Hertisan Powder for solution for infusion safety card

Therapeutic indication

Breast cancer

Metastatic breast cancer

Hertisan is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer: (MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.
- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.
- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

Early breast cancer

Hertisan is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC).

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter

Hertisan should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay

Metastatic gastric cancer

Hertisan in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Hertisan should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used.

Dosage and administration:

HER2 testing is mandatory prior to initiation of therapy . Hertisan treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy and should be administered by a healthcare professional only.

Hertisan intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only.

Metastatic breast cancer

Three-weekly schedule

The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Weekly schedule

The recommended initial loading dose of Hertisanis 4 mg/kg body weight. The recommended weekly maintenance dose of Hertisanis 2 mg/kg body weight, beginning one week after the loading dose.

Administration in combination with paclitaxel or docetaxel

In the pivotal trials (H0648g, M77001), paclitaxel or docetaxel was administered the day following the first dose of trastuzumab (for dose, see the Summary of Product Characteristics (SmPC) for paclitaxel or docetaxel) and immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated.

Administration in combination with an aromatase inhibitor

In the pivotal trial (BO16216) trastuzumab and anastrozole were administered from day 1. There were no restrictions on the relative timing of trastuzumab and anastrozole at administration (for dose, see the SmPC for anastrozole or other aromatase inhibitors).

Early breast cancer

Three-weekly and weekly schedule

As a three-weekly regimen the recommended initial loading dose of Hertisanis 8 mg/kg body weight. The recommended maintenance dose of Hertisan three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.
As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide.

Metastatic gastric cancer

Three-weekly schedule

The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Breast cancer and gastric cancer

Duration of treatment

Patients with MBC or MGC should be treated with Hertisan until progression of disease.
Patients with EBC should be treated with Hertisan for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond one year is not recommended .

Dose reduction

No reductions in the dose of Hertisan were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. Refer to the SmPC for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.
If left ventricular ejection fraction (LVEF) drops ≥ 10 ejection fraction (EF) points from baseline AND to below 50 %, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or symptomatic congestive heart failure (CHF) has developed, discontinuation of Hertisan should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

Missed doses

If the patient has missed a dose of Hertisan by one week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.
If the patient has missed a dose of Hertisan by more than one week, a re-loading dose of Hertisan should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) as soon as possible. Subsequent Hertisan maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules respectively.

Special populations

Dedicated pharmacokinetic studies in older people and those with renal or hepatic impairment have not been carried out. In a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition.

Paediatric population

There is no relevant use of trastuzumab in the paediatric population.

Method of administration

Hertisan loading dose should be administered as a 90-minute intravenous infusion. Do not administer as an intravenous push or bolus.
Hertisan intravenous infusion should be administered by a healthcare provider prepared to manage anaphylaxis and an emergency kit should be available. Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms .Interruption or slowing the rate of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.
If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

Precautions :

Traceability

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded.
HER2 testing must be performed in a specialised laboratory which can ensure adequate validation of the testing procedures .

Currently no data from clinical trials are available on re-treatment of patients with previous exposure to trastuzumab in the adjuvant setting.

Cardiac dysfunction

General considerations

Patients treated with trastuzumab are at increased risk for developing CHF (New York Heart Association [NYHA] class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving trastuzumab therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin) containing chemotherapy. These may be moderate to severe and have been associated with death .In addition, caution should be exercised in treating patients with increased cardiac risk, e.g. hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age.

All candidates for treatment with Hertisan®, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging. Monitoring may help to identify patients who develop cardiac dysfunction. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Hertisan®. A careful risk-benefit assessment should be made before deciding to treat with Hertisan®.

Trastuzumab may persist in the circulation for up to 7 months after stopping treatment based on population pharmacokinetic analysis of all available data . Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. In all patients cardiac function should be monitored during treatment (e.g. every 12 weeks). Monitoring may help to identify patients who develop cardiac dysfunction. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6 - 8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of Hertisan therapy has been seen.

The safety of continuation or resumption of trastuzumab in patients who experience cardiac dysfunction has not been prospectively studied. If LVEF percentage drops ≥10 ejection fraction (EF) points from baseline AND to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or symptomatic CHF has developed, discontinuation of Hertisan should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

If symptomatic cardiac failure develops during Hertisan therapy, it should be treated with standard medicinal products for CHF. Most patients who developed CHF or asymptomatic cardiac dysfunction in pivotal trials improved with standard CHF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a beta-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued on therapy without additional clinical cardiac events.

Metastatic breast cancer

Hertisan and anthracyclines should not be given concurrently in combination in the MBC setting.

Patients with MBC who have previously received anthracyclines are also at risk of cardiac dysfunction with trastuzumab treatment, although the risk is lower than with concurrent use of trastuzumab and anthracyclines.

Early breast cancer

For patients with EBC, cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Hertisan®. In patients who receive anthracycline containing chemotherapy further monitoring is recommended and should occur yearly up to 5 years from the last administration of Hertisan®, or longer if a continuous decrease of LVEF is observed.

Patients with history of myocardial infarction (MI), angina pectoris requiring medical treatment, history of or existing CHF (NYHA II –IV), LVEF of < 55%, other cardiomyopathy, cardiac arrhythmia requiring medical treatment, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medical treatment eligible), and hemodynamic effective pericardial effusion were excluded from adjuvant and neoadjuvant EBC pivotal trials with trastuzumab and therefore treatment cannot be recommended in such patients.

Adjuvant treatment

Hertisan and anthracyclines should not be given concurrently in combination in the adjuvant treatment setting.

In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when trastuzumab was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin and was more marked when trastuzumab was administered concurrently with taxanes than when administered sequentially to

taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months. In one of the 3 pivotal studies conducted in which a median follow-up of 5.5 years was available (BCIRG006) a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events was observed in patients who were administered trastuzumab concurrently with a taxane following anthracycline therapy up to 2.37% compared to approximately 1% in the two comparator arms (anthracycline plus cyclophosphamide followed by taxane and taxane, carboplatin and trastuzumab).

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (> 50 years), low LVEF (<55%) at baseline, prior to or following the initiation of paclitaxel treatment, decline in LVEF by 10-15 points, and prior or concurrent use of anti-hypertensive medicinal products. In patients receiving trastuzumab after completion of adjuvant chemotherapy the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of trastuzumab and a body mass index (BMI) >25 kg/m2.

Neoadjuvant-adjuvant treatment

In patients with EBC eligible for neoadjuvant-adjuvant treatment, Hertisan should be used concurrently with anthracyclines only in chemotherapy-naive patients and only with low-dose anthracycline regimens i.e. maximum cumulative doses of doxorubicin 180 mg/m2 or epirubicin 360 mg/m2.

If patients have been treated concurrently with a full course of low-dose anthracyclines and Hertisan in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery. In other situations, the decision on the need for additional cytotoxic chemotherapy is determined based on individual factors.

Experience of concurrent administration of trastuzumab with low dose anthracycline regimens is currently limited to two trials. In the pivotal trial MO16432, trastuzumab was administered concurrently with neoadjuvant chemotherapy that contained three cycles of doxorubicin (cumulative doxorubicin dose 180 mg/m2). The incidence of symptomatic cardiac dysfunction was low in the trastuzumab arms (up to 1.7 %).

Clinical experience is limited in patients above 65 years of age.

Infusion-related reactions (IRRs) and hypersensitivity

Serious IRRs to trastuzumab infusion including dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema have been reported . Pre-medication may be used to reduce risk of occurrence of these events. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the infusion should be discontinued, or the rate of infusion slowed, and the patient should be monitored until resolution of all observed symptoms. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. The majority of patients experienced resolution of symptoms and subsequently received further infusions of trastuzumab. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta- agonists, and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction.

Therefore, these patients should not be treated with Hertisan .

Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms and pulmonary symptoms more than six hours after the start of the trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

Pulmonary events

Severe pulmonary events have been reported with the use of trastuzumab in the post-marketing setting . These events have occasionally been fatal. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. These events may occur as part of an infusion-related reaction or with a delayed onset. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with Hertisan . Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

Contraindication :

- Hypersensitivity to Herticad®, murine proteins, or to any of the excipients .
- Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

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Pregnancy and lactation:

Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception during treatment with Hertisan and for 7 months after treatment has concluded .

Pregnancy

Reproduction studies have been conducted in Cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab intravenous formulation and have revealed no evidence of impaired fertility or harm to the foetus. Placental transfer of trastuzumab during the early (days 20–50 of gestation) and late (days 120–150 of gestation) foetal development period was observed. It is not known whether trastuzumab can affect reproductive capacity. As animal reproduction studies are not always predictive of human response, Hertisan should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus.

In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving trastuzumab. Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with Herticad®, or if a patient becomes pregnant while receiving Hertisan or within 7 months following the last dose of Herticad®, close monitoring by a multidisciplinary team is desirable.

Breast-feeding

A study conducted in lactating Cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab intravenous formulation demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age. It is not known whether trastuzumab is secreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breastfeed during Hertisan therapy and for 7 months after the last dose.

(This card focuses on major safety information for medicinal products in order to minimize possible side effects that arise from improper use of medicinal products).

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