WHO-PQ RECOMMENDED PATIENT INFORMATION LEAFLET

This patient information leaflet focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*] https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

Information for the patient

[BT-ON014 trade name] †
Trastuzumab + Bacteriostatic Water for Injection (diluent)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have questions about the medicine, ask your health care provider.
- 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 seem to be the same as yours.
- If you get any side effects, talk to your health care provider.This includes unwanted effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What [BT-ON014 trade name] is and what it is used for

[BT-ON014 trade name] contains the active substance trastuzumab, which is a monoclonal antibody. Monoclonal antibodies attach to specific proteins or antigens. Trastuzumab is designed to attach 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 [BT-ON014 trade name] binds to HER2 it stops the growth of such cells and causes them to die.

Your health care provider may prescribe [BT-ON014 trade name] for the treatment of breast cancer when:

- You have early breast cancer, with high levels of HER2. [BT-ON014 trade name] may be combined with other cancer medicines, and is usually part of a sequence of treatments that may also include surgery or radiotherapy.
- You have metastatic breast cancer (breast cancer that has spread beyond the original tumour) with high levels of HER2.

  [BT-ON014 trade name] may be given with another cancer medicine, paclitaxel or docetaxel, as first treatment for metastatic breast cancer, or it may be used alone if other treatments have proved unsuccessful.

  [BT-ON014 trade name] 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).

2. What you need to know before you are given [BT-ON014 trade name]

Do not use [BT-ON014 trade name]:

- if you are allergic to trastuzumab, murine (mouse) proteins, or any of the other ingredients of this medicine (listed in section 6).
- if you have severe breathing problems at rest due to your cancer or if you need oxygen treatment.

†Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Warnings and precautions

Your health care provider will closely supervise your therapy.

Heart checks

Treatment with [BT-ON014 trade name] may affect the heart. The risk may be increased when [BT-ON014 trade name] is given with a taxane (a type of cancer medicine such as paclitaxel or docetaxel) or if you have ever used an anthracycline (another type of cancer medicine that includes medicines called doxorubicin and epirubicin). The effects can be moderate to severe and could cause death.

Therefore, your heart function will be checked before treatment, at least every three months while you are getting the medicine, and for up to two to five years afterwards. If you develop any signs of heart failure (when the heart cannot pump blood round the body well enough), 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 [BT-ON014 trade name] treatment.

Talk to your health care provider before you are given [BT-ON014 trade name] if:

- you have had heart failure, heart attack, angina or coronary artery disease, heart valve disease (heart murmurs), ever needed treatment for abnormal heart rhythm or other heart problems such as cardiomyopathy, have high blood pressure, or have ever taken any high blood pressure medicine.
- you have ever had or are currently using doxorubicin or epirubicin.
- you suffer from breathlessness, especially if you are currently using a taxane. [BT-ON014 trade name] 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 [BT-ON014 trade name].
- you have ever had any other treatment for cancer.

If you receive [BT-ON014 trade name] 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

[BT-ON014 trade name] is not recommended for anyone under the age of 18 years.

Other medicines and [BT-ON014 trade name]

Tell your health care provider if you are taking, have recently taken or might take any other medicines.

It may take up to 7 months for [BT-ON014 trade name] to be removed from the body. Therefore, you should tell your health care provider that you have had [BT-ON014 trade name] if you start any new medicine in the 7 months after stopping treatment.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your health care provider for advice before taking this medicine.

Pregnancy

- You should use effective contraception during treatment with [BT-ON014 trade name] and for at least 7 months after treatment has ended.
- Your health care provider will advise you of the risks and benefits of taking [BT-ON014 trade name] 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 [BT-ON014 trade name]. This condition may be harmful to your baby in the womb and has been associated with the death of the baby because its lungs did not develop fully.

Breast-feeding

Do not breast-feed your baby during [BT-ON014 trade name] therapy and for 7 months after the last dose of [BT-ON014 trade name] as this medicine may pass to your baby through your breast milk. Ask your health care provider for advice before taking any medicine.

Driving and using machines

[BT-ON014 trade name] 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.

Other ingredients of this medicinal product

Sorbitol

[BT-ON014 trade name] contains sorbitol. Sorbitol is a source of fructose. If you have hereditary fructose intolerance (HFI), a rare genetic disorder, you cannot break down fructose which may cause side effects. Therefore, you must not receive this medicine unless it is considered strictly necessary.

You must tell your health care giver before receiving this medicine if you have HFI or if you can no longer take sweet foods or drinks because you feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.

Sodium

[BT-ON014 trade name] contains less than 1 mmol sodium (23 mg) per dose, that is to say, is essentially 'sodium-free'.

Benzyl alcohol

The bacteriostatic water for injection (diluent) contains benzyl alcohol. Benzyl alcohol may cause allergic reactions.

3. How [BT-ON014 trade name] is given

Before starting the treatment, your health care provider will determine the amount of HER2 in your tumour. Only patients whose tumours have a large amount of HER2 will be treated with [BT-ON014 trade name]. [BT-ON014 trade name] should only be given by a health care provider.

Your health care provider will prescribe a dose and treatment regimen that is right for you. The dose of [BT-ON014 trade name] depends on your body weight. It is given as an infusion (drip) into a vein. This medicine is not suitable to be injected under the skin.

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. If the first dose is well tolerated the next doses may be given over 30 minutes (see section 2 under "Warnings and precautions").

Infusions may be given every 3 weeks or once a week, depending on which treatment regimen your healthcare provider thinks best for you. The number of infusions you receive will depend on how you respond to the treatment. Your health care provider will discuss this with you.

If you stop using [BT-ON014 trade name]

Do not stop using this medicine without talking to your health care provider first. All doses should be given at the right time every week or every three weeks (depending on your treatment regimen). This helps your medicine work as well as it can.

It may take up to 7 months for [BT-ON014 trade name] to be removed from your body. Therefore, your health care provider may continue to check how your heart is working, even after you finish treatment.

If you have any further questions on the use of this medicine, ask your health care provider.

4. Possible side effects

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

Some of these side effects may be serious and may lead to hospitalization.

During an [BT-ON014 trade name] 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, wheezing, 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 infusion (drip) into your vein, and during the first few hours after the start of the infusion. They are usually temporary. You will be monitored by a health care provider during the infusion and for a few hours afterwards – at least six hours from the start of the first infusion and two hours from the start of later infusions. If you develop a reaction, they will slow down or stop the infusion and may give you treatment for 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 health care provider immediately. Sometimes, symptoms may improve and then get worse later.

Serious side effects

Other side effects can occur at any time during treatment with [BT-ON014 trade name], 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, 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 health care provider will monitor your heart regularly during and after treatment but you should tell your health care provider immediately if you notice any of the above symptoms.
- Tumour lysis syndrome (a complication due to breakdown of cancer cells leading to 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 [BT-ON014 trade name] has finished, you should see your health care provider and tell them that you have previously been treated with [BT-ON014 trade name].

Very common side effects: may affect more than 1 in 10 people

- infections
- diarrhoea
- constipation
- heartburn (dyspepsia)
- fatigue
- skin rashes
- chest pain
- abdominal (stomach) pain

- joint pain
- low counts of red blood cells and white blood cells (which help fight infection) seen in blood tests, sometimes with fever
- muscle pain
- conjunctivitis (discharge with itching of the eyes and crusty eyelids)
- watery eyes
- nose bleeds
- runny nose
- hair loss
- tremor
- hot flush
- dizziness
- nail disorders
- weight loss
- loss of appetite
- inability to sleep (insomnia)
- altered taste
- low platelet count
- bruising
- numbness or tingling of the fingers and toes
- redness, swelling or sores in your mouth or throat
- pain, swelling, redness or tingling of hands or feet
- breathlessness
- headache
- cough
- vomiting
- nausea (feeling sick)

Common side effects: may affect up to 1 in 10 people

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

- bone pain
- itchiness
- acne
- leg cramps

Uncommon side effects: may affect up to 1 in 100 people

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

Rare side effects: may affect up to 1 in 1000 people

- jaundice (yellowing of the skin and the whites of the eyes)
- anaphylactic reactions (serious sudden allergic reaction with symptoms such as rash, itchy skin, difficulty breathing or feeling dizzy or faint)

Side effects of not known frequency: 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 (a dangerous decrease of blood pressure causing symptoms like rapid, shallow breathing, cold, clammy skin, a rapid, weak pulse, dizziness, weakness and fainting)
- 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
- abnormally low levels of fluid around baby in womb
- failure of lungs of the baby to develop in the womb
- abnormal development of the kidney of the baby in the womb

Some of the side effects you experience may be due to your underlying breast cancer. If you receive [BT-ON014 trade name] in combination with chemotherapy, some of them may also be due to the chemotherapy.

If you get any side effects, talk to your health care provider.

Reporting of side effects

If you get any side effects,talk to your health care provider.This includes unwanted effects not listed in this leaflet.If available, you can also report side effects directly through the national reporting system. By reporting side effects, you can help provide more information on the safety of this medicine.

See section 6 for the supplier’s contact details.

5. How to store [BT-ON014 trade name]

Keep this medicine out of the sight and reach of children.

Store under refrigeration at 2°C-8°C, in the original package in order to protect from light.
Use reconstituted solution within 28 days when stored at 2°C-8°C.
Infusion solution should be used immediately, unless reconstitution and dilution have taken place under aseptic conditions.

Do not use this medicine after the expiry date stated on the vial or carton, after "EXP". The expiry date refers to the last day of that month.

Do not use this medicine if you notice visible signs of deterioration or that it is different from the description below.

Do not throw away any medicines in wastewater or household waste. Ask your health care provider 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 [BT-ON014 trade name] contains

The active ingredient of [BT-ON014 trade name] is trastuzumab.

The other ingredients are:
- L-histidine hydrochloride
- L-histidine
- D-sorbitol
- Macrogol 3350
- Hydrochloric acid (for pH adjustment)
- Sodium hydroxide (for pH adjustment)

What [BT-ON014 trade name] looks like and contents of the pack

[BT-ON014 trade name] is a sterile, off-white to pale yellow lyophilized powder for concentrate for solution for infusion.

The bacteriostatic water for injection is a colourless, transparent solution, free of visible particles and is intended to use for the reconstitution of [BT-ON014 trade name] to yield a multi-dose solution containing 21 mg/mL trastuzumab

Upon reconstitution with the supplied bacteriostatic water for injection (BWFI), the powder gives a colourless to pale yellow transparent solution, free of visible particles.

[BT-ON014 trade name] packaging
The packaging consists of a clear, colourless Type I glass vial, closed with a 20 mm chlorobutyl rubber stopper with fluoro-polymer laminate on the product contact side. The rubber stopper is sealed with an aluminium seal that has a plastic flip-off cap.

420 mg trastuzumab are filled into each vial.

Diluent packaging
20mL of the diluent bacteriostatic water for injection are filled into a colorless Type I glass vial (USP/Ph. Eur.) and closed with a chlorobutyl rubber stopper with fluoro-polymer laminate on the product contact side. The

rubber stopper is sealed with an aluminum seal that has a plastic flip-off cap component. The seal and cap do not come into contact with the diluent.

One vial of *[BT-ON014 trade name]* and one vial of diluent are packed into one carton.

Supplier and Manufacturer

Supplier
Biocon Biologics Limited
16 Great Queen Street
Covent Garden, London
United Kingdom
WC2B 5AH
Tel. No.: +91 80 6775 6775
+91 80 6775 1107
Fax No.: +91 80 6775 1030
Email: DrugSafety@biocon.com
ContactUs.BBL@biocon.com

Manufacturers (drug product + diluent)
Biocon Limited
Plot Nos. 2, 3, 4 & 5, Phase IV
Bommasandra-Jigani Link Road
Bommasandra post
Bengaluru – 560 099
India
Tel. No.: +91 80 6775 6775
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For any information about this medicine, contact the local representative of the supplier.

This leaflet was last revised in May 2021.

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines

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The following information is intended for health care providers only.

Handling
[BT-ON014 trade name] should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted solution may result in problems with the amount of product that can be withdrawn from the vial.

A volume overfill of 4.8 % ensures that the labelled dose of 420 mg trastuzumab can be withdrawn from each vial.

The reconstituted solution should not be frozen.

Instructions for reconstitution

1. Appropriate aseptic technique should be used.
2. Using a sterile syringe, slowly inject 20 mL of bacteriostatic water for injection into the vial containing the lyophilised drug product, i.e., [BT-ON014 trade name]. Direct the stream into the lyophilised cake.
3. To aid reconstitution, the vial should be swirled gently. DO NOT SHAKE.
4. Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes.
    - The reconstituted product results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.
    - Reconstitution yields a 21 mL solution for multi-dose use, containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0.
5. The reconstituted product is physico-chemically and microbiologically stable for 28 days when refrigerated at 2°C to 8°C after dissolving in the supplied bacteriostatic water for injection.

No incompatibilities between [BT-ON014 trade name] and polyvinylchloride, polyethylene or polypropylene bags have been observed.

Instructions for dilution

1. Determine the volume of [BT-ON014 trade name] solution required:
   • Based on a loading dose of trastuzumab of 4mg /kg, or a subsequent weekly dose of 2 mg /kg:

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

   • Based on a loading dose of trastuzumab of 8 mg /kg, or a subsequent 3-weekly dose of 6 mg /kg:

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

2. The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9 % sodium chloride solution. Do not use with glucose-containing solutions (see section 6.2).
3. The bag should be gently inverted to mix the solution in order to avoid foaming. Once the infusion is prepared it should be administered immediately. If reconstitution and dilution have taken place under aseptic conditions, the infusion solution can be stored up to 24 hours when refrigerated at 2°C to 8°C.

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.