PRODUCT MONOGRAPH

PrPERJETA®

pertuzumab for injection

420 mg/14 mL vial

For Intravenous Infusion Only

Sterile Concentrate for Solution for Infusion

Antineoplastic

Professed Standard

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PrPERJETA®

pertuzumab for injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous (IV) infusion	420mg/14 mL	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

Description
PERJETA (pertuzumab) is a recombinant humanized monoclonal antibody based upon the human IgG1(κ) framework sequence and is a first-in-class human epidermal growth factor receptor 2 (HER) dimerization inhibitor.

INDICATIONS AND CLINICAL USE

Metastatic Breast Cancer
PERJETA (pertuzumab) is indicated in combination with HERCEPTIN (trastuzumab) and docetaxel for the treatment of patients with HER2- positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Early Breast Cancer
PERJETA is indicated in combination with HERCEPTIN and chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer with lymph node positive and/or hormone receptor negative disease (see Clinical Trials section).

Selection of Patients/Diagnostic Tests:
Patients treated with PERJETA should have HER2 positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) or a ratio of ≥ 2.0 by in situ hybridization (ISH) assessed by a validated test.

Geriatrics
No overall differences in efficacy of PERJETA were observed between adult patients ≥65 and <65 years of age. The incidence of the following all grade adverse events was at least 5% higher in patients aged ≥65 years of age, compared to patients aged <65 years of age: decreased

appetite, anemia, weight decreased, asthenia, dysgeusia, peripheral neuropathy, hypomagnesemia and diarrhea. No dose adjustment is required in the elderly population (≥65 years of age).

Pediatrics
The safety and efficacy of PERJETA in children and adolescents below 18 years of age have not been established.

CONTRAINDICATIONS

PERJETA (pertuzumab) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Refer to the Product Monographs of HERCEPTIN and docetaxel for further information on the contraindications of these drugs.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Left Ventricular Dysfunction: Subclinical and clinical cardiac failure has been observed in a clinical trial with PERJETA in neoadjuvant setting. Evaluate left ventricular function in all patients prior to and during treatment with PERJETA. For more information, including information on discontinuation criteria, see WARNINGS AND PRECAUTIONS: Cardiovascular, Left Ventricular Dysfunction.

Embryo-Fetal Toxicity: Exposure to PERJETA (pertuzumab) can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception (see WARNINGS AND PRECAUTION: Special Population, Pregnant Women).

Hypersensitivity reactions /anaphylaxis and Infusion-related reactions: PERJETA has been associated with severe hypersensitivity reactions, anaphylaxis and infusion-related reactions. Events with fatal outcomes have been observed (see WARNINGS AND PRECAUTION: Immune). Patients should be evaluated and carefully monitored during and after infusions. Permanent discontinuation should be considered in patients with severe reactions.

PERJETA can cause fetal harm when administered to a pregnant woman. Treatment of pregnant cynomolgus monkeys with pertuzumab resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death (see TOXICOLOGY: Teratogenicity). If PERJETA is

administered during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be informed of the potential hazard to a fetus (see WARNINGS AND PRECAUTIONS: Special Populations, Pregnant Women).

General

Therapy with PERJETA should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Cardiovascular

Left ventricular dysfunction

Decreases in LVEF have been reported with drugs that block HER2 activity, including PERJETA. The incidence of symptomatic left ventricular systolic dysfunction (LVD [congestive heart failure]) was higher in patients treated with PERJETA in combination with HERCEPTIN and chemotherapy compared to treatment with HERCEPTIN and chemotherapy. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF. The majority of cases of symptomatic heart failure reported in the adjuvant setting were in patients who had received anthracycline-based chemotherapy (see ADVERSE REACTIONS).

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

Prior to the initiation of PERJETA and HERCEPTIN, candidate patients should undergo thorough baseline cardiac assessment including history and physical exam, electrocardiogram (ECG) and either 2D echocardiogram or multiple gated acquisition (MUGA) scan to ensure that LVEF is within normal limits. A careful risk-benefit assessment should be made before deciding to treat with PERJETA and HERCEPTIN. Cardiac assessments, as performed at baseline, should be repeated at regular intervals (see Table 1 below). If the LVEF declines as indicated in Table 1 and has not improved, or has declined further at the subsequent assessment, discontinuation of PERJETA and HERCEPTIN should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. Following discontinuation of treatment, cardiac assessments should be performed every 6 months up until 24 months from the last administration of PERJETA and/or HERCEPTIN.

Table 1 – Dose Recommendations for Left Ventricular Dysfunction

	Pre-treatment LVEF:	Monitor LVEF every:	Withhold PERJETA and HERCEPTIN for at least 3 weeks for an LVEF decrease to:		Resume PERJETA and HERCEPTIN after 3 weeks if LVEF has recovered to:	
Metastatic Breast Cancer	≥ 50%	~12 weeks	Either		Either	
			<40%	40%-45% with a fall of ≥10%-points below pre-treatment value	>45%	40%-45% with a fall of <10%-points below pre-treatment value
Early Breast Cancer	≥ 55%*	~12 weeks	<50% with a fall of ≥10%-points below pre-treatment value		Either	
					≥ 50%	< 10% points below pre-treatment value

*for patients receiving anthracycline-based chemotherapy, a LVEF of ≥ 50% is required after completion of anthracyclines, before starting PERJETA and HERCEPTIN

Gastrointestinal

Diarrhea

PERJETA may elicit severe diarrhea (see ADVERSE REACTIONS). In case of onset of severe diarrhea an anti-diarrheal treatment should be instituted and interruption of the treatment with PERJETA should be considered if no improvement of the condition is achieved. When the diarrhea is under control the treatment with PERJETA may be reinstated.

Hematologic

Febrile Neutropenia

Patients treated with PERJETA, HERCEPTIN and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, HERCEPTIN and docetaxel, especially during the first 3 cycles of treatment (see ADVERSE REACTIONS). As nadir neutrophil counts were similar in PERJETA-treated and placebo-treated patients, the higher incidence of febrile neutropenia in PERJETA-treated patients may be related to the higher incidence of mucositis and diarrhea in these patients. Symptomatic treatment for mucositis and diarrhea should be considered.

Immune

Hypersensitivity reactions/anaphylaxis

Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have been observed in patients treated with PERJETA (see ADVERSE REACTIONS). Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. PERJETA must be permanently discontinued in case of NCI-CTCAE Grade 4 hypersensitivity reactions (anaphylaxis), bronchospasm or acute respiratory distress syndrome (ARDS). PERJETA is contraindicated in patients who are hypersensitive to pertuzumab or to any ingredient in the formulation (see CONTRAINDICATIONS).

Infusion-related reactions
PERJETA has been associated with infusion-related reactions, including events with fatal outcomes (see ADVERSE REACTIONS). Close observation of the patient during and for 60 minutes after the first infusion and during and for 30 minutes following subsequent infusions of PERJETA is recommended. If a significant infusion-related reaction occurs, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be considered in patients with severe infusion reactions. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction (see DOSAGE AND ADMINISTRATION).

Special Populations
Pregnant Women: There are no studies of PERJETA in pregnant women. Based on findings in animal studies, PERJETA could cause fetal harm when administered to a pregnant woman. The effects of PERJETA are likely to be present during all trimesters of pregnancy. PERJETA administered to cynomolgus monkeys during organogenesis led to oligohydramnios, delayed renal development and embryo fetal death (see TOXICOLOGY: Teratogenicity). Women of child-bearing potential should use effective contraception while receiving PERJETA in combination with HERCEPTIN and for 7 months following the last doses of PERJETA and HERCEPTIN. Male patients with female partners of child bearing potential should also use effective contraception while receiving PERJETA in combination with HERCEPTIN and for 7 months following the last dose.

Monitor patients who become pregnant during PERJETA therapy for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care. The efficacy of intravenous hydration in the management of oligohydramnios due to PERJETA exposure is not known.

Labour and Delivery: The safe use of PERJETA during labour and delivery has not been established.

Nursing Women: Because human IgG is secreted in human milk, and the potential for absorption and harm to the infant is unknown, a decision should be made to discontinue nursing or the PERJETA-treatment taking into account the importance to the mother and the elimination half- life of pertuzumab (see ACTION AND CLINICAL PHARMACOLOGY: Excretion).

Pediatrics (< 18 years of age): The safety and efficacy of PERJETA in children and adolescents below 18 years of age have not been established.

Geriatrics (≥ 65 years of age): No overall differences in efficacy of PERJETA were observed between adult patients ≥65 and <65 years of age. The incidence of the following all grade adverse events was at least 5% higher in patients aged ≥65 years of age, compared to patients aged <65 years of age: decreased appetite, anemia, weight decreased, asthenia, dysgeusia,

peripheral neuropathy, hypomagnesemia and diarrhea. No dose adjustment is required in the elderly population (≥65 years of age).

Renal Impairment: The safety and efficacy of PERJETA have not been studied in patients with renal impairment.

Hepatic Impairment: The safety and efficacy of PERJETA have not been studied in patients with hepatic impairment.

Race: In the pivotal trial WO20698/TOC4129g (CLEOPATRA), an increased incidence of neutropenia and febrile neutropenia was observed for Asian patients in both treatment arms compared with patients of other races and from other geographic regions. Among Asian patients, there was no difference in the incidence of neutropenia between the PERJETA-treated group (58.6%) and the placebo-treated group (58.6%). However, the incidence of febrile neutropenia was higher in the PERJETA-treated group (25.8%) compared with the placebo-treated group (11.3%). In the APHINITY trial, the incidence of febrile neutropenia in Asian patients was 15.9% in the PERJETA-treated group and 9.9% in the placebo-treated group.
The reason for this difference is not known.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The safety of PERJETA (pertuzumab) has been evaluated in more than 6000 patients in Phase I, II and III clinical trials. Patients in these studies had various malignancies, and were predominantly treated with PERJETA in combination with other antineoplastic agents. Those studies included the pivotal trials WO20698/TOC4129g (CLEOPATRA) (n=808) and BO25126 (APHINITY) (n=4804). The safety of PERJETA was generally consistent across studies, although the incidence and most common adverse drug reactions (ADRs) varied depending on whether PERJETA was administered as monotherapy or in combination with other antineoplastic agents.

Metastatic Breast Cancer

Table 2 summarizes the adverse drug reactions (ADRs) from the pivotal clinical trial CLEOPATRA in which PERJETA was given in combination with HERCEPTIN and docetaxel vs placebo with HERCEPTIN and docetaxel. The most common ADRs (>30%) seen in patients

treated with PERJETA in combination with HERCEPTIN and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash and peripheral neuropathy. The most common NCI-CTCAE (version 3) Grade 3-4 ADRs (≥10%) were neutropenia, febrile neutropenia and leukopenia. The most common serious adverse reactions were febrile neutropenia, neutropenia and diarrhea.

Table 2 - Summary of Adverse Drug Reactions Occurring in ≥1% from the Pivotal Clinical Trial CLEOPATRA

Adverse Drug Reaction (ADR) (MedDRA) System Organ Class	Placebo + HERCEPTIN + docetaxel n =396 Frequency rate %		PERJETA + HERCEPTIN + docetaxel n =408 Frequency rate %	
	All Grades	Grades 3-4	All Grades	Grades 3-4
General disorders and administration site conditions				
Fatigue	37.4	3.3	38.0	2.2
Asthenia	30.8	1.8	27.7	2.7
Edema peripheral	28.0	0.8	24.0	0.5
Mucosal inflammation/Mucositis	19.9	1.0	27.2	1.5
Pyrexia	18.2	0.5	20.1	1.2
Chills	3.8	-	8.3	-
Skin and subcutaneous tissue disorders				
Alopecia	60.6	0.3	60.8	-
Rash	24.0	0.8	37.5	0.7
Nail disorder	23.2	0.3	23.5	1.2
Pruritus	10.1	-	17.6	-
Dry skin	6.1	-	11.3	-
Erythema	5.1	-	5.9	-
Dermatitis acneiform	1.8	-	3.7	-
Gastrointestinal disorders				
Diarrhea	48.7	5.1	68.4	9.3
Nausea	42.4	0.5	44.9	1.2
Vomiting	24.5	1.5	26.0	1.5
Constipation	25.5	1.0	15.9	-
Stomatitis	15.9	0.3	19.9	0.5
Dyspepsia	12.1	-	13.2	-
Blood and lymphatic system disorders				
Neutropenia	50.0	46.2	53.4	49.0
Anaemia	19.7	3.5	24.0	2.5
Leukopenia	20.7	14.9	18.4	12.3
Febrile neutropenia*	7.6	7.3	13.7	13.0
Nervous system disorders				
Headache	19.2	1.0	25.7	1.7
Neuropathy peripheral	19.9	1.8	22.3	2.7
Dysgeusia	15.7	-	18.4	-
Peripheral sensory neuropathy	14.9	0.3	12.3	0.5
Dizziness	13.4	-	15.0	0.7

Adverse Drug Reaction (ADR) (MedDRA) System Organ Class	Placebo + HERCEPTIN + docetaxel n =396 Frequency rate %		PERJETA + HERCEPTIN + docetaxel n =408 Frequency rate %	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Musculoskeletal and connective tissue disorders				
Myalgia	25.0	0.8	24.3	1.2
Arthralgia	17.4	0.8	19.4	0.2
Infections and infestations				
Upper respiratory tract infection	14.4	-	20.8	0.7
Nasopharyngitis	14.9	0.3	16.9	-
Paronychia	4.0	0.3	7.6	-
Respiratory, thoracic and mediastinal disorders				
Cough	19.9	0.3	23.5	0.5
Dyspnea	15.9	2.0	15.2	1.0
Pleural effusion	5.6	1.3	5.1	0.2
Metabolism and nutrition disorders				
Decreased appetite	26.8	1.5	29.7	1.7
Eye disorders				
Lacrimation increased	13.9	-	14.7	-
Psychiatric disorders				
Insomnia	13.9	-	15.7	-
Cardiac disorders				
Left ventricular dysfunction[1]	8.6	3.3	6.6	1.5
Immune system disorders				
Hypersensitivity	5.3	0.8	6.9	1.0
Drug hypersensitivity	3.8	1.5	4.4	0.5
Anaphylactic reaction	0.5	0.3	1.0	0.5
Infusion-Related Reactions[2]	9.8	0.3	13.2	0.2

***** In this table this denotes an adverse reaction that has been reported in association with a fatal outcome

[1]Including Symptomatic Left Ventricular Systolic Dysfunction (CHF) (1.5% in the PERJETA-treated group vs. 1.8% in the placebo-treated group)

[2]Incidences reflect those occurring on the first day of infusion, when only PERJETA was administered

Listing 1: The following adverse reactions were reported at an incidence of < 1% in the pivotal clinical trial CLEOPATRA:

Respiratory, Thoracic and Mediastinal Disorders: Interstitial Lung Disease

Table 3 - Summary of Adverse Events (AEs) with a ≥2% Higher Incidence in the PERJETA-treated Group Compared to the Placebo-treated Group from the Pivotal Clinical Trial CLEOPATRA

Adverse Event (AE) (MedDRA) System Organ Class	Placebo + HERCEPTIN + docetaxel n =396 Frequency rate %		PERJETA + HERCEPTIN + docetaxel n =408 Frequency rate %	
	All Grades	Grades 3-4	All Grades	Grades 3-4
General disorders and administration site conditions				
Influenza like illness	2.3	-	5.6	0.2
Gastrointestinal disorders				
Dysphagia	0.3	-	2.7	0.2
Musculoskeletal and connective tissue disorders				
Pain in extremity	13.4	0.3	17.9	0.5
Back Pain	12.1	1.0	16.4	1.5
Muscle spasms	5.1	-	10.3	0.2
Infections and infestations				
Pharyngitis	2.3	0.3	5.1	0.2
Cellulitis	3.3	0.5	5.4	1.7
Cystitis	1.5	-	3.7	-
Rash pustular	-	-	2.5	0.5
Metabolism and nutrition disorders				
Hypokalaemia	5.3	1.3	9.1	1.5
Eye disorders				
Conjunctivitis	4.3	-	7.6	0.2
Dry eye	2.0	-	5.6	-
Investigations				
Weight decreased	4.8	0.3	8.8	0.5
Renal and urinary disorders				
Dysuria	2.8	-	5.6	-
Respiratory, thoracic and mediastinal disorders				
Rhinorrhea	5.8	-	7.8	-
Vascular Disorders				
Hypertension	8.3	1.8	11.0	2.0

AEs including ADRs reported in patients receiving PERJETA and HERCEPTIN after discontinuation of docetaxel

In the pivotal trial CLEOPATRA, ADRs were reported less frequently after discontinuation of docetaxel treatment. After discontinuation of docetaxel, ADRs in the PERJETA and HERCEPTIN treatment group occurred in <10% of patients with the exception of diarrhea (28.1%), rash (18.3%), upper respiratory tract infection (18.3%), headache (17.0%),

nasopharyngitis (17.0%), pruritus (13.7%), fatigue (13.4%), asthenia (13.4%), nausea (12.7%) and arthralgia (11.4%).

After discontinuation of docetaxel treatment, AEs (regardless of causality) that were reported with a ≥ 2% difference in patients in the PERJETA-treated arm compared with the placebo-treated arm were diarrhea, abdominal pain, gastritis, upper respiratory tract infection, urinary tract infection, herpes zoster, pain in extremity, rash, dermatitis acneiform, pruritus, , peripheral neuropathy, headache, hypoaesthesia, fatigue, asthenia, mucosal inflammation, edema, muscle spasms, back pain, musculoskeletal chest pain, paronychia, onycholysis, oropharyngeal pain, hypokalemia, conjunctivitis, hypertension, and lymphoedema.

Early Breast Cancer

Table 4 summarizes the ADRs from the pivotal clinical trial APHINITY, in which PERJETA was given in combination with HERCEPTIN and chemotherapy or placebo in combination with HERCEPTIN and chemotherapy. Table 4 reports the ADRs that occurred in at least 1% of patients in the PERJETA-treated group.

When PERJETA was administered in combination with HERCEPTIN and chemotherapy, the most common ADRs (>30%) were diarrhea, nausea, alopecia, fatigue, and vomiting. The most common NCI-CTCAE (version 4.0) Grade 3-4 ADRs (> 2%) were neutropenia, febrile neutropenia, diarrhea, neutrophil count decreased, anemia, white blood cell count decreased, leukopenia, fatigue, nausea, and stomatitis.

Table 4 - Summary of Adverse Drug Reactions Occurring in ≥1% of Patients Receiving PERJETA in the Pivotal Clinical Trial APHINITY

Adverse Drug Reaction (ADR) **(MedDRA)** **System Organ Class**	**Placebo + HERCEPTIN + chemotherapy** **n=2405** **Frequency rate %**		**PERJETA + HERCEPTIN + chemotherapy** **n=2364** **Frequency rate %**	
	All Grades	**Grades 3-4**	**All Grades**	**Grades 3-4**
Cardiac disorders				
Cardiac Failure	0.7	0.2	1.4	0.7
General disorders and administration site conditions				
Fatigue	44.3	2.5	48.8	3.9
Mucosal inflammation	18.6	0.7	23.4	1.7
Asthenia	20.8	1.7	21.4	1.4
Pyrexia	19.5	0.7	20.0	0.6
Edema peripheral	20.1	0.2	17.1	-
Skin and subcutaneous tissue disorders				
Alopecia	66.9	<0.1	66.7	<0.1
Rash	20.3	0.2	25.8	0.4
Pruritus	9.0	<0.1	14.0	0.1

Palmar-plantar erythrodysaesthesia syndrome	6.6	0.4	9.1	1.2
Dry skin	11.1	<0.1	13.2	0.1
Nail disorder	11.8	0.1	11.8	0.2
Gastrointestinal disorders				
Diarrhea	45.2	3.7	71.2	9.8
Nausea	65.5	2.5	69.0	2.4
Vomiting	30.5	1.8	32.5	1.9
Constipation	31.6	0.3	28.9	0.5
Stomatitis	23.8	1.0	28.4	2.2
Dyspepsia	14.2	-	13.7	-
Abdominal pain	10.9	0.6	12.1	0.5
Abdominal pain upper	9.1	0.2	10.4	0.3
Blood and lymphatic system disorders				
Anemia	23.2	4.7	27.7	6.9
Neutropenia	23.4	15.7	24.8	16.3
Febrile neutropenia*	11.1	11.1	12.1	12.1
Leukopenia	9.2	4.4	9.1	4.4
Nervous system disorders				
Dysgeusia	21.5	<0.1	26.0	0.1
Headache	23.4	0.4	22.5	0.3
Peripheral sensory neuropathy	17.5	0.5	18.1	0.6
Neuropathy peripheral	15.3	0.6	15.5	0.5
Parasthesia	10.0	0.2	11.8	0.5
Dizziness	11.4	0.2	11.4	-
Musculoskeletal and connective tissue disorders				
Arthralgia	32.5	1.1	28.7	0.9
Myalgia	29.5	1.3	26.0	0.9
Pain in extremity	10.5	0.2	10.0	0.2
Infections and infestations				
Nasopharyngitis	11.8	0.1	13.4	<0.1
Upper respiratory tract infection	7.4	0.2	8.1	0.3
Paronychia	2.3	<0.1	3.9	0.1
Respiratory, thoracic, and mediastinal disorders				
Epistaxis	13.6	-	18.2	<0.1
Cough	14.6	<0.1	15.8	<0.1
Dyspnea	11.5	0.5	11.9	0.4
Metabolism and nutrition disorders				
Decreased appetite	19.9	0.4	23.9	0.8
Hypokalaemia	4.0	0.6	6.5	1.9
Hypomagnesaemia	3.3	0.1	6.3	0.9
Dehydration	2.1	0.2	4.0	1.2
Hypophosphataemia	0.6	0.2	1.0	0.6
Vascular disorders				
Hot flush	21.2	0.4	20.4	0.2
Eye disorders				
Lacrimation increased	13.4	<0.1	13.1	-
Psychiatric disorders				
Insomnia	16.6	<0.1	17.1	0.3
Investigations				

Neutrophil count decreased	13.7	9.6	13.8	9.6
Weight decreased	3.2	1.1	8.0	4.2
Injury, poisoning and procedural complications				
Radiation skin injury	11.1	0.3	12.6	0.3
Immune system disorders				
Hypersensitivity	2.9	0.4	3.4	0.4
Drug hypersensitivity	0.5	<0.1	1.3	0.2

* In this table this denotes an ADR that has been reported in association with a fatal outcome

Listing 2: The following Adverse Drug Reactions were reported in <1% of patients in the PERJETA-treated group in the pivotal clinical trial APHINITY:

Cardiac disorders: Cardiac failure congestive (<0.1% in the PERJETA-treated group vs. <0.1% in the placebo-treated group), left ventricular dysfunction (0.0% in the PERJETA-treated group vs. <0.1% in the placebo-treated group)

Nervous system disorders: Cerebral haemorrhage (All Grades: 0.1% in the PERJETA-treated group vs. 0.0% in the placebo-treated group; Grade ≥3: 0.1% in the PERJETA-treated group vs. 0.0% in the placebo-treated group). One Grade 5 cerebral haemorrhage was reported in the PERJETA-treated group.

Respiratory, thoracic, and mediastinal disorders: Pleural effusion (0.1% in the PERJETA-treated group vs. 0.2% in the placebo-treated group)

Table 5 - Summary of ADRs Occurring in ≥1% of Patients Receiving PERJETA in the Pivotal Clinical Trial APHINITY by Treatment Regimen and Chemotherapy Type

Adverse Drug Reaction (ADR) **(MedDRA)** **System Organ Class**	**Placebo + HERCEPTIN + chemotherapy** **n=2405** **Frequency rate %**		**PERJETA + HERCEPTIN + chemotherapy** **n=2364** **Frequency rate %**	
	Placebo + HERCEPTIN + anthracycline N=1894	**Placebo + HERCEPTIN + non-anthracycline N=510**	**PERJETA + HERCEPTIN + anthracycline N=1834**	**PERJETA + HERCEPTIN + non-anthracycline N=528**
Cardiac disorders				
Cardiac Failure	0.8	0.4	1.6	0.8
General disorders and administration site conditions				
Fatigue	40.9	57.1	45.8	59.5
Mucosal Inflammation	18.4	19.4	23.4	23.1
Asthenia	22.5	14.1	23.9	12.5
Pyrexia	20.6	15.3	21.2	15.9
Oedema Peripheral	18.0	27.8	16.6	18.8

Adverse Drug Reaction (ADR) (MedDRA) System Organ Class	Placebo + HERCEPTIN + chemotherapy n=2405 Frequency rate %		PERJETA + HERCEPTIN + chemotherapy n=2364 Frequency rate %	
	Placebo + HERCEPTIN + anthracycline N=1894	Placebo + HERCEPTIN + non-anthracycline N=510	PERJETA + HERCEPTIN + anthracycline N=1834	PERJETA + HERCEPTIN + non-anthracycline N=528
Skin And Subcutaneous Tissue Disorders				
Alopecia	68.0	62.9	69.3	58.0
Rash	20.5	19.4	26.1	24.6
Pruritus	9.0	9.0	13.8	14.6
Palmar-plantar erythrodysaesthesia syndrome	7.1	4.5	10.7	3.8
Dry Skin	11.5	9.8	14.3	9.3
Nail Disorder	11.6	12.7	12.1	11.0
Gastrointestinal disorders				
Diarrhoea	40.8	61.6	67.3	84.7
Nausea	65.8	64.3	69.1	69.1
Vomiting	30.5	30.4	30.4	39.8
Constipation	30.5	35.7	29.7	26.3
Stomatitis	24.6	21.2	30.5	21.0
Dyspepsia	13.4	17.1	13.4	15.0
Abdominal Pain	9.8	14.9	11.0	16.1
Abdominal Pain upper	9.8	6.5	11.1	7.8
Blood And Lymphatic System Disorders				
Anaemia	19.2	37.6	23.0	44.3
Neutropenia	23.3	23.5	24.5	25.9
Febrile Neutropenia	10.8	12.2	12.8	9.7
Leukopenia	10.1	5.9	10.3	5.3
Nervous System Disorders				
Dysgeusia	19.5	28.8	24.6	30.9
Headache	23.3	23.7	22.9	21.0
Peripheral Sensory Neuropathy	16.7	20.6	18.4	16.9
Neuropathy Peripheral	13.3	22.9	14.0	20.6
Paraesthesia	10.1	9.4	13.0	7.6
Dizziness	10.6	14.7	10.7	13.8
Musculoskeletal And Connective Tissue Disorders				
Arthralgia	33.1	30.4	29.9	24.2
Myalgia	29.7	29.0	27.1	22.3
Pain In Extremity	9.8	12.9	9.7	11.0
Infections And Infestations				
Nasopharyngitis	13.4	6.1	15.3	6.4

Adverse Drug Reaction (ADR) (MedDRA) System Organ Class	Placebo + HERCEPTIN + chemotherapy n=2405 Frequency rate %		PERJETA + HERCEPTIN + chemotherapy n=2364 Frequency rate %	
	Placebo + HERCEPTIN + anthracycline N=1894	Placebo + HERCEPTIN + non-anthracycline N=510	PERJETA + HERCEPTIN + anthracycline N=1834	PERJETA + HERCEPTIN + non-anthracycline N=528
Upper Respiratory Tract Infection	6.8	9.6	8.1	8.1
Paronychia	2.4	1.8	4.4	2.5
Respiratory, Thoracic And Mediastinal Disorders				
Epistaxis	13.6	13.3	18.4	17.6
Cough	14.9	13.5	15.9	15.7
Dyspnoea	10.6	15.1	11.1	14.8
Metabolism And Nutrition Disorders				
Decreased Appetite	18.8	23.7	22.8	27.8
Hypokalaemia	2.6	9.8	3.7	16.3
Hypomagnesaemia	1.1	11.6	1.9	22.0
Dehydration	1.0	6.5	1.3	13.4
Hypophosphataemia	0.2	2.2	0.3	3.4
Vascular Disorders				
Hot Flush	21.0	21.8	20.7	19.3
Eye Disorders				
Lacrimation Increased	12.2	17.8	12.1	16.7
Psychiatric Disorders				
Insomnia	15.3	21.8	16.2	20.1
Investigations				
Neutrophil Count Decreased	14.9	9.2	15.0	9.8
Weight decreased	3.1	3.5	7.2	11.4
Injury, poisoning and procedural complications				
Radiation Skin Injury	10.7	12.5	12.4	13.3
Immune System Disorders				
Hypersensitivity	2.6	3.9	3.1	4.4
Drug Hypersensitivity	0.5	0.6	0.9	2.5

ADRs reported in patients receiving PERJETA and HERCEPTIN after discontinuation of chemotherapy

In the pivotal trial APHINITY, the frequency of ADRs decreased during the targeted treatment alone phase. All ADRs in the PERJETA treatment group occurred in <10% of patients with the exception of diarrhea (18.1%), arthralgia (15.3%), radiation skin injury (12.4%), and hot flush (12.1%).

Metastatic and Early Breast Cancer

Further Information on Selected Adverse Drug Reactions

Left ventricular dysfunction
In the pivotal trial WO20698/TOC4129g (CLEOPATRA), the incidence of LVD during study treatment was 8.6% in the placebo with HERCEPTIN and docetaxel treated group and 6.6% in the PERJETA with HERCEPTIN and docetaxel treated group. The incidence of symptomatic LVD was 1.8% in the placebo-treated group and 1.5% in the PERJETA-treated group.
In a clinical trial with neoadjuvant treated patients, in which patients received four cycles of PERJETA as neoadjuvant treatment, the incidence of LVD (during the overall treatment period) was higher in the PERJETA, HERCEPTIN and docetaxel-treated groups (7.5%) compared to the HERCEPTIN and docetaxel treated group (1.9%). LVEF recovered to ≥50% in all patients. There was one case of symptomatic LVD in the PERJETA and HERCEPTIN-treated group.

In another clinical trial with neoadjuvant treated patients, the incidence of LVD (during the overall treatment period) was 8.3% in the group treated with PERJETA plus HERCEPTIN and 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by PERJETA plus HERCEPTIN and docetaxel; 9.3% in the group treated with PERJETA plus HERCEPTIN and docetaxel following FEC; and 6.6% in the group treated with PERJETA in combination with docetaxel, carboplatin and HERCEPTIN (TCH). The incidence of symptomatic LVD (congestive heart failure) was 1.3% in the group treated with PERJETA plus HERCEPTIN and docetaxel following FEC (this excludes a patient that experienced symptomatic LVD during FEC treatment prior to receiving PERJETA plus HERCEPTIN and docetaxel) and also 1.3% in the group treated with PERJETA in combination with TCH. No patients in the group treated with PERJETA plus HERCEPTIN and FEC followed by PERJETA plus HERCEPTIN and docetaxel experienced symptomatic LVD.

In the pivotal trial APHINITY, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10% from baseline and to <50% or cardiac death was <1% (0.7% of PERJETA-treated patients vs 0.3% of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 46.7% of PERJETA-treated patients and 66.7% of placebo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cut-off. The majority of the events were reported in anthracycline-treated patients. Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF of at least 10% from baseline and to <50% were reported in 2.7% of PERJETA-treated patients and 2.8% of placebo-treated patients, of whom 79.7% of PERJETA-treated patients and 80.6% of placebo-treated patients had recovered at the data cut-off.

Infusion-related reactions
An infusion-related reaction was defined in the pivotal trials as any event reported as hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release syndrome occurring during an infusion or on the same day as the infusion. In the pivotal trial CLEOPATRA, the initial dose of PERJETA was given the day before HERCEPTIN and docetaxel to allow for the examination of PERJETA associated reactions. On the first day, the overall frequency of events was 9.8% in the placebo-treated group and 13.2% in the PERJETA-

treated group, with the majority of reactions being mild or moderate. The most common infusion-related reactions in the PERJETA-treated group (≥1.0%) were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity and vomiting.

During the 2nd cycle when all drugs were administered on the same day, the most common infusion-related reactions in the PERJETA-treated group (≥1.0%) were fatigue, dysgeusia, hypersensitivity, myalgia and vomiting (see WARNINGS AND PRECAUTIONS: Infusion-related reactions).

In the pivotal trial APHINITY, PERJETA was administered on the same day as the other study treatment drugs. Infusion-related reactions occurred in 20.9% of patients in the PERJETA-treated group and 18.0% in the placebo-treated group on the first day of administration (in combination with HERCEPTIN and chemotherapy). The incidence of Grade 3-4 adverse events was 1.2% for the PERJETA-treated group and 0.7% for the placebo-treated group. The type and severity of events were consistent with those observed in CLEOPATRA, with a majority of reactions being of mild or moderate severity.

Hypersensitivity reactions/anaphylaxis
In the pivotal trial CLEOPATRA in metastatic breast cancer, the overall frequency of events reported as hypersensitivity/anaphylaxis was 9.3% in the placebo-treated patients and 11.3% in the PERJETA-treated patients, of which 2.5% and 2.0% were NCI-CTCAE (version 3) Grade 3-4, respectively. Two (2) patients in the placebo-treated group and 4 patients in the PERJETA-treated group experienced anaphylaxis (see WARNINGS AND PRECAUTIONS: Hypersensitivity reactions/anaphylaxis).
Overall, the majority of hypersensitivity reactions were mild or moderate in severity and resolved upon treatment.

In the pivotal trial APHINITY, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In APHINITY, the overall frequency of hypersensitivity/anaphylaxis was highest in the PERJETA and TCH treated group (7.6%), of which 1.3% of events were NCI-CTCAE Grade 3-4. The incidence of hypersensitivity/anaphylaxis events was 4.9% in the placebo + TCH group, of which 1.6% of events were NCI-CTCAE Grade 3-4.

Febrile neutropenia
In the pivotal trial CLEOPATRA in metastatic breast cancer, no events of febrile neutropenia were reported after cessation of docetaxel. The median total dose of docetaxel was 940.8 mg and 1008.0 mg in the PERJETA-treated and the placebo-treated patients, respectively. Febrile neutropenia occurred in 13.7% of PERJETA-treated patients and 7.6% of placebo-treated patients. Treatment-related deaths occurred in 1.2% of patients in the PERJETA-treated group and 1.5% of patients in the placebo-treated group and were mainly due to febrile neutropenia and/or infection.

In the APHINITY trial, febrile neutropenia occurred in 12.1% of PERJETA-treated patients and 11.1% of placebo-treated patients.

Diarrhea
In the pivotal trial CLEOPATRA in metastatic breast cancer, diarrhea occurred in 68.4% of Perjeta-treated patients and 48.7% of placebo-treated patients. Most events were mild to moderate in severity and occurred in the first few cycles of treatment. The incidence of NCI-CTCAE Grade 3-4 diarrhea was 9.3% in PERJETA-treated patients vs 5.1% in placebo-treated patients. The median duration of the longest episode was 18 days in PERJETA -treated patients and 8 days in placebo-treated patients. Diarrheal events responded well to proactive management with anti-diarrheal agents.

In the APHINITY trial, a higher incidence of diarrhoea was reported in the PERJETA -treated arm (71.2%) compared to the placebo arm (45.2%). Grade ≥ 3 diarrhoea was reported in 9.8% of patients in the PERJETA arm vs. 3.7% in the placebo arm. The majority of the reported events were Grade 1 or 2 in severity. The highest incidence of diarrhoea (all Grades) was reported during the targeted therapy+taxane chemotherapy period (61.4% of patients in the PERJETA arm vs. 33.8% of patients in the placebo arm). The incidence of diarrhea was much lower after chemotherapy cessation, affecting 18.1% of patients in the PERJETA arm vs. 9.2% of patients in the placebo arm in the post-chemotherapy targeted therapy period. The median duration of the longest event was 35 days in the PERJETA + HERCEPTIN + chemotherapy arm versus 13 days in the PERJETA + HERCEPTIN arm. Elderly patients (≥ 65 years) had a higher risk of diarrhea compared with younger patients (< 65 years).

Rash
In the pivotal trial CLEOPATRA in metastatic breast cancer, rash occurred in 51.7% of PERJETA-treated patients, compared with 38.9% of placebo-treated patients. Most events were Grade 1 or 2 in severity, occurred in the first two cycles, and responded to standard therapies, such as topical or oral treatment for acne.

In the APHINITY trial, the adverse event of rash occurred in 25.8% of patients in PERJETA arm vs. 20.3% of patients in placebo arm. The majority of rash events were Grade 1 or 2.

Laboratory Abnormalities
In the pivotal trial CLEOPATRA, the incidence of NCI-CTCAE (version 3) Grade 3-4 leukopenia was higher in the PERJETA-treated group (64.6% of PERJETA-treated patients and 61.0% of placebo-treated patients, including 13.1% and 13.8% Grade 4 leukopenia, respectively).

The incidence of NCI-CTCAE (version 3) Grade 3-4 neutropenia was balanced in the PERJETA-treated and control groups in the pivotal trial CLEOPATRA (86.3% of PERJETA-treated patients and 86.6% of placebo-treated patients, including 60.7% and 64.8% Grade 4 neutropenia, respectively) and in the pivotal trial APHINITY

In the APHINITY trial, the incidence of NCI-CTCAE v.4 Grade 3-4 neutropenia was 40.6% in patients treated with PERJETA, trastuzumab and chemotherapy compared with 39.1% in patients treated with placebo, trastuzumab and chemotherapy, including 28.3% and 26.5% Grade 4 neutropenia, respectively.

Laboratory abnormalities reported from the post-marketing setting are consistent with data from clinical trials of PERJETA.

Study BO17929 in Metastatic Breast Cancer

In the Phase II BO17929 trial, a total of 83 patients (from Cohorts 1, 2 and 3) received treatment with PERJETA in combination with HERCEPTIN and 29 patients received treatment with PERJETA alone.

Most Commonly Reported ADRs

In Cohorts 1&2 (PERJETA + HERCEPTIN; N=66), ADRs reported with a frequency of ≥30%: diarrhea and fatigue; with a frequency of 20-<30%: nausea, headache, and rash; and with a frequency of 10-<20%: arthralgia, asthenia, constipation, decreased appetite, dizziness, nail disorder, myalgia, nasopharyngitis, pruritus, and vomiting.

In Cohort 3 (PERJETA alone; N=29), ADRs reported with a frequency of ≥30%: diarrhea and nausea; with a frequency of 20-<30%: vomiting; and with a frequency of 10-<20%: arthralgia, asthenia, decreased appetite, dyspnoea, fatigue, pruritus, and rash.

In Cohort 3 (PERJETA + HERCEPTIN; N=17), no ADRs with a frequency of ≥30% were reported. ADRs reported with a frequency of 20-<30%: diarrhea, nausea, vomiting, and fatigue; and with a frequency of 10-<20%: asthenia, chills, constipation, decreased appetite, dizziness, headache, left ventricular dysfunction, pruritus, rash, and upper respiratory tract infection.

Table 6 – Overview of Safety in Study BO17929

Number (%) of patients with	Cohorts 1 and 2 PERJETA + HERCEPTIN (N=66)	Cohort 3 PERJETA alone (N=29)	Cohort 3 PERJETA + HERCEPTIN (N=17)
Any AE	64 (96.9)	27 (93.1)	15 (88.2)
Related	54 (81.8)	20 (69.0)	12 (70.6)
NCI-CTCAE Grade ≥3	11 (16.7)	5 (17.2)	4 (23.5)
Related	6 (9.1)	0	2 (11.8)
Serious AE	11 (16.7)	1 (3.4)	1 (5.9)
Related	3 (4.5)	0	1 (5.9)
Events to Monitor			
Symptomatic Cardiac Dysfunction	0	0	0
LVEF decrease[a] (Local Read)	3 (4.5)	1 (3.4)	1 (5.9)
LVEF decrease[a] (Central Read)	2 (3.0)	1 (3.4)	0
All grades diarrhea	42 (63.6)	14 (48.3)	5 (29.4)
CTC Grade 3, 4 or 5 diarrhea[b]	2 (3.0)	1 (3.4)	1 (5.9)
Infusion-related AEs[c]	5 (7.6)	0	0

[a] Decrease of ≥ 10% points to value <50%

[b] All cases were Grade 3 diarrhea

[c] Infusion-related AEs assessed for first four cycles of treatment only in cohorts 1&2

Left Ventricular Dysfunction in Study BO17929
No symptomatic cardiac AEs were reported in this study. Five patients experienced an asymptomatic decline in LVEF (of at least 10%-points from baseline to an absolute value below 50%).

Post-Market Adverse Drug Reactions
Safety reports from the post-marketing setting are consistent with safety data from clinical trials of PERJETA.

The following adverse drug reaction has been identified from post marketing experience with Perjeta based on spontaneous case reports and literature cases. The adverse drug reaction is listed according to system organ class in MedDRA.

Table 7 Adverse Drug Reactions from Post-Marketing Experience

System Organ Class	Adverse reaction	Frequency
Metabolism and nutrition disorders	Tumor Lysis Syndrome (TLS)	Rare (≥0.01% and <0.1%) in breast cancer patients

DRUG INTERACTIONS

Drug-Drug Interactions
A sub-study in 37 patients in the pivotal trial WO20698/TOC4129g (CLEOPATRA) showed no evidence of drug-drug interaction between pertuzumab and trastuzumab or between pertuzumab and docetaxel. This lack of drug-drug interaction was confirmed by pharmacokinetic data in a sub-study of 70 patients from the APHINITY trial.

Five studies evaluated the effects of pertuzumab on the pharmacokinetics of co-administered cytotoxic agents, which included, docetaxel, paclitaxel, gemcitabine, capecitabine, carboplatin, and erlotinib. There was no evidence of any pharmacokinetic interaction between pertuzumab and any of these agents. The pharmacokinetics of pertuzumab in these studies was comparable to those observed in single-agent studies.

Drug-Lifestyle Interactions
PERJETA has a minor influence on the ability to drive and use machines. Dizziness may occur during treatment with PERJETA. Patients experiencing infusion-related reactions to PERJETA should be advised not to drive and use machines until symptoms abate.

DOSAGE AND ADMINISTRATION

Patients treated with PERJETA should have HER2- positive tumour status, defined as a score of 3+ by IHC or a ratio of ≥ 2.0 by ISH assessed by a validated test.

To ensure accurate and reproducible results, the testing must be performed in a laboratory which can ensure validation of the testing procedures. For full instructions on assay performance and interpretation, please refer to the package inserts of validated HER2 testing assays.

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is PERJETA.

PERJETA therapy should only be administered under the supervision of a health professional experienced in the treatment of cancer patients.

PERJETA must be diluted by a health professional and administered as an intravenous infusion. Do not administer as an intravenous push or bolus.

Recommended Dose and Dose Adjustment

Recommended Dose:

Metastatic and Early Breast Cancer

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 a period of 30 to 60 minutes. An observation period of 30 to 60 minutes is recommended after completion of each PERJETA infusion. The observation period should be completed prior to any subsequent dose of HERCEPTIN or chemotherapy (see WARNINGS AND PRECAUTIONS: Infusion-related reactions and WARNINGS AND PRECAUTIONS: Hypersensitivity reactions/anaphylaxis).

PERJETA and HERCEPTIN should be administered sequentially and can be given in any order. When administered with PERJETA, the recommendation is to follow a 3-weekly schedule for HERCEPTIN administered as an IV infusion with an initial loading dose of 8 mg/kg followed every 3 weeks thereafter by a dose of 6 mg/kg body weight.

In patients receiving a taxane, PERJETA and HERCEPTIN should be administered prior to the taxane. When administered with PERJETA, the recommended initial dose of docetaxel is 75 mg/m^2.

In patients receiving an anthracycline-based regimen, PERJETA and HERCEPTIN should be administered following completion of the anthracycline treatment.

Metastatic Breast Cancer

PERJETA should be administered in combination with HERCEPTIN and docetaxel until disease progression or unmanageable toxicity. Treatment with PERJETA and HERCEPTIN may continue even if treatment with docetaxel is discontinued.

In the pivotal clinical trial CLEOPATRA, for the loading dose of PERJETA in Cycle 1, it was administered on the first day; HERCEPTIN was administered on the following day and followed by docetaxel on the same day. If all three medications could be tolerated in Cycle 1, in the subsequent cycles they could be administered in the same sequence on the same day.

Early Breast Cancer

In the adjuvant setting (after surgery), PERJETA should be administered in combination with HERCEPTIN for a total of one year (maximum 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first), as part of a complete regimen for early breast cancer, including standard anthracycline- and/or taxane-based chemotherapy. PERJETA and HERCEPTIN should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued (see CLINICAL TRIALS).

Dose Adjustments:
Dose reductions are not recommended for PERJETA and HERCEPTIN (see the HERCEPTIN Product Monograph).
For chemotherapy dose modifications, see relevant Product Monograph.

Patients may continue therapy during periods of reversible chemotherapy-induced myelosuppression, but they should be monitored carefully for complications of neutropenia during this time. For docetaxel dose modifications, see the Product Monograph for docetaxel. A reduction in docetaxel dose was required in approximately 25% of patients in both treatment arms in the pivotal trial CLEOPATRA.

Infusion-related reactions
The infusion rate of PERJETA may be slowed or the administration interrupted if the patient develops an infusion-related reaction.

Hypersensitivity reactions/anaphylaxis
The infusion should be discontinued immediately and permanently if the patient experiences a serious hypersensitivity reaction (e.g. anaphylaxis) (see WARNINGS AND PRECAUTIONS: Hypersensitivity reactions/anaphylaxis).

Left ventricular dysfunction:
See WARNINGS AND PRECAUTIONS: Left ventricular dysfunction for information on dose recommendations in the event of left ventricular dysfunction. The Product Monograph for HERCEPTIN should be referred for further information.

Missed Dose
Delayed or Missed doses
For recommendations on delayed or missed doses, please refer to Table 8 below.

Table 8 – Recommendations Regarding Delayed or Missed Doses

Time between two sequential infusions	PERJETA	HERCEPTIN
< 6 weeks	The 420 mg dose of PERJETA IV should be administered as soon as possible. Do not wait until the next planned dose.	The 6 mg/kg dose of HERCEPTIN IV should be administered as soon as possible. Do not wait until the next planned dose.
≥ 6 weeks	The loading dose of 840 mg PERJETA IV should be re-administered as a 60 minute infusion, followed by a maintenance dose of 420 mg IV administered over a period of 30 to 60 minutes every 3 weeks thereafter.	The loading dose of 8 mg/kg of HERCEPTIN IV should be re-administered over approximately 90 minutes, followed by a maintenance dose of 6 mg/kg IV administered over a period of 30 or 90 minutes every 3 weeks thereafter.

Treatment discontinuation:
PERJETA should be discontinued if HERCEPTIN treatment is discontinued.

Administration
Instructions for dilution
PERJETA is for single use only and is administered intravenously by infusion.

PERJETA does not contain any antimicrobial preservative. Therefore, care must be taken to ensure the sterility of the prepared solution for infusion. PERJETA should be prepared by a health professional using aseptic technique.

14 mL of PERJETA liquid concentrate should be withdrawn from the vial and diluted into a 250 mL PVC or non-PVC polyolefin 0.9% sodium chloride infusion bag. Do not withdraw saline out of the infusion bag.

For the preparation of the initial dose of PERJETA (840 mg), dilute the content of two vials of PERJETA (2 x 420 mg) into one 250 mL IV bag. The concentration of the final diluted solution will be approximately 3.02 mg/mL. For the preparation of subsequent PERJETA doses (420 mg), dilute the content of one vial of PERJETA (1 x 420mg) into one 250 mL IV bag. The resulting concentration will be approximately 1.59 mg/mL.

Dextrose (5%) solution should not be used (see Incompatibilities).

The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral drug products should be inspected visually for particulates and discolouration prior to administration. Once the infusion is prepared it should be administered immediately (see STORAGE AND STABILITY).

Incompatibilities
No incompatibilities between PERJETA and polyvinylchloride, polyethylene or non-PVC polyolefin bags have been observed.

Dextrose (5%) solution should not be used to dilute PERJETA since the drug is chemically and physically unstable in such solutions.

PERJETA should not be mixed or diluted with other drugs.

OVERDOSAGE

For the management of suspected drug overdose, please contact your regional poison control centre.

There is no experience with overdosage in human clinical trials. Single doses higher than 25 mg/kg (1727 mg) have not been tested.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PERJETA (pertuzumab) is a recombinant humanized monoclonal antibody that specifically targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2) and thereby blocks ligand-dependent heterodimerization of HER2 with other HER family members, including HER1 (EGFR), HER3 and HER4. As a result, PERJETA 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, respectively. In addition, PERJETA mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

While PERJETA alone inhibited the proliferation of human tumour cells, the combination of PERJETA and HERCEPTIN significantly augmented anti- tumour activity in HER2-overexpressing xenograft models.

Pharmacokinetics

Across multiple clinical trials in various indications there were no dose-related changes in the pharmacokinetics of pertuzumab at doses ranging from 2-25 mg/kg. In seven clinical trials where PK parameters were obtained, the estimated mean clearance (CL) ranged from 0.232 - 0.329 L/day, the steady-state volume of distribution (Vss) from 3.53 - 7.05 L, and the half-life from 11.1 - 22.3 days.

No differences in pertuzumab PK were observed in patients with early breast cancer compared to patients with metastatic breast cancer.

Absorption: Pertuzumab is administered as an IV infusion.

Distribution: Following intravenous administration, the mean Vss across two dose groups ranged from 3.53 – 4.12 L in metastatic breast cancer patients (Study BO16934), from 4.89 – 7.05 L in advanced solid tumour patients (across 12 dose groups in Studies TOC2297g, JO17076, BO17003 and BO17021), 4.45 – 5.23 L across two dose groups in hormone-resistant

prostate cancer patients (Study BO17004) and 4.9 L in one dose group in non−small cell lung cancer patients (Study WO20024).

Metabolism: The metabolism of pertuzumab has not been directly studied. Antibodies are cleared principally by catabolism.

Excretion: The mean CL of pertuzumab ranged from 0.247 – 0.270 L/day across two dose groups in metastatic breast cancer patients (Study BO16934), from 0.232 – 0.329 L/day in advanced solid tumour patients (across 12 dose groups in Studies TOC2297g, JO17076, BO17003 and BO17021), 0.253 – 0.270 L/day across two dose groups in hormone-resistant prostate cancer patients (Study BO17004) and 0.240 L/day in one dose group in non−small cell lung cancer patients (Study WO20024).

The mean half-life of pertuzumab ranged from 11.4 – 12.2 days in metastatic breast cancer patients (Study BO16934), 11.1 – 22.3 days in advanced solid tumour patients (Studies TOC2297g, JO17076, BO17003 and BO17021), 13.7 – 19.3 days in hormone-resistant prostate cancer patients (Study BO17004) and 17.9 days in non−small cell lung cancer patients (Study WO20024).

Special Populations and Conditions

Geriatrics: No dedicated studies have been conducted in geriatric patients with pertuzumab.

Renal Insufficiency: No formal pharmacokinetic study has been conducted in patients with renal impairment.

STORAGE AND STABILITY

Store vials in a refrigerator at 2-8°C.

PERJETA should not be used after the expiry date (EXP) shown on the vial and carton.

Keep vial in the outer carton in order to protect from light.

DO NOT FREEZE. DO NOT SHAKE.

PERJETA drug product does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

The solution of PERJETA for infusion diluted in US Pharmacopeia (USP) polyvinylchloride (PVC) or non-PVC polyolefin bags containing 0.9% Sodium Chloride Injection may be stored at 2–8°C (36-46°F) for up to 24 hours prior to use. Diluted PERJETA has been shown to be stable for up to 24 hours (up to 30°C). However, since diluted PERJETA contains no preservative, it should be used immediately. If it is not used immediately the diluted solution should be stored refrigerated (2-8°C) and used within 24 hours.

SPECIAL HANDLING INSTRUCTIONS

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Any unused medicinal product or waste material should be disposed of in accordance with local medical waste or collection systems.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PERJETA is supplied as a single-use vial containing 14 mL preservative free liquid concentrate, at a concentration of 30 mg/mL for dilution for intravenous infusion. Each vial of PERJETA drug product contains a total of 420 mg pertuzumab. Non-medicinal ingredients are (alphabetical order); glacial acetic acid, L-histidine, polysorbate 20, sucrose, water for injection.

Packaging:
Each carton contains one vial of 420 mg PERJETA.

PERJETA is also supplied within a kit (PERJETA®-HERCEPTIN® Combo Pack). Each kit contains one vial of 420 mg PERJETA and one vial of 440 mg HERCEPTIN lyophilized, sterile powder and one 20 mL vial of Bacteriostatic Water For Injection (BWFI) containing 1.1% benzyl alcohol. For information on the preparation for administration of HERCEPTIN refer to the package insert within the HERCEPTIN carton.

PERJETA, HERCEPTIN or Bacteriostatic Water For Injection (BWFI) should not be used after the expiry date (EXP) shown on the vial.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

PERJETA (pertuzumab) is a recombinant humanized monoclonal antibody based upon the human IgG1(κ) framework sequence composed of two light chains consisting of 214 amino acid residues and two heavy chains consisting of 448 or 449 amino acid residues. The molecular mass of intact pertuzumab is approximately 148,088 Daltons for the antibody form with each heavy chain terminating at glycine residue 448 and containing predominantly a G0 oligosaccharide.

PERJETA acts by blocking the association of HER2 with the other HER family members, including HER1 (EGFR), HER3, and HER4. Pertuzumab can also prevent formation of HER2 homodimerization. As a result, pertuzumab inhibits ligand-initiated intracellular signaling pathways, mitogen-activated protein (MAP) kinase, and phosphoinositide 3 (PI3) kinase. Inhibition of these signaling pathways can result in growth arrest and apoptosis.

PERJETA is supplied as a clear to slightly opalescent, colorless to pale brown sterile liquid solution (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

CLINICAL TRIALS

HER2 overexpression was determined at a central laboratory and defined as a score of 3+ by IHC or an ISH amplification ratio ≥ 2.0 in the trials outlined below.

Metastatic Breast Cancer (MBC)

Study WO20698/TOC4129g (CLEOPATRA)
WO20698/TOC4129g (CLEOPATRA) is a multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial conducted in 808 patients with HER2-positive metastatic or unresectable breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Patients were randomized 1:1 to receive placebo + HERCEPTIN + docetaxel or PERJETA + HERCEPTIN + docetaxel. Randomization was stratified by prior treatment status (de novo or prior adjuvant/neoadjuvant therapy) and geographic region (Europe, North America, South America and Asia). Patients with prior adjuvant or neoadjuvant therapy were required to have a disease free interval of at least 12 months before enrolment into the trial.

PERJETA and HERCEPTIN were administered intravenously as outlined in DOSAGE AND ADMINISTRATION. Patients were treated with PERJETA and HERCEPTIN until disease progression, withdrawal of consent or unmanageable toxicity. Docetaxel was given as an initial dose of 75 mg/m^2 IV infusion every 3 weeks for at least 6 cycles. The dose of docetaxel could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated.

At the time of the primary analysis, the mean number of cycles of study treatment received in the placebo treatment group was 16.2 and in the PERJETA-treated group was 19.9.

The primary endpoint of the study was progression-free survival (PFS) as assessed by an independent review facility (IRF) and defined as the time from the date of randomization to the date of disease progression or death (from any cause) if the death occurred within 18 weeks of the last tumour assessment.

Key secondary efficacy endpoints were overall survival (OS), progression-free survival (investigator-assessed), objective response rate.

Patient demographic and baseline characteristics were balanced between the treatment arms. The median age was 54 (range 22 to 89 years), 59% were White, 32% were Asian, and 4% were Black. All were women with the exception of 2 patients. Seventeen percent of patients were enrolled in North America, 14% in South America, 38% in Europe, and 31% in Asia. Tumour prognostic characteristics, including hormone receptor status (positive 48%, negative 50%), presence of visceral disease (78%) and non-visceral disease only (22%) were similar in the study arms. Approximately half of the patients received prior adjuvant or neoadjuvant anti-HER2 therapy or chemotherapy (placebo 47%, PERJETA 46%). Among patients with hormone receptor positive tumours, 45% received prior adjuvant hormonal therapy and 11% received hormonal therapy for metastatic disease. Eleven percent of patients received prior adjuvant or neoadjuvant trastuzumab.

At the time of the primary progression-free survival analysis, a total of 242 patients (59%) in the placebo-treated group and 161 patients (47.5%) in the PERJETA-treated group had IRF-confirmed progressive disease or had died.

At the time of primary analysis, the study demonstrated a statistically significant improvement in IRF-assessed PFS (hazard ratio [HR] = 0.62, 95% CI = 0.51, 0.75, $p<0.0001$) in the PERJETA-treated group compared with the placebo-treated group, and an increase in median PFS of 6.1 months (median PFS of 12.4 months in the placebo + HERCEPTIN + docetaxel treated group vs 18.5 months in the PERJETA-treated group) (see Figure 1). The results for investigator-assessed PFS were comparable to those observed for IRF-assessed PFS.

Consistent results were observed across several patient subgroups including age (< 65 or ≥ 65 years), race, geographic region, prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy (yes or no), and prior adjuvant/neoadjuvant trastuzumab (yes or no). In the subgroup of patients with disease limited to non-visceral metastasis (n=178), the hazard ratio was 0.96 (95% CI: 0.61, 1.52) (see Figure 2).

At a second OS analysis performed (confirmatory analysis) one year after the primary analysis of efficacy, 267 patients had died with more deaths occurring in the placebo-treated group compared with the PERJETA-treated group (154 deaths (37. 9%) versus 113 deaths (28.1%), respectively). A statistically significant OS benefit in favour of the PERJETA-treated group was demonstrated (HR 0.66, Adjusted (98.62%) CI =0.49, 0.90, p = 0.0008 log-rank test). The median time to death was 37.6 months in the placebo-treated group but had not yet been reached

in the PERJETA-treated group (see Table 9 and Figure 3). OS results in patient subgroups were consistent with those observed for all patients with the exception of the subgroup of patients with disease limited to non-visceral metastases [HR = 1.42 (95% CI: 0.71, 2.84)].

The final analysis of OS was performed when 389 (48.1%) patients had died [221 (54.4%) in the placebo-treated group and 168 (41.8%) in the PERJETA-treated group]. This occurred approximately 21 months after the confirmatory OS analysis. The median time to death was 40.8 months in the placebo-treated group and 56.5 months in the PERJETA-treated group (see Table 7). The final OS analysis is considered descriptive as confirmatory statistical significance had already been achieved at the second interim analysis.

Duration of IRF-assessed objective response was assessed in the 233 patients in the placebo-treated group and 275 patients in the PERJETA-treated group with a best overall response of CR or PR, as assessed by the IRF. The median duration of response was 12.5 months in the placebo-treated patients compared to 20.2 months in the PERJETA-treated patients.

The efficacy results from the CLEOPATRA trial are summarised in Table 9:

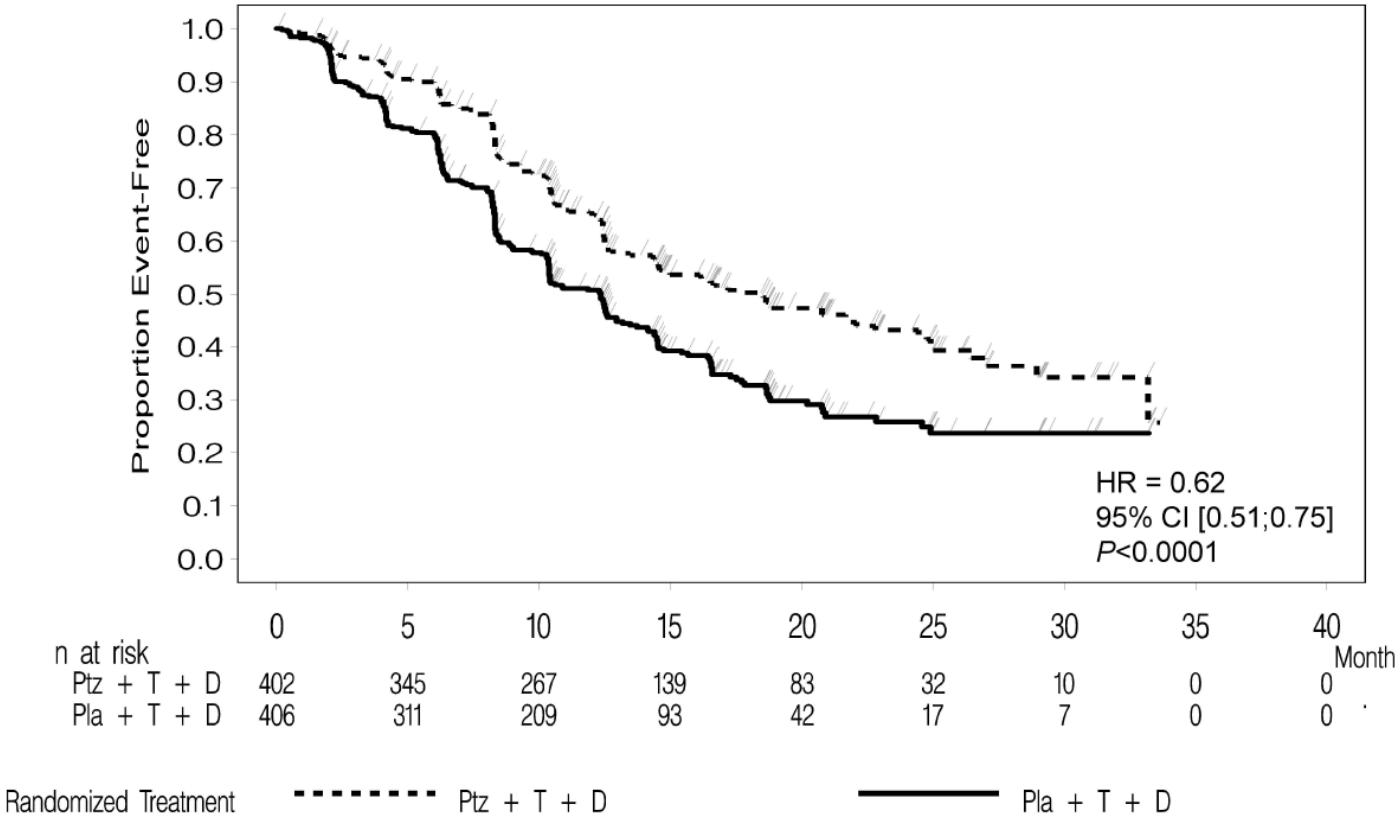
Table 9: Summary of Efficacy from CLEOPATRA Study (ITT Population)

Parameter	**Placebo + HERCEPTIN + docetaxel n=406**	**PERJETA + HERCEPTIN + docetaxel n=402**	**HR (95% CI)**	**p-value**
Primary Endpoint:				
Progression-Free Survival (IRF review)				
No. of patients with an event	242 (59%)	191 (47.5%)	0.62 [0.51;0.75]	<0.0001
Median PFS (months)	12.4	18.5		
Secondary Endpoints:				
Overall Survival				
Confirmatory analysis (2nd Interim analysis)				
No. of patients with an event*	154 (37.9%)	113 (28. 1%)	0.66 [0.49;0.90]#	0.0008*
Median months	37.6	Not reached		
Final analysis**				
No. of patients with an event	221 (54.4%)	168 (41.8%)	0.68 [0.56; 0.84]**	
Median months	40.8	56.5		
Objective Response Rate (ORR) ^				
No. of patients with measureable disease	336	343		
ORR (CR+PR)	233 (69.3 %)	275 (80.2 %)		
Complete response (CR) Partial Response (PR)	14 (4.2 %) 219 (65.2 %)	19 (5.5 %) 256 (74.6 %)		

*OS data based upon data with additional 1 year follow up after the primary data cutoff. The p-value met the O'Brien Fleming stopping boundary of the Lan DeMets alpha spending function for the second interim analysis of overall survival ($p \leq 0.0138$). The result was therefore statistically significant.
adjusted CI presented for OS, to reflect the stopping boundary of $p \leq 0.0138$. The interval represents the 98.62% CI

**Final analysis of overall survival, cut-off date 11 Feb 2014. Final OS analysis considered descriptive only as the confirmatory statistical significance had already been achieved at the second interim analysis.
^Objective response rate is based on IRF-assessed tumour assessments

Figure 1: Kaplan-Meier Curve of IRF-assessed Progression-Free Survival (ITT Population)



D= docetaxel; HR= hazard ratio; Ptz= pertuzumab (PERJETA); T=trastuzumab (HERCEPTIN)

Figure 2: IRF-assessed PFS by Patient Subgroup (ITT Population)

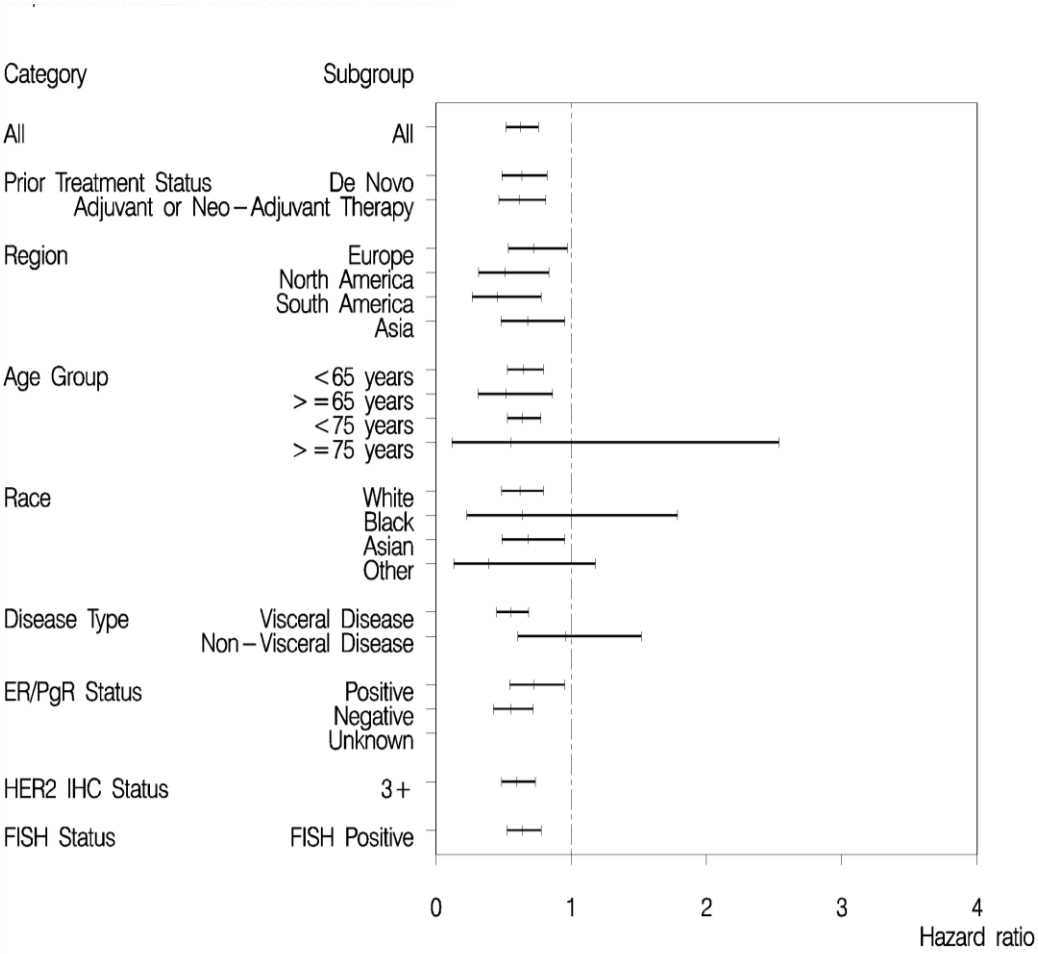
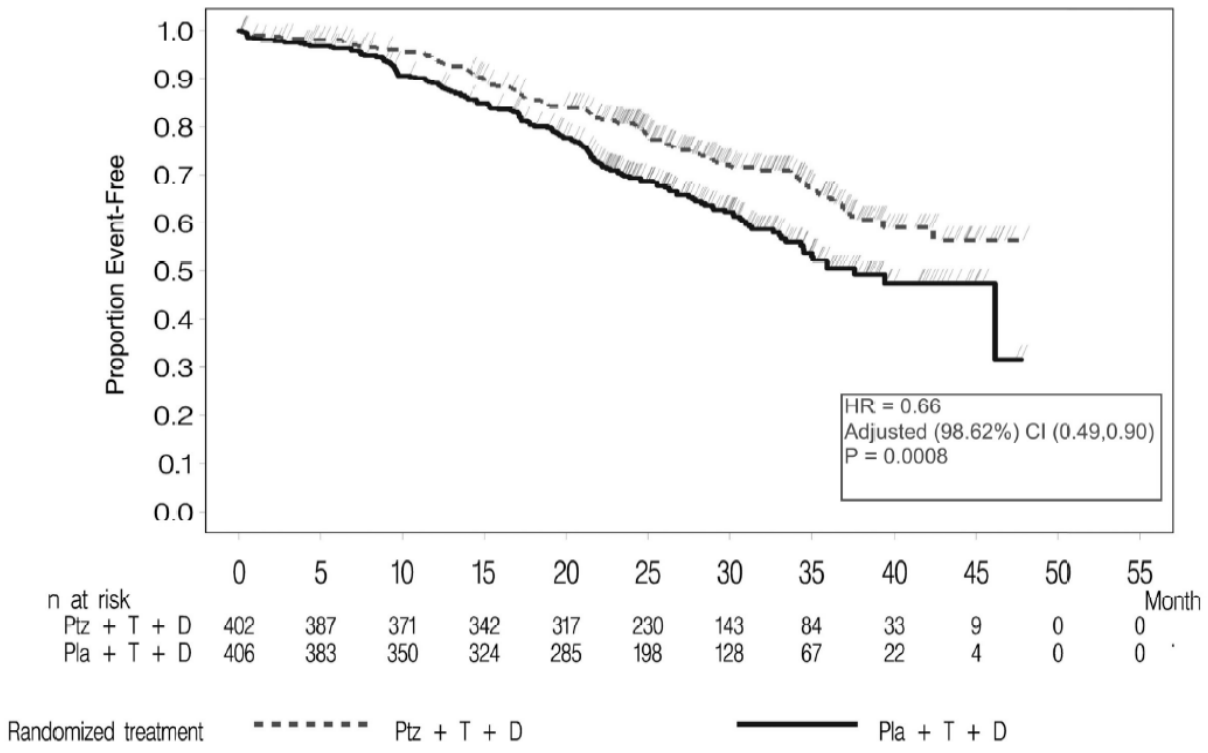


Figure 3: Kaplan-Meier Curve of Overall Survival (2nd Interim Analysis, ITT Population)



D= docetaxel; HR= hazard ratio; Ptz= pertuzumab (PERJETA); T=trastuzumab (HERCEPTIN)

Study BO17929

BO17929 is a Phase II, single arm, non-randomized study with PERJETA and was conducted in patients with HER2-positive MBC who had received prior treatment with a HERCEPTIN-based therapy. The trial was divided into 3 cohorts.

Cohorts 1 and 2: Sixty six patients in cohorts 1 and 2 received at least one dose of PERJETA and HERCEPTIN. All patients had received prior treatment for metastatic disease; half were receiving second-line treatment for metastatic disease, while 35% were receiving third-line treatment and beyond. In addition, 71% had received neoadjuvant chemotherapy. At the time of the primary analysis, the median duration of treatment on study was nine cycles (27 weeks). The ORR and CBR at the time of the primary analysis are presented in Table 10. The median PFS and time to progression (TTP) were 24 weeks. Median time to response was 11 weeks, and in those patients with a response, the median duration of response was 25 weeks. Patients who had a CR tended to have had a longer duration of previous HERCEPTIN therapy (28 months (range 8-76) versus 9 months (range 2-35) for those without CBR). The sum of measurable tumour burden was lower in the CR group (median of 27mm, range 11-46 for CR group; 73mm, range 17-168 for patients without a CBR) although the ranges were wide. Patients with CR tended to have fewer lesions, and correspondingly had fewer lesion sites. Four of this group had target and non-target lesions in lymph nodes only and the fifth had target lesions solely within the lung. Patients who did not experience CBR generally had a greater overall number of lesions at multiple sites.

Cohort 3: Twenty nine patients received at least one cycle of PERJETA. Of these 29 patients, 12 participated in the single-agent Phase only, and 17 went on to receive PERJETA and HERCEPTIN treatment when they had documented progression on PERJETA alone. All 29 patients had progressed on first-line therapy in the metastatic setting, and 41.4% had also progressed after second line therapy. All patients in Cohort 3 received at least one full dose of PERJETA. Patients on PERJETA and HERCEPTIN treatment received a median of 12 cycles overall. Table 10 shows that PERJETA alone had modest activity in patients after failure of HERCEPTIN (middle column). However, when Herceptin was added back in, there was an increase in response. These responses occurred in patients whose disease had recently progressed on each antibody when given separately. In addition 3 patients had stable disease lasting six months or longer for a total clinical benefit rate of 35.3%.

Table 10 Study BO17929: Descriptive Efficacy Data

	Cohorts 1 and 2 PERJETA + HERCEPTIN (n = 66)	Cohort 3 PERJETA alone (n = 29)	Cohort 3 PERJETA + HERCEPTIN (n = 17)
Response	n (%)	n (%)	n (%)
Complete response (CR)	4 (6.1)	0 (0.0)	0 (0.0)
Partial response (PR)	12 (18.2)	1 (3.4)	3 (17.6)
Objective response rate (ORR)	16 (24.2)	1 (3.4)	3 (17.6)
Stable disease (SD) ≥ 6 months	17 (25.8)	2 (6.9)	3 (17.6)
Clinical benefit response (CBR) rate (CR + PR + SD ≥ 6 months)	33 (50.0)	3 (10.3)	6 (35.3)
Progressive disease (PD)	33 (50.0)	26 (89.7)	9 (52.9)
Missing (no response assessment)	0 (0.0)	0 (0.0)	2 (11.8)

NOTE: >6 months = 8 cycles of therapy

Early Breast Cancer

Study BO25126 (APHINITY)

APHINITY is a multicenter, randomized, double-blind, placebo-controlled Phase III trial conducted in 4804 patients with HER2-positive early breast cancer who had their primary tumour excised prior to randomization. Patients were randomized to receive PERJETA or placebo, in combination with adjuvant HERCEPTIN and chemotherapy. Patients were stratified by nodal status, central hormone receptor status, adjuvant chemotherapy regimen and protocol version. Investigators selected one of the following anthracycline-based or non-anthracycline-based chemotherapy regimens for individual patients:

- 3 or 4 cycles of FEC or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC), followed by 3 or 4 cycles of docetaxel or 12 cycles of weekly paclitaxel
- 4 cycles of AC or EC, followed by 3 or 4 cycles of docetaxel or 12 cycles of weekly paclitaxel
- 6 cycles of docetaxel in combination with carboplatin

PERJETA and HERCEPTIN were administered intravenously (see DOSAGE AND ADMINISTRATION) every 3 weeks starting on Day 1 of the first taxane-containing cycle, for a total of 52 weeks (maximum 18 cycles) or until recurrence, withdrawal of consent or unmanageable toxicity. Standard doses of 5-fluorouracil, epirubicin, doxorubicin, cyclophosphamide, docetaxel, paclitaxel and carboplatin were administered. After completion of chemotherapy, patients received radiotherapy and/or hormone therapy as per local clinical standard.

The primary endpoint of the study was invasive disease-free survival (IDFS), defined as the time from randomization to first occurrence of ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause. Secondary efficacy endpoints included, among others, overall survival (OS).

Demographics were well balanced between the two treatment arms. The median age was 51 years, and over 99% of patients were female. The majority of patients had node-positive (63%) and/or hormone receptor-positive disease (64%), and were Caucasian (71%). All patients had an ECOG performance score of 0 (88%) or 1 (12%). The number of patients that received anthracycline-based versus non-anthracycline-based chemotherapy was 78% and 22%, respectively.

PERJETA-treated patients and placebo-treated patients both received a median number of 18 cycles of anti-HER2 therapy. After a median follow-up to 45.4 months, the APHINITY study demonstrated 19% reduction in risk of recurrence or death in patients randomized to receive PERJETA compared with patients randomized to receive placebo, hazard ratio (HR) = 0.81 (95% CI: 0.66, 1.00).

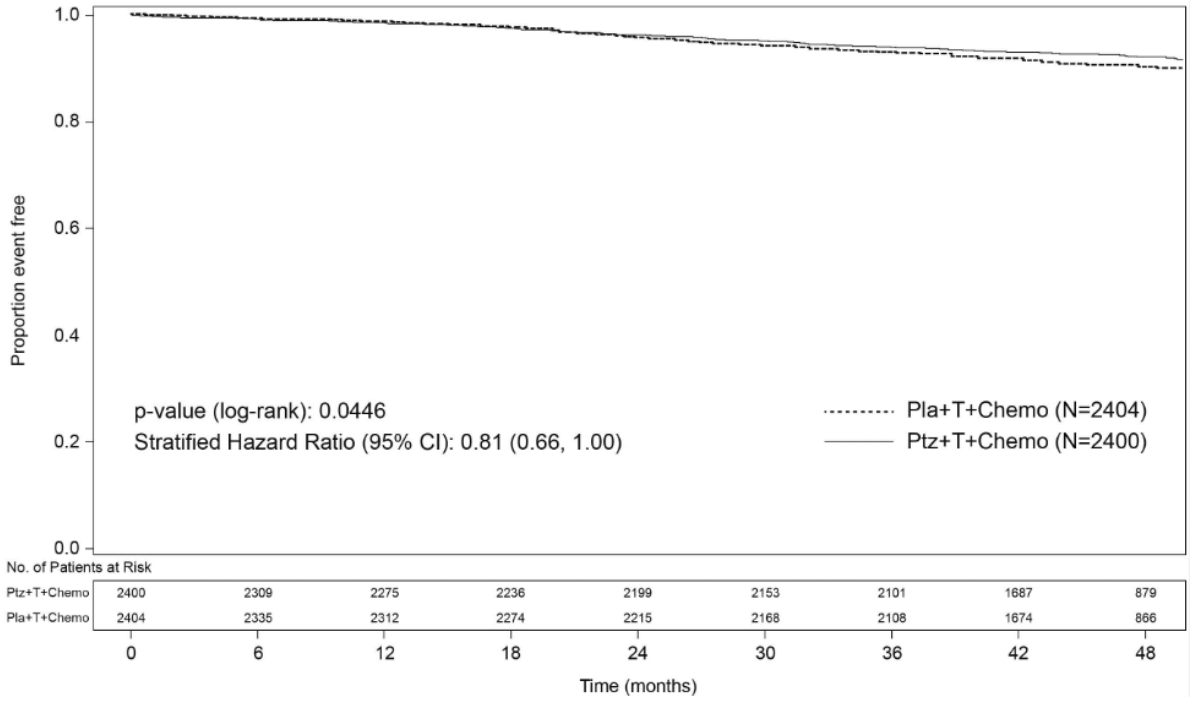
The efficacy results from the APHINITY trial are summarized in Table 11 and in Figures 4.

Table 11 Overall Efficacy from APHINITY Study (ITT Population)

	PERJETA + HERCEPTIN + chemotherapy N=2400	**Placebo + HERCEPTIN + chemotherapy N=2404**
Primary Endpoint		
Invasive Disease Free Survival (IDFS)		
Number (%) of patients with event	171 (7.1%)	210 (8.7%)
HR [95% CI]	0.81 [0.66, 1.00]	
p-value[1]	0.0446	
3 year event-free rate[2] [95% CI]	94.1 [93.1, 95.0]	93.2 [92.2, 94.3]
Secondary Endpoints		
Overall Survival (OS)[3]		
Number (%) of patients with event	80 (3.3%)	89 (3.7%)
HR [95% CI]	0.89 [0.66, 1.21]	
p-value[1]	0.4673	
3 year event-free rate[2] [95% CI]	97.7 [97.0, 98.3]	97.7 [97.1, 98.3]

ITT: Intent-to-treat; HR: Hazard Ratio; CI: Confidence Intervals,
[1] Log Rank test, stratified; all analyses stratified by nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen.
[2] 3-year event-free rate derived from Kaplan-Meier estimates
[3] Data from first interim analysis performed at 26% of target events for final OS analysis. Alpha level for OS analysis controlled by the O'Brien Fleming method with Lan-DeMets alpha spending function.

Figure 4: Kaplan-Meier Curve of Invasive Disease Free Survival



Pla = placebo; Ptz = pertuzumab (PERJETA); T = trastuzumab (HERCEPTIN)

The estimate of IDFS at 4-years was 92.3% in the PERJETA-treated group versus 90.6% in the placebo-treated group. At the time of the estimate the median follow-up was 45.4 months. Within the anthracycline subgroup, the estimate of IDFS at 4-years was 92.1% in the PERJETA-treated group versus 90.1% in the placebo-treated group. Within the non-anthracycline subgroup, the estimate of IDFS at 4-years was 92.9% in the PERJETA-treated group versus 92.1% in the placebo-treated group.

In a subgroup analysis, the benefits of PERJETA were more apparent for patients with node-positive or hormone receptor-negative disease. The findings for these patients are presented in Table 12.

Table 12 Invasive Disease-Free Survival (IDFS) Efficacy Results by Lymph Node and Hormone Receptor Status from APHINTY Study[1]

Nodal Status:	**Positive**		**Negative**	
	PERJETA + HERCEPTIN + chemotherapy N=1503	**Placebo + HERCEPTIN + chemotherapy N=1502**	**PERJETA + HERCEPTIN + chemotherapy N=897**	**Placebo + HERCEPTIN + chemotherapy N=902**
Number (%) of patients with event	139 (9.2%)	181 (12.1%)	32 (3.6%)	29 (3.2%)
HR [95% CI]	0.77 (0.62, 0.96)		1.13 (0.68, 1.86)	
3 year event-free rate [95% CI][2]	92.0 (90.6, 93.4)	90.2 (88.6, 91.7)	97.5 (96.5, 98.6)	98.4 (97.6, 99.2)
Hormone Receptor Status:	**Positive**		**Negative**	
	PERJETA + HERCEPTIN + chemotherapy N=1536	**Placebo + HERCEPTIN + chemotherapy N=1546**	**PERJETA + HERCEPTIN + chemotherapy N=864**	**Placebo + HERCEPTIN + chemotherapy N=858**
Number (%) of patients with event	100 (6.5%)	119 (7.7%)	71 (8.2%)	91 (10.6%)
HR [95% CI]	0.86 (0.66, 1.13)		0.76 (0.56, 1.04)	
3 year event-free rate [95% CI][2]	94.8 (93.7, 95.9)	94.4 (93.2, 95.5)	92.8 (91.0, 94.5)	91.2 (89.2, 93.1)

HR: Hazard Ratio; CI: Confidence Intervals
[1] Exploratory analyses of pre-specified subgroups without adjustment for multiple comparisons
[2] 3-year event-free rate derived from Kaplan-Meier estimates

DETAILED PHARMACOLOGY
Not Applicable

MICROBIOLOGY
Not Applicable

TOXICOLOGY

General
In cynomolgus monkeys, weekly IV administration of pertuzumab at doses up to 150 mg/kg/dose was generally well tolerated. With doses of 15 mg/kg and higher, intermittent mild treatment-associated diarrhea was noted. Slight increases in BUN, (which did not worsen with chronic dosing, and not associated with any macroscopic or microscopic renal findings), were also observed in repeat dose studies. These BUN abnormalities occurred in the absence of other renal

laboratory abnormalities (e.g. creatinine, electrolytes). Chronic dosing (7 to 26 weekly doses) resulted in episodes of diarrhea-related dehydration in a subset of monkeys, which were managed with intravenous fluid replacement therapy. In a chronic toxicity study, the poor condition of 3 animals, one of which had to be euthanized, was attributed to dehydration and pre-renal azotemia secondary to frequent diarrhea. Although there was not a consistent correlation, slight increases in BUN may be, at least in part, due to frequent diarrhea in these studies. The presence of diarrhea was a confounding factor that prevented determination of a direct or indirect kidney effect with pertuzumab treatment. Based on the available preclinical data to date and the potential role of HER2 in kidney function, a direct kidney effect caused by pertuzumab treatment could not be ruled out from the preclinical studies.

In the embryo-fetal toxicity study, all fetuses at all dose levels exhibited adverse, renal histopathological changes (i.e., hypoplasia of the glomeruli, renal tubules, collecting tubules and renal pelvis) demonstrating that HER2 plays a role in kidney development.

The findings from the repeat-dose toxicity studies with pertuzumab are summarized in Table 13.

Table 13 Repeat-Dose Toxicity Studies

Study No.	Study Type	Species and Strain	No./Sex/Group	Method of Administration	Pertuzumab Doses (mg/kg) [a]	Duration of Dosing
99-520-1820	Repeat-Dose Toxicity	Cynomolgus monkey	2/M, 2/F	IV	10, 50, <u>100</u>	4 weeks [b]
Comments: Pertuzumab was well tolerated at doses up to 100 mg/kg administered twice weekly.						
00-377-1821	Repeat-Dose Toxicity	Cynomolgus monkey	4-6/M 4-6/F	IV	15, 50, <u>150</u>	one dose weekly for 7 weeks
Comments: Pertuzumab was generally well tolerated up to the highest dose tested of 150 mg/kg. A pertuzumab-related increase in diarrhea as well as the persistence of diarrhea was noted at doses ≥ 15 mg/kg. This finding did not adversely affect the health of the animals and showed evidence of reversibility.						
00-604-1560	Repeat-Dose Toxicity	Cynomolgus monkey	3/F	SC	<u>250</u>	one dose weekly for 4 weeks
Comments: Pertuzumab was well tolerated at the subcutaneous dose of 250 mg/kg/week and did not significantly affect peripheral blood platelet count, morphology, or coagulation times in cynomolgus monkeys. There were no observations of significant pertuzumab related increased incidence of diarrhea in this study.						
01-458-1821	Repeat-Dose Toxicity	Cynomolgus monkey	4-6/M 4-6/F	IV	[c] 15, 50, 150	one dose weekly for 26 weeks
Comments: Pertuzumab administered IV for 26 weeks was generally well tolerated up to 150 mg/kg. A pertuzumab related increase in diarrhea as well as the persistence of diarrhea was noted at doses ≥ 15 mg/kg. The cause of morbidity leading to early euthanasia for one 50 mg/kg/dose monkey was not determined; however, the findings were consistent with an electrolyte imbalance and dehydration secondary to recurrent and persistent diarrhea. Based on the incidence and persistence of diarrhea and slight elevations in urea nitrogen at all dose levels, a no observable effect level was not determined.						

[a] Unless otherwise specified. For Repeat-Dose Toxicity, the highest No Observed Adverse Effect Level (NOAEL) is underlined.

[b] 2 doses per week for 4 weeks.

[c] NOAEL not determined.

Carcinogenicity
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of pertuzumab.

Genotoxicity
Studies have not been performed to evaluate the mutagenic potential of pertuzumab.

Impairment of Fertility
No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of up to six month duration in cynomolgus monkeys. The findings from the repeat-dose toxicity studies with pertuzumab are summarized in Table 10 above.

Reproductive Toxicity
Reproductive toxicology studies have been conducted in cynomolgus monkeys at loading doses of 30 to 150 mg/kg and maintenance doses of 10 to 100 mg/kg achieving clinically relevant exposures. Intravenous administration of pertuzumab from Gestation Day (GD) 19 through 50 (period of organogenesis) has been shown to be embryotoxic with a dose dependent increase in embryo-fetal deaths between GD 25 to 70. At Caesarean section on GD100, oligohydramnios, decreased relative lung and kidney weights and microscopic evidence of renal hypoplasia consistent with delayed renal development were identified in all pertuzumab dose groups. The findings from the reproductive toxicology studies with pertuzumab are summarized in Table 11.

Data from additional toxicology studies are summarized in Table 12.

Table 14 Reproductive and Developmental Toxicity

Study No.	Study Type	Species and Strain	No./Sex/Group	Method of Administration	Pertuzumab Doses (mg/kg) [a]	Duration of Dosing
07-0925	Reproductive and Developmental Toxicity	Cynomolgus monkey	12/F	IV	[a] 30/10, 100/33.3, 150/100	Loading: GD19 Maintenance: GD26-50 (twice weekly)
Comments: Administration of pertuzumab to pregnant cynomolgus monkeys between GD 19 and 50 was generally well tolerated by the dams but was associated with high embryo and fetal lethality and oligohydramnios accompanied by delayed development of the fetal kidneys, as well as some secondary external, visceral, and skeletal abnormalities at clinically relevant concentrations. A fetal no-observable-effect level was not determined.						

[a] Loading/Maintenance dose.

Table 15 Other Toxicity Studies

Study No.	Type of Study	Species and Strain	No./Sex/Group	Method of Administration	Pertuzumab Doses (mg/kg)	Duration of Dosing
00-562-1821	Hemolytic Potential & Blood Compatibility	Cynomolgus monkey and human blood, serum, and plasma	NA	In vitro	21.6, 10.8, or 5.4 mg/mL	NA
Comments: At concentrations up to 21.6 mg/mL pertuzumab did not cause hemolysis of cynomolgus monkey or human erythrocytes and was compatible with cynomolgus monkey and human serum and plasma.						
01-014-1821	Tissue Cross-Reactivity	Human tissue	NA	In vitro	1.0 or 10.0 µg/mL	NA
Comemnts: Cross-reactivity to pertuzumab was demonstrated in a membranous pattern with normal human tonsil, parathyroid gland, mammary gland, haired skin, ureter, urinary bladder, placenta, and kidney tissues.						
01-015-1821	Tissue Cross-Reactivity	Cynomolgus monkey tissue	NA	In vitro	1.0 or 10.0 µg/mL	NA
Comments: Cross-reactivity to pertuzumab was demonstrated in a membranous pattern with normal epithelium from cynomolgus monkey sweat and sebaceous glands, mammary gland, placenta, kidney, ureter, urinary bladder, and prostate gland.						

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PART III: CONSUMER INFORMATION

PrPERJETA®
pertuzumab for injection

This leaflet is part III of a three-part "Product Monograph" published when PERJETA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PERJETA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
PERJETA, pronounced "per-JE-tah" is used to treat people with breast cancer when:
- there are a large number of "HER2-positive" cancer cells involved – your doctor will test for this.
- the cancer has spread to other parts of the body (metastasized)
- the cancer has not spread to other parts of the body and treatment is going to be given after surgery (treatment after surgery is called adjuvant therapy)

As well as PERJETA you will also receive HERCEPTIN and medicines called chemotherapy.

Information about these medicines is described in separate patient information leaflets. Ask your doctor or nurse to give you information about these other medicines.

What it does:
PERJETA is a type of medicine called a "monoclonal antibody" which attaches itself to specific targets in your body.

PERJETA recognizes and attaches to a protein in your body called "human epidermal growth factor 2" or HER2 for short. HER2 is found in large amounts on the surface of some cancer cells where it stimulates their growth. When PERJETA attaches to the HER2 cancer cells, it may slow or stop the cancer cells from growing, or may kill them.

When it should not be used:
Do not use PERJETA if you are allergic to this drug or to any ingredient in the formulation. See *"What the medicinal ingredient is"* and "*What the non-medicinal ingredients are"*. If you are not sure, talk to your doctor or nurse before you are given PERJETA.

PERJETA is not recommended for anyone under the age of 18 years because there is no information on how well it works in this age group.

What the medicinal ingredient is:
The medicinal ingredient in PERJETA is pertuzumab (pronounced per-TOOZ-ue-mab). Each vial of PERJETA contains 420 mg of pertuzumab

What the non-medicinal ingredients are:
Non-medicinal ingredients are (alphabetical order): glacial acetic acid, L-histidine, polysorbate 20, sucrose, water for injection.

What dosage forms it comes in:
PERJETA is a clear to slightly pearly (opalescent), colourless to pale brown solution for intravenous (IV) infusion. PERJETA is supplied as a single-use vial containing 14 mL preservative-free liquid concentrate, at a concentration of 30 mg/mL for dilution for intravenous infusion.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Heart Problems: PERJETA may cause heart problems, including those without symptoms (such as reduced heart function) and those with symptoms (such as congestive heart failure). Your health care provider may run tests to monitor your heart function before and during treatment with PERJETA. Based on test results your doctor may hold or discontinue treatment with PERJETA. See "*Serious side effects*" for more details about signs of heart problems to look out for.

Embryo-Fetal Toxicity: Exposure to PERJETA can result in embryo-fetal death and birth defects. Studies in animals have shown a reduction in the amount of amniotic fluid, delayed renal development, and death. Your health care provider will advise you of these risks and the need for effective contraception while you are taking PERJETA in combination with HERCEPTIN and 7 months after the last dose of treatment because of the length of time PERJETA and HERCEPTIN can remain in the body.

Hypersensitivity reactions / anaphylaxis and Infusion-related reactions: PERJETA has been associated with severe reactions. Deaths have been reported. You will be observed and carefully monitored during and after infusions. If you have a severe reaction, your doctor may need to completely stop your PERJETA treatment.

BEFORE you use PERJETA talk to your healthcare provider if:
- You have ever had heart problems (such as heart failure, heart attack, treatment for serious irregular heartbeats, uncontrolled high blood pressure) - your doctor will run tests to check if your heart is working properly
- You have ever had heart problems during previous treatment with HERCEPTIN
- You have ever had a chemotherapy medicine from the class called anthracycline, e.g. doxorubicin - these medicines can damage heart muscle and increase the risk of heart problems with PERJETA

If any of the above applies to you (or you are not sure), talk to your healthcare provider before you are given PERJETA.

Pregnancy, breast-feeding and contraception

- Before starting treatment, you must tell your healthcare provider if you are pregnant, think you may be pregnant or are planning to have a baby. You should also tell your healthcare provider if you are breast-feeding.
- Tell your healthcare provider straight away if you get pregnant during treatment with PERJETA and HERCEPTIN or during the 7 months after stopping treatment.
- Ask your healthcare provider about whether you can breast-feed during or after treatment with PERJETA.

PERJETA may harm the unborn baby. You should use effective contraception during treatment with PERJETA and HERCEPTIN and for 7 months after stopping treatment. If you are a male patient taking PERJETA with a female partner who can become pregnant you should use effective contraception during treatment with PERJETA and HERCEPTIN and for 7 months after stopping treatment. Talk to your healthcare provider about the best contraception for you.

INTERACTIONS WITH THIS MEDICATION

Before starting treatment, please tell your healthcare provider if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

It may take up to 7 months for PERJETA and HERCEPTIN to be removed from the body. Therefore, you should tell your doctor that you have had PERJETA if you start any new medication in the 7 months after stopping treatment.

PROPER USE OF THIS MEDICATION

Usual dose:
PERJETA will be given to you by your healthcare provider in a hospital or clinic.
- It is given by a drip into a vein (intravenous infusion) once every three weeks.
- The amount of medicine you are given and how long the infusion will last are different for the first, second and following doses.
- The number of infusions you will be given depends on how you respond to treatment and whether you are receiving treatment after surgery (adjuvant therapy) or for disease which has spread.
- PERJETA is given with other cancer treatments (HERCEPTIN and chemotherapy).

The first infusion:
- you will be given 840 mg of PERJETA over 60 minutes
- you will also be given HERCEPTIN and chemotherapy

For all following infusions, if the first infusion was well tolerated:
- you will be given 420 mg of PERJETA over 30 to 60 minutes
- you will also be given HERCEPTIN and chemotherapy

For further information on dosing of HERCEPTIN and chemotherapy (which can cause side effects as well), please refer to the package insert for these products. If you have questions about these medications, please ask your healthcare provider.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget or miss your appointment to receive PERJETA make another appointment as soon as possible.

If it has been 6 weeks or more since your last visit:
- a higher PERJETA dose of 840 mg will be given

You will then return to receiving a dose of 420mg PERJETA for following infusions.

If you stop having PERJETA
Do not stop having this medicine without talking to your doctor first.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Unwanted effects are possible with all medicines. Talk to your doctor, nurse or pharmacist if you are worried about side effects or find them very bothersome, and report any new or continuing symptoms to your doctor immediately. Your doctor will be able to tell you what to do and may be able to help you with these side effects.

Very common (may affect more than 1 in 10 people):
- hair loss
- dizziness
- loss of, or altered, taste
- producing more tears
- headache
- sore throat, red, sore or runny nose, flu-like symptoms and a fever
- feeling sick (nausea, vomiting)
- having less of an appetite
- nail problems
- rash, dry, itchy or acne like skin
- joint or muscle pain, muscle weakness
- weak, numb, tingling or prickling sensations mainly affecting the feet and legs
- pain in the body, arms, legs, and abdomen
- inflammation of your digestive tract (e.g. sore mouth)
- swollen ankles or other body parts due to your body holding onto too much water
- not being able to sleep

- decrease in the number of red and white blood cells – shown in a blood test
- fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- cough
- nose bleeds
- heartburn
- hot flushes

Common (may affect up to 1 in 10 people):
- inflammation of the nail bed where the nail and skin meet

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

If you experience any of the above symptoms after treatment with PERJETA has been stopped, you should consult your doctor immediately and inform them that you have previously been treated with PERJETA.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist immediately	
		Only if severe	In all cases
Very Common	Diarrhea	✓	
	Swelling of your face and throat with difficulty breathing, feeling sick (nausea), fever, chills, feeling tired, headache, loss of appetite, constipation and mouth ulcers.		✓
	Swollen ankles or other body parts		✓
	Shortness of breath and cough		✓
	Hot flushes		✓
	Loss of appetite	✓	
	Constipation	✓	
Common	Chest pain, nausea, discomfort radiating to the back, jaw, throat, or arm.		✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist immediately	
		Only if severe	In all cases
Rare	Vomiting, muscle cramps, numbness or tingling	✓	
	Decreased urination		✓

This is not a complete list of side effects. For any unexpected effects while taking PERJETA, contact your doctor or pharmacist.

HOW TO STORE IT

PERJETA will be stored by the health professionals at the hospital or clinic. The storage details are as follows:

- 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 vial and carton.
- Store vials in a refrigerator at 2-8°C.
- Keep vial in the outer carton in order to protect from light.
- Do not freeze or shake PERJETA.
- Do not use this medicine if you notice any particles in the liquid or it is the wrong colour (see "*What dosage forms it comes in")*.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

•Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html
•Call toll-free at 1-866-234-2345
•Complete a Canada Vigilance Reporting Form and:
– Fax toll-free to 1-866-678-6789, or
– Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more detailed information, please also see Part I: WARNINGS AND PRECAUTIONS of the PERJETA product monograph. The product monograph is a document prepared for healthcare professionals and can be found at:
www.rochecanada.com
or by contacting the sponsor, Hoffmann-La Roche Limited, at: 1-888-762-4388.

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