate for solution for infusion
Ontruzant® 420 mg powder for concentrate for solution for infusion
trastuzumab

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 or pharmacist.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ontruzant is and what it is used for

Ontruzant contains the active substance trastuzumab, which is a monoclonal antibody. Monoclonal antibodies attach to specific proteins or antigens. Trastuzumab is designed to bind selectively to an antigen 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 Ontruzant binds to HER2 it stops the growth of such cells and causes them to die.

Your doctor may prescribe Ontruzant for the treatment of breast and gastric cancer when:
- You have early breast cancer, with high levels of a protein called HER2.
- You have metastatic breast cancer (breast cancer that has spread beyond the original tumour) with high levels of HER2. Ontruzant may be prescribed in combination with the chemotherapy medicine paclitaxel or docetaxel as first treatment for metastatic breast cancer or it may be prescribed alone if other treatments have proved unsuccessful. It is also used in combination with medicines called aromatase inhibitors with patients with high levels of HER2 and hormone receptor-positive metastatic breast cancer (cancer that is sensitive to the presence of female sex hormones).
- You have metastatic gastric cancer with high levels of HER2, when it is in combination with the other cancer medicines capecitabine or 5-flououracil and cisplatin.

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

Do not use Ontruzant if
- you are allergic to trastuzumab, to murine (mouse) proteins, or to any of the other ingredients of this medicine (listed in section 6).
- you have severe breathing problems at rest due to your cancer or if you need oxygen treatment.

Warnings and precautions
Your doctor will closely supervise your therapy.

Heart checks
Treatment with Ontruzant (alone or with a taxane) may affect the heart, especially if you have ever used an anthracycline (taxanes and anthracyclines are two other kinds of medicine used to treat cancer).
The effects may be moderate to severe and could cause death. Therefore, your heart function will be checked before, during (every three months) and after (up to two to five years) treatment with Ontruzant. If you develop any signs of heart failure (inadequate pumping of blood by the heart), your heart function may be checked more frequently (every six to eight weeks), you may receive treatment for heart failure or you may have to stop Ontruzant treatment.

Talk to your doctor, pharmacist or nurse before you are given Ontruzant if:

- you have had heart failure, coronary artery disease, heart valve disease (heart murmurs), high blood pressure, taken any high blood pressure medicine or are currently taking any high blood pressure medicine.

- you have ever had or are currently using a medicine called doxorubicin or epirubicin (medicines used to treat cancer). These medicines (or any other anthracyclines) can damage heart muscle and increase the risk of heart problems with Ontruzant.

- you suffer from breathlessness., especially if you are currently using a taxane. Ontruzant can cause breathing difficulties, especially when it is first given. This could be more serious if you are already breathless. Very rarely, patients with severe breathing difficulties before treatment have died when they were given Ontruzant.

- you have ever had any other treatment for cancer.

If you receive Ontruzant with any other medicine to treat cancer, such as paclitaxel, docetaxel, an aromatase inhibitor, capecitabine, 5-fluorouracil, or cisplatin you should also read the patient information leaflets for these products.

Children and adolescents
Ontruzant is not recommended for anyone under the age of 18 years.

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

It may take up to 7 months for Ontruzant to be removed from the body. Therefore, you should tell your doctor, pharmacist or nurse that you have had Ontruzant if you start any new medicine in the 7 months after stopping treatment.

Pregnancy
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.
- You should use effective contraception during treatment with Ontruzant and for at least 7 months after treatment has ended.
- Your doctor will advise you of the risks and benefits of taking Ontruzant during pregnancy. In rare cases, a reduction in the amount of (amniotic) fluid that surrounds the developing baby within the womb has been observed in pregnant women receiving Ontruzant. This condition may be harmful to your baby in the womb and has been associated with the lungs not developing fully resulting in foetal death.

Breast-feeding
Do not breast-feed your baby during Ontruzant therapy and for 7 months after the last dose, as Ontruzant may pass to your baby through your breast milk.

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

Driving and using machines
Ontruzant may affect your ability to drive a car or operate machines. If during treatment you experience symptoms, such as dizziness, sleepiness, chills or fever, you should not drive or use machines until these symptoms disappear.

Sodium
This medicine contains less than 1 mmol of sodium (23 mg) per dose, that is to say essentially sodium-free.

3. How Ontruzant is given

Before starting the treatment, your doctor will determine the amount of HER2 in your tumour. Only patients with a large amount of HER2 will be treated with Ontruzant. Ontruzant should only be given by a doctor or nurse. Your doctor will prescribe a dose and treatment regimen that is right for ***you***. The dose of Ontruzant depends on your body weight.

Ontruzant is given as an infusion into a vein (intravenous infusion, "drip"). This intravenous formulation is not for subcutaneous use and should be given as an intravenous infusion only.

The first dose of your treatment is given over 90 minutes and you will be observed by a health professional while it is being given in case you have any side effects (see section 2 under "Warnings and precautions"). If the first dose is well tolerated the next doses may be given over 30 minutes. The number of infusions you receive will depend on how you respond to the treatment. Your doctor will discuss this with you.

In order to prevent medication errors, it is important to check the vial labels to ensure that the medicine being prepared and given is Ontruzant (trastuzumab) and not another trastuzumab-containing product (e.g. trastuzumab emtansine or trastuzumab deruxtecan).

Ontruzant is given every 3 weeks for early breast cancer, metastatic breast cancer and metastatic gastric cancer. Ontruzant may also be given once a week for metastatic breast cancer.

If you stop using Ontruzant
Do not stop using this medicine without talking to your doctor first. All doses should be taken at the right time every week or every three weeks (depending on your dosing schedule). This helps your medicine work as well as it can.

It may take up to 7 months for Ontruzant to be removed from your body. Therefore, your doctor may decide to continue to check your heart functions, even after you finish treatment.

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, Ontruzant can cause side effects, although not everybody gets them. Some of these side effects may be serious and may lead to hospitalisation.

During an Ontruzant infusion, chills, fever and other flu like symptoms may occur. These are very common (may affect more than 1 in 10 people). Other infusion-related symptoms are: feeling sick (nausea), vomiting, pain, increased muscle tension and shaking, headache, dizziness, breathing difficulties, high or low blood pressure, heart rhythm disturbances (palpitations, heart fluttering or irregular heart beat), swelling of the face and lips, rash and feeling tired. Some of these symptoms can be serious and some patients have died (see section 2 under "Warnings and precautions").

These effects mainly occur with the first intravenous infusion ("drip" into your vein) and during the first few hours after the start of the infusion. They are usually temporary. You will be observed by a health care professional during the infusion and for at least six hours after the start of the first infusion and for two hours after the start of other infusions. 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.

Occasionally, symptoms start later than six hours after the infusion begins. If this happens to you, contact your doctor immediately. Sometimes, symptoms may improve and then get worse later.

Serious side effects

Other side effects can occur at any time during treatment with Ontruzant, not just related to an infusion. **Tell a doctor or nurse straight away, if you notice any of the following side effects:**

- Heart problems can sometimes occur during treatment and occasionally after treatment has stopped and can be serious. They include weakening of the heart muscle possibly leading to heart failure, inflammation of the lining around the heart and heart rhythm disturbances. This can lead to symptoms such as breathlessness (including breathlessness at night), cough, fluid retention (swelling) in the legs or arms, palpitations (heart fluttering or irregular heart beat) (see section 2. Heart checks).

Your doctor will monitor your heart regularly during and after treatment but you should tell your doctor immediately if you notice any of the above symptoms.

- Tumour lysis syndrome (a group of metabolic complications occurring after cancer treatment characterized by high blood levels of potassium and phosphate, and low blood levels of calcium). Symptoms may include kidney problems (weakness, shortness of breath, fatigue and confusion), heart problems (fluttering of the heart or a faster or slower heartbeat), seizures, vomiting or diarrhoea and tingling in the mouth, hands or feet.

If you experience any of the above symptoms when your treatment with Ontruzant has finished, you should see your doctor and tell them that you have previously been treated with Ontruzant.

The following list of side effects can occur at any time during treatment with Ontruzant, not just related to an infusion.

Very common side effects of Ontruzant (may affect more than 1 in 10 people):
- infections
- diarrhoea
- constipation
- dyspepsia (heartburn)
- fatigue
- skin rashes
- chest pain
- abdominal pain
- joint pain
- low counts of red blood cells and white blood cells (which help fight infection) sometimes with fever
- muscle pain

- conjunctivitis
- watery eyes
- nose bleeds
- runny nose
- hair loss
- tremor
- hot flush
- dizziness
- nail disorders
- weight loss
- loss of appetite
- insomnia (inability to sleep)
- altered taste
- low platelet count
- bruising
- numbness or tingling of the fingers and toes, which occasionally may extend to the rest of the limb
- redness, swelling or sores in your mouth and/or throat
- pain, swelling, redness or tingling of hands and/or feet
- breathlessness
- headache
- cough
- vomiting
- nausea

Common side effects of Ontruzant (may affect up to 1 in 10 people):

- allergic reactions
- throat infections
- bladder and skin infections
- inflammation of the breast
- inflammation of the liver
- kidney disorders
- hypertonia (increased muscle tone or tension)
- pain in the arms and/or legs
- itchy rash
- somnolence (sleepiness)
- haemorrhoids
- itchiness
- leg cramps
- dry mouth and skin
- dry eyes
- sweating
- feeling weak and unwell
- anxiety
- depression
- asthma
- infection of lungs
- lung disorders
- back pain
- neck pain
- bone pain
- acne

Uncommon side effects of Ontruzant (may affect up to 1 in 100 people):

- deafness
- bumpy rash
- wheezing
- inflammation or scarring of the lungs

Rare side effects of Ontruzant (may affect up to 1 in 1000 people):

- jaundice (yellowish discoloration of the skin or eyes)
- anaphylactic reactions

Other side effects that have been reported with Ontruzant use (frequency cannot be estimated from the available data):

- abnormal or impaired blood clotting
- high potassium levels
- swelling or bleeding at the back of the eyes
- shock
- abnormal heart rhythm
- respiratory distress
- respiratory failure
- acute accumulation of fluid in the lungs
- acute narrowing of the airways
- abnormally low oxygen levels in the blood
- difficulty in breathing when lying flat
- liver damage
- swelling of the face, lips and throat
- kidney failure

During pregnancy:

- abnormally low levels of fluid around baby in womb
- failure of the lungs of the baby to develop in the womb
- abnormal development of the kidneys of the baby in the womb

Some of the side effects you experience may be due to your underlying cancer. If you receive Ontruzant in combination with chemotherapy, some of them may also be due to the chemotherapy.

If you get any side effects, talk to your doctor, pharmacist or nurse.

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 at: 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 Ontruzant

Ontruzant 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 on the vial label after EXP. The expiry date refers to the last day of that month.
- The unopened vial should be stored in a refrigerator (2°C - 8°C).
- Do not freeze the reconstituted solution.
- Infusion solutions should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user, and would not normally be longer than 24 hours 2°C - 8°C.
- Do not use Ontruzant if you notice any particulate matter or discoloration prior to administration.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Ontruzant contains

- The active substance is trastuzumab. Each vial contains either:

- 150 mg trastuzumab that has to be dissolved in 7.2 mL of water for injection, or
- 420 mg trastuzumab that has to be dissolved in 20 mL of water for injection.

- The resulting solution contains approximately 21 mg/mL trastuzumab.
- The other ingredient(s) are L-histidine hydrochloride monohydrate, L-histidine, α,α-trehalose dihydrate, polysorbate 20.

What Ontruzant looks like and contents of the pack

Ontruzant is a powder for concentrate for solution for intravenous infusion, which is supplied in a glass vial with a rubber stopper containing either 150 mg or 420 mg of trastuzumab. The powder is a white to pale yellow pellet. Each carton contains 1 vial of powder.

Marketing Authorisation Holder

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The following information is intended for healthcare professionals only

Ontruzant is provided in sterile, preservative-free, non-pyrogenic, single use vials.

In order to prevent medication errors it is important to check the vial labels to ensure that the medicine being prepared and given is Ontruzant (trastuzumab) and not another trastuzumab-containing product (e.g. trastuzumab emtansine or trastuzumab deruxtecan).

Always keep this medicine in the closed original pack at a temperature of 2ºC - 8ºC in a refrigerator.

Appropriate aseptic technique should be used for reconstitution and dilution procedures. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed.

A vial of Ontruzant aseptically reconstituted with sterile water for injections (not supplied) is chemically and physically stable for 7 days at 2ºC - 8ºC after reconstitution and must not be frozen.

After aseptic dilution in polyvinylchloride, polyethylene or polypropylene bags containing sodium chloride 9 mg/mL (0.9 %) solution for injection, chemical and physical stability of Ontruzant has been demonstrated for up to 30 days at 2ºC - 8ºC, and subsequently for 24 hours at temperatures not exceeding 30°C.

From a microbiological point of view, the reconstituted solution and Ontruzant infusion solution 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 not normally be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place under controlled and validated aseptic conditions.

Aseptic preparation, handling and storage:
Aseptic handling must be ensured when preparing the infusion. Preparation should be:

- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.
- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.
- followed by adequate storage of the prepared solution for intravenous infusion to ensure maintenance of the aseptic conditions

Ontruzant 150 mg powder for concentrate for solution for infusion
Each 150 mg vial of Ontruzant is reconstituted with 7.2 mL of water for injections (not supplied). Use of other reconstitution solvents should be avoided. This yields a 7.4 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab. A volume overage of 4% ensures that the labelled dose of 150 mg can be withdrawn from each vial.

Ontruzant 420 mg powder for concentrate for solution for infusion
Each 420 mg vial of Ontruzant is reconstituted with 20 mL of water for injections (not supplied). Use of other reconstitution solvents should be avoided. This yields a 21 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab. A volume overage of 5% ensures that the labelled dose of 420 mg can be withdrawn from each vial.

Ontruzant vial		Volume of sterile water for injections		Final concentration
150 mg vial	+	7.2 mL	=	21 mg/mL
420 mg vial	+	20 mL	=	21 mg/mL

Instructions for aseptic reconstitution

Ontruzant should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted Ontruzant may result in problems with the amount of Ontruzant that can be withdrawn from the vial.

- Using a sterile syringe, slowly inject the appropriate volume (as noted above) of water for injections in the vial containing the lyophilised Ontruzant, directing the stream into the lyophilised cake.
- Swirl vial gently to aid reconstitution. DO NOT SHAKE!

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted Ontruzant results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.

Instructions for aseptic dilution of the reconstituted solution

Determine the volume of the solution required:

- based on a loading dose of 4 mg trastuzumab/kg body weight, or a subsequent weekly dose of 2 mg trastuzumab/kg body weight:

$$\textbf{Volume}\ (\text{mL}) = \frac{\textbf{Body weight}\ (\text{kg}) \times \textbf{dose}\ (\textbf{4}\ \text{mg/kg for loading or}\ \textbf{2}\ \text{mg/kg for maintenance})}{\textbf{21}\ (\text{mg/mL, concentration of reconstituted solution})}$$

- based on a loading dose of 8 mg trastuzumab/kg body weight, or a subsequent 3-weekly dose of 6 mg trastuzumab/kg body weight:

$$\textbf{Volume}\ (\text{mL}) = \frac{\textbf{Body weight}\ (\text{kg}) \times \textbf{dose}\ (\textbf{8}\ \text{mg/kg for loading or}\ \textbf{6}\ \text{mg/kg for maintenance})}{\textbf{21}\ (\text{mg/mL, concentration of reconstituted solution})}$$

The appropriate amount of solution should be withdrawn from the vial using a sterile needle and syringe and added to a polyvinylchloride, polyethylene or polypropylene infusion bag containing 250 mL of 0.9% sodium chloride solution. Do not use with glucose-containing solutions. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration.