Perjeta®

Pertuzumab

Composition

Active substance: Pertuzumab.

Excipients: Glacial acetic acid, L-histidine, sucrose, polysorbate 20 (produced from genetically modified maize), water for injection.

Pharmaceutical form and amount of active substance per unit

Concentrate for solution for infusion.

1 rubber-stoppered vial with 14 ml concentrate contains 420 mg pertuzumab.

Indications and potential uses

Perjeta is indicated in combination with Herceptin and docetaxel for the treatment of patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received prior chemotherapy for their metastatic disease.

Dosage and administration

It is mandatory for Perjeta treatment to be initiated under the supervision of a physician with experience in treating cancer patients.

Tumour status in patients treated with Perjeta should be HER2-positive, defined as an immunohistochemistry score of 3+ or an ISH amplification ratio of ≥2.0 determined using a validated test.

Perjeta should be administered as an intravenous infusion and not as an intravenous bolus injection.

Standard dosage

The recommended initial dose of Perjeta is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by a dose of 420 mg administered over 30 to 60 minutes.

Herceptin is administered as an intravenous infusion at an initial dose of 8 mg/kg, followed by a dose of 6 mg/kg every 3 weeks.

See the corresponding prescribing information for the dosage of docetaxel.

It is recommended to continue triple combination treatment with Perjeta until disease progression or the occurrence of unacceptable toxicity. If docetaxel is discontinued, treatment with Perjeta and Herceptin may continue.

Delayed or missed doses

If the time between two sequential infusions is less than 6 weeks, the 420 mg dose of Perjeta should be administered as soon as possible, without waiting for the next planned dose. If the time between two sequential infusions is 6 weeks or more, the initial dose of 840 mg Perjeta should be readministered as an intravenous infusion over 60 minutes, followed every 3 weeks thereafter by a dose of 420 mg administered over 30 to 60 minutes.

Special dosage instructions

Children and adolescents

The safety and efficacy of Perjeta have not been studied in children and adolescents under 18 years of age.

Elderly patients

No differences in the safety and efficacy of Perjeta were observed between adult patients aged ≥65 and <65 years. Dose adjustment is not required in elderly patients.

Renal impairment

The safety and efficacy of Perjeta have not been studied in patients with renal impairment (see *Pharmacokinetics, pharmacokinetics in special patient groups*).

Hepatic impairment

The safety and efficacy of Perjeta have not been studied in patients with hepatic impairment.

Contraindications

Hypersensitivity to the active ingredient or to any of the excipients.

Warnings and precautions

Infusion-associated reactions and hypersensitivity reactions/anaphylaxis

Infusion and hypersensitivity reactions have been reported on Perjeta treatment. Close patient observation is recommended when administering Perjeta during and for 60 minutes after the first infusion and during and for 30 minutes after subsequent infusions. If a significant infusion-associated reaction occurs, the infusion should be slowed or interrupted. In severe hypersensitivity reactions it should be discontinued immediately. Patients should be assessed and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation of Perjeta should be considered in patients with severe infusion reactions. Clinical assessment should be based on the severity of the preceding reaction and the response to the adverse effect treatment administered.

Left ventricular dysfunction

Patients who have received prior anthracyclines or prior radiotherapy to the chest area are at higher risk of decreased LVEF.

Perjeta has not been studied in patients with a pretreatment LVEF value of ≤50%, a prior history of congestive heart failure (CHF), decreases in LVEF to <50% during prior adjuvant Herceptin therapy or conditions that could impair left ventricular function (such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or prior anthracycline exposure to 360 mg/m^2 doxorubicin or its equivalent).

LVEF must be assessed prior to initiation of Perjeta therapy and at regular intervals (e.g. every three months) during treatment to ensure that it is within the institution's normal limits. If LVEF is <40% or 40% to 45% in conjunction with a 10% or greater decrease below the pretreatment value, Perjeta and Herceptin should be withheld and LVEF assessment repeated within approximately 3 weeks. If LVEF has not improved or has even declined further, discontinuation of Perjeta and Herceptin dosing should be strongly considered unless the benefits for the individual patient are deemed to outweigh the risks. Perjeta and Herceptin dosing must be withheld for at least 3 weeks if

- LVEF drops to less than 40%.
- an LVEF of 40% to 45% occurs in conjunction with a 10% or greater decrease below the pretreatment value.

Perjeta and Herceptin dosing may be resumed if the LVEF has recovered to greater than 45% or to 40% to 45% associated with less than a 10% decrease below the pretreatment value.

If after a repeat assessment within approximately 3 weeks the LVEF has not improved or has even declined further, discontinuation of Perjeta and Herceptin dosing should be strongly considered unless the benefits for the individual patient are deemed to outweigh the risks.

Interactions

Studies have investigated the effects of pertuzumab on the pharmacokinetics of the coadministered cytotoxics trastuzumab, docetaxel, gemcitabine, erlotinib and capecitabine. There was no evidence of pharmacokinetic interaction between pertuzumab and any of these agents.

Pregnancy and lactation

Pregnancy

Perjeta should not be used during pregnancy except if the potential benefit for the mother outweighs the possible risk to the fetus. Women of childbearing age and male patients'

female partners of childbearing age should use a reliable method of contraception during treatment with Perjeta and for 6 months after the last dose.

No studies have been conducted with Perjeta in pregnant women. Perjeta administered to cynomolgus monkeys during organogenesis caused oligohydramnios, delayed renal development and embryo-fetal death (see *Pharmacokinetics, teratogenicity*).

Lactation

Since human IgG is excreted in human milk and the possible risk of absorption and harm to the nursing infant is unknown, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance to the mother and elimination half-life of pertuzumab (see *Pharmacokinetics, elimination*).

Effects on ability to drive and use machines

No studies have been performed on the effects on the ability to drive or operate machines.

Undesirable effects

The safety of Perjeta was assessed in over 1400 patients in either the CLEOPATRA pivotal study or in Phase I and II studies. The studies were performed in patients with various malignancies.

The adverse effect frequency data are based on the pivotal study of Perjeta in combination with Herceptin and docetaxel.

The most common adverse effects (>50%) were diarrhea, alopecia and neutropenia. The most common Grade 3–4 adverse effects (>10%) were neutropenia, febrile neutropenia and leukopenia.

The frequency categories are listed using MedDRA terminology: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

Infections and infestations

Very common: Upper airway infections (16.7% [Grade 3–4 0.7%]), nasopharyngitis (11.8% [Grade 3–4 0%]).

Common: Paronychia.

Blood and lymphatic system disorders

Very common: Neutropenia (52.8% [Grade 3–4 48.9%]), anemia (23.1% [Grade 3–4 2.5%]), leukopenia (18.2% [Grade 3–4 12.3%]), febrile neutropenia (13.8% [Grade 3–5 13.8%]).

Immune system disorders

Common: Hypersensitivity.

Metabolic and nutritional disorders

Very common: Decreased appetite (29.2% [Grade 3–4 1.7%]).

Psychiatric disorders

Very common: Insomnia (13.3%).

Nervous system disorders

Very common: Peripheral neuropathy (21.1% [Grade 3–4 2.7%]), headaches (20.9% [Grade 3–4 1.2%]), dysgeusia (18.4%), peripheral sensory neuropathy (12.0% [Grade 3–4 0.5%]), dizziness (12.5% [Grade 3–4 0.5%]).

Eye disorders

Very common: Increased lacrimation (14.0%).

Cardiac disorders

Common: Left ventricular dysfunction, including symptomatic left ventricular systolic dysfunction.

Respiratory organs (respiratory, thoracic and mediastinal disorders)

Very common: Dyspnea (14.0% [Grade 3–4 1.0%]).

Common: Pleural effusion (5.2%).

Gastrointestinal disorders

Very common: Diarrhea (66.8% [Grade 3–4 7.9%]), nausea (42.3% [Grade 3–4 1.2%]), vomiting (24.1% [Grade 3–4 1.5%]), constipation (15.0% [Grade 3–4 0%]), stomatitis (18.9% [Grade 3–4 0.5%]).

Skin and subcutaneous tissue disorders

Very common: Alopecia (60.9% [Grade 3–4 0%]), rash (33.7% [Grade 3–4 0.7%]), nail disorders (22.9% [Grade 3–4 1.2%]), pruritus (14.0%), dry skin (10.6% [Grade 3–4 0%]).

Musculoskeletal system (locomotor apparatus, connective tissue and bone disorders)

Myalgia (22.9% [Grade 3–4 1.0%]), arthralgia (15.5% [Grade 3–4 0.2%]).

General disorders

Very common: Exhaustion (37.6% [Grade 3–4 2.2%]), asthenia (26.0% [Grade 3–4 2.5%]), peripheral edema (23.1% [Grade 3–4 0.5%]), mucosal inflammation (27.8% [Grade 3–4 1.5%]), fever (18.7% [Grade 3–4 1.2%]).

Further data on selected adverse effects

Most hypersensitivity reactions were generally mild to moderate in severity and resolved after treatment. Based on change in the study medication, most reactions were classified as being due to the infusions of docetaxel.

Overdosage

No experience with overdosage is available from clinical trials in humans.

Properties and effects

ATC code: L01XC13

Mechanism of action/pharmacodynamics

Pertuzumab is a recombinant humanised monoclonal antibody. It binds specifically to the extracellular dimerisation domain (Subdomain II) of the HER2 receptor, while trastuzumab binds to Domain IV. Pertuzumab thereby blocks the formation of ligand-

dependent heterodimerisation of HER2 with other family members, including HER1, HER3 and HER4.

As a result pertuzumab inhibits ligand-initiated intracellular signalling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

While pertuzumab alone inhibits the proliferation of human tumour cells, the combination of pertuzumab and Herceptin significantly augments antitumour activity in HER2-overexpressing xenograft models.

Clinical efficacy

Metastatic and locally recurrent breast cancer

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This multicentre, randomised, double-blind, placebo-controlled Phase III clinical study was conducted in 808 patients with metastatic or locally recurrent unresectable HER2-positive breast cancer. Patients were randomised 1:1 and treated with placebo plus Herceptin and docetaxel or Perjeta plus Herceptin and docetaxel.

The primary endpoint of the study was progression-free survival (PFS assessed by an independent review facility [IRF]). The secondary efficacy endpoints were overall survival (OS), investigator-assessed PFS, overall response rate (ORR), duration of response and time to symptom progression evaluated using the FACT-B quality of life questionnaire. Demographic characteristics were balanced.

The difference in median PFS was 6.1 months (median PFS of 12.4 months in the group treated with placebo compared to 18.5 months in the group treated with Perjeta (hazard ratio [HR] = 0.62; 95% CI = 0.51, 0.75; $p<0.0001$). The results for investigator-assessed PFS were comparable to those for IRF-assessed PFS.

At the time of the primary efficacy analysis, 165 patients had died. Median time to death was not reached at the time of the analysis (HR 0.64; $p=0.0053$).

With respect to health-related quality of life, which was determined by the time to symptom progression on the FACT-B TOI-PFB subscale, defined as a reduction of 5 points in the subscale score, there was no statistically significant difference between the treatment groups (HR = 0.97; 95% CI = 0.81, 1.16).

Immunogenicity

Patients in the pivotal study were tested at multiple time-points for anti-therapeutic antibodies (ATA) to Perjeta. Approximately 6.2% (23/372) patients in the placebo-treated group and 2.8% (11/386) of patients in the Perjeta-treated group tested positive for ATA. Of these 34 patients, none experienced anaphylactic/hypersensitivity reactions that were clearly ATA-related.

Pharmacokinetics

Distribution

The volume of distribution is 3.07 l.

Metabolism

The metabolism of pertuzumab has not been directly studied. In principle, antibodies are broken down like other proteins.

Elimination

The clearance of pertuzumab is approximately 0.239 L/day. The elimination half-life is approximately 17.2 days.

Pharmacokinetics in special patient groups

Elderly patients

No specific studies of pertuzumab have been performed in elderly patients. In a population pharmacokinetic analysis age had no significant influence on the pharmacokinetics of pertuzumab. In this analysis 32.5% (n=143) of the patients were ≥65 years old and 9.1% (n=40) of the patients were ≥75 years old.

Children and adolescents

The pharmacokinetics of pertuzumab have not been studied in pediatric patients.

Renal impairment

No pharmacokinetic studies have been performed in patients with renal impairment. Based on the population pharmacokinetic analysis, renal impairment is not expected to influence pertuzumab exposure. However, the population pharmacokinetic analysis included only limited data from patients with moderate or severe renal impairment.

Hepatic impairment

No pharmacokinetic studies have been performed with pertuzumab in patients with hepatic impairment.

Preclinical data

Carcinogenicity

No long-term animal studies have been performed to assess the carcinogenic potential of pertuzumab.

Mutagenicity

No studies have been performed to assess the mutagenic potential of pertuzumab.

Fertility

No specific fertility studies have been performed in animals to assess the effect of pertuzumab. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of up to 6 months duration in cynomolgus monkeys.

Teratogenicity

Reproductive toxicity studies were performed in cynomolgus monkeys with loading doses of 30 to 150 mg/kg and maintenance doses of 10 to 100 mg/kg, achieving clinically relevant doses. Intravenous administration of pertuzumab from gestational day (GD) 19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent

increases in embryo-fetal deaths between GD25 to GD70. Delayed renal development and oligohydramnios were observed on GD100.

Other

Weekly intravenous pertuzumab administration at doses up to 150 mg/kg was generally well-tolerated in cynomolgus monkeys. Mild intermittent treatment-induced diarrhea was observed at doses of 15 mg/kg and above. Chronic dosing (7 to 26 weekly doses) in a subgroup of the monkeys resulted in episodes of diarrhea-induced dehydration that were treated with intravenous fluid replacement therapy.

Additional information

Incompatibilities

No incompatibilities have been observed between Perjeta and polyvinyl chloride, polyethylene or PVC-free polyolefin bags.

Glucose solution (5%) must not be used to dilute Perjeta as Perjeta has proved unstable in such solutions.

Perjeta must not be mixed or diluted with other medicinal products.

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Special precautions for storage

Store in a refrigerator (2–8°C). Store the container inside the outer package in order to protect the contents from light.

Do not freeze. Do not shake.

Store medicines out of reach of children.

Instructions for handling and disposal

Perjeta contains no antimicrobial preservatives. Care is required in preparation in order to ensure the sterility of the reconstituted solution and for this reason the dilution of Perjeta should be performed by healthcare professionals using aseptic technique.

The entire liquid concentrate of Perjeta should be withdrawn from the vial and diluted in a 250 ml polyvinyl chloride (PVC) or PVC-free polyolefin infusion bag with 0.9% sodium chloride.

Glucose solutions (5%) must not be used for dilution (see *Incompatibilities*). To mix the solution the bag should be gently inverted to avoid foaming.

Parenteral drug products should be inspected visually for particulates and discolouration prior to administration. Chemical and physical in-use stability has been demonstrated for 24 hours at up to 30°C. For microbiological reasons the ready-to-use solution should be used immediately after opening.

Any medicinal products unused after the end of treatment or by the expiry date should be returned in their original packaging to the place of supply (physician or pharmacist) for proper disposal.

Packs

Vials 420mg/14ml 1

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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