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Enhertu (*trastuzumab deruxtecan*)

An overview of Enhertu and why it is authorised in the EU

What is Enhertu and what is it used for?

Enhertu is a medicine used for treating adults with:

- HER2-positive breast cancer that is metastatic (has spread to other parts of the body) or cannot be removed by surgery. HER2-positive means that the cancer cells produce a protein called HER2 in large quantities on their surface, which makes the tumour cells grow more quickly. Enhertu is used on its own in patients who have received one or more HER2-targeted treatments;
- HER2-low breast cancer that cannot be removed by surgery or is metastatic. HER2-low means that the cancer cells produce some HER2 on their surface, but less than HER2-positive cancer cells. Enhertu is used in patients who have previously received treatment after the disease had spread or whose disease came back during or within 6 months of treatment following surgery. It is used on its own in these patients;
- advanced non-small cell lung cancer (NSCLC) whose cancer cells have a mutation (change) in the gene for the HER2 protein, called an activating HER2 mutation. It is used on its own in patients who had previously been treated with platinum-based chemotherapy with or without immunotherapy (treatment that boosts the immune system's ability to fight the cancer);
- HER2-positive advanced gastric cancer (cancer of the stomach) or gastro-oesophageal junction cancer (cancer at the junction between the stomach and the oesophagus). It is used on its own in patients who have previously received trastuzumab, another HER2-targeted treatment.

Enhertu contains the active substance trastuzumab deruxtecan.

How is Enhertu used?

Enhertu can only be obtained with a prescription. It should be prescribed by a doctor and given under the supervision of a healthcare professional who has experience in the use of cancer medicines.

It is given by infusion (drip) into a vein over 90 minutes once every three weeks. Patients who tolerate the first 90-minute infusion can receive subsequent infusions over 30 minutes. Treatment may be continued for as long as it remains effective. The dose depends on the patient's body weight and the type of cancer that is being treated.

The infusion may cause allergic reactions, so the patient should be monitored during and after the infusion for signs such as fever and chills. If the patient develops side effects, the doctor may reduce the dose or stop treatment temporarily or permanently.

For more information about using Enhertu, see the package leaflet or contact your doctor or pharmacist.

How does Enhertu work?

The active substance in Enhertu, trastuzumab deruxtecan, is made up of two active components which are linked together:

- trastuzumab is a monoclonal antibody (a type of protein) that has been designed to attach to HER2. By attaching to HER2, trastuzumab activates cells of the immune system, which then kill the cancer cells. Trastuzumab also stops HER2 from stimulating the growth of cancer cells. HER2 is produced at high levels in about a fifth of gastric cancers and a quarter of breast cancers, and at lower levels in about half of the remaining breast cancers. In lung cancer with an activating HER2 mutation, HER2 is overactive.
- deruxtecan is a toxic substance that kills cells when they attempt to divide and grow. It becomes active once the trastuzumab component has attached to HER2 and enters the cancer cell. Deruxtecan blocks an enzyme called topoisomerase I which is involved in copying cell DNA needed to make new cells. By blocking topoisomerase I, cancer cells are prevented from multiplying and eventually die.

What benefits of Enhertu have been shown in studies?

Breast cancer

An ongoing main study showed that Enhertu was effective at shrinking the tumour in patients with metastatic breast cancer or breast cancer that could not be removed by surgery. All patients had received two or more HER2-targeted treatments. The tumour shrank in around 61% of 184 patients treated with the recommended dose of Enhertu.

An additional study involved 524 patients previously treated with a HER2-targeted treatment (trastuzumab) and a taxane for HER2-positive breast cancer that was metastatic or could not be removed by surgery. The study showed that patients treated with Enhertu lived for at least 18.5 months without their disease getting worse compared with at least 5.6 months for patients treated with trastuzumab emtansine.

Another main study found that Enhertu increased the time patients with HER2-low breast cancer lived without their disease getting worse. The study involved 557 patients with breast cancer that was metastatic or could not be removed by surgery and who had been previously treated with another cancer medicine. The study found that patients who received Enhertu lived for an average of 9.9 months without their disease getting worse compared with 5.1 months for those who received another cancer medicine chosen by the doctor.

Non-small cell lung cancer (NSCLC)

An ongoing study looked at treatment with Enhertu in 152 patients with NSCLC that had activating HER2 mutations and had spread and whose cancer had come back or got worse after at least one previous treatment that included platinum-based chemotherapy. The results showed that the overall response rate (the proportion of patients who have no sign of cancer or whose tumours shrank) was

49% (50 out of 102) in patients treated with the intended dose of Enhertu, and the response lasted an average of 16.8 months. In this study, Enhertu was not compared with any other medicine or placebo (dummy treatment).

Gastric cancer and gastro-oesophageal junction cancer

The benefits of Enhertu in gastric and gastro-oesophageal cancer were investigated in one main study involving 79 patients whose cancer had worsened following HER2-targeted treatment consisting of trastuzumab. The study did not compare Enhertu with any other medicines or placebo. In 42% (33 out of 79) of patients the cancer responded to treatment, as observed by shrinkage in the size of the cancer, which lasted on average for 8 months.

What are the risks associated with Enhertu?

For the full list of side effects and restrictions with Enhertu, see the package leaflet.

The most common side effects with Enhertu (which may affect more than 1 in 5 people) include nausea (feeling sick), tiredness, vomiting, alopecia (hair loss), constipation, decreased appetite, anaemia (low levels of red blood cells), neutropenia (low levels of neutrophils, a type of white blood cell that fights infection), diarrhoea, muscle and bone pain, increased levels of certain liver enzymes (transaminases), thrombocytopenia (low levels of blood platelets which can lead to bleeding and bruising) and leucopenia (low levels of white blood cells).

The most common serious side effects include neutropenia, anaemia, nausea, tiredness, leucopenia, lymphopenia (low levels of lymphocytes, a type of white blood cell), vomiting, thrombocytopenia, hypokalaemia (low blood potassium levels which can cause weakness, muscle cramps, tingling and heart rhythm disturbance), diarrhoea, pneumonia, neutropenia with fever, decreased appetite, increased levels of certain liver enzymes, increased blood levels of the enzyme alkaline phosphatase, dyspnoea (difficulty breathing), weight loss, reduced ejection fraction (a measure of how well the heart pumps blood), increased blood levels of bilirubin (a marker of liver damage) and interstitial lung disease (disorders causing scarring in the lungs).

The frequency and seriousness of side effects that can occur with Enhertu depend on the type of cancer that is being treated.

Why is Enhertu authorised in the EU?

Enhertu was effective at treating HER2-positive breast cancer in patients who had received one or more HER2-targeted treatments. In addition, it was effective at treating HER2-low breast cancer in patients who had previously received another cancer medicine. The side effects of Enhertu are considered manageable and similar to those of other trastuzumab-containing medicines, although the risk of lung disease may be higher with Enhertu. These side effects, including those affecting the lungs, are mostly reversible and can be managed by changing the dose and closely monitoring the patient.

Treatment with Enhertu also showed benefits in a group of patients with gastric and gastro-oesophageal cancer who had previously received treatment including trastuzumab and had few treatment options. It was therefore considered to address an unmet medical need in these patients, although the lack of a comparison group in the main study limited the evaluation of the benefits and risks associated with its use.

Enhertu was also effective at treating patients with advanced NSCLC with HER2 mutations who had previously received platinum-based therapy with or without immunotherapy. These patients have few

available treatment options and Enhertu was considered to address this unmet medical need. The main trial did not compare Enhertu with another cancer medicine or placebo, and the company was requested to submit more comprehensive data.

Enhertu has been given 'conditional authorisation'. This means that the European Medicines Agency decided that the benefits of Enhertu are greater than its risks, but the company will have to provide additional evidence after authorisation.

Conditional authorisation is granted on the basis of less comprehensive data than are normally required. It is granted for medicines that fulfil an unmet medical need to treat serious diseases and when the benefits of having them available earlier outweigh any risks associated with using the medicines while waiting for further evidence. Every year, the Agency will review any new information that becomes available until data become comprehensive, and this overview will be updated as necessary.

What information is still awaited for Enhertu?

Since Enhertu has been given conditional authorisation, the company that markets Enhertu will provide results from a study to evaluate the safety and effectiveness of Enhertu in patients with gastric or gastro-oesophageal junction cancer that is metastatic or cannot be removed by surgery and has worsened following treatment with a trastuzumab-based regimen. The study will compare Enhertu with ramucirumab given in combination with paclitaxel. The company will also provide results from a study to evaluate the safety and effectiveness of Enhertu in patients with NSCLC whose cancer has an HER2 mutation and is advanced or metastatic or cannot be removed by surgery. The study will compare Enhertu with pembrolizumab given in combination with pemetrexed-platinum chemotherapy.

What measures are being taken to ensure the safe and effective use of Enhertu?

The company that markets Enhertu will provide educational material to healthcare professionals to inform them that Enhertu can cause lung disease and what symptoms to watch out for. In addition, because of a potential risk of confusion between Enhertu and other trastuzumab-containing medicines, including Kadcyla, due to their similar sounding active substances (trastuzumab deruxtecan, trastuzumab emtansine and trastuzumab), the educational material will include information to alert healthcare professionals not to use these medicines interchangeably and to inform them on how to avoid medication errors.

A patient alert card including this information will also be provided to patients who are prescribed Enhertu.

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Enhertu have also been included in the summary of product characteristics and the package leaflet.

As for all medicines, data on the use of Enhertu are continuously monitored. Side effects reported with Enhertu are carefully evaluated and any necessary action taken to protect patients.

Other information about Enhertu

Enhertu received a conditional marketing authorisation valid throughout the EU on 18 January 2021.

Further information on Enhertu can be found on the Agency's website: ema.europa.eu/medicines/human/EPAR/enhertu.

This overview was last updated in 10-2023.