PRODUCT MONOGRAPH

**PR**PERJETA™

pertuzumab

420 mg/14 mL vial

Concentrate for solution for infusion

Antineoplastic

Professed Standard

Hoffmann-La Roche Limited
2455 Meadowpine Blvd.
Mississauga, Ontario, Canada
L5N 6L7

Date of Approval:
April 12, 2013

Submission Control No: 158419

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Clinically Relevant Non-medicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous (IV) infusion</td>
<td>420mg/14 mL</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>For a complete listing see Dosage Forms, Composition and Packaging section.</em></td>
</tr>
</tbody>
</table>

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

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.

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
Embryo-Fetal Toxicity

Exposure to PERJETA 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.

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 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 (pertuzumab). In the pivotal trial WO20698/TOC4129g (CLEOPATRA) PERJETA in combination with HERCEPTIN and docetaxel was not associated with increases in the incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decreases in LVEF compared with placebo and HERCEPTIN and docetaxel (see ADVERSE REACTIONS). However patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF.

PERJETA has not been studied in patients with: a pre-treatment LVEF value of \( \leq 50\% \); 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 \( > 360\text{mg/m}^2\) of doxorubicin or its equivalent.

Candidates for treatment with PERJETA and HERCEPTIN 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 the institution’s 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 every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of PERJETA and/or HERCEPTIN.

If LVEF is <40% or 40-45% associated with ≥10% points below the pre-treatment value, PERJETA and HERCEPTIN should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If the LVEF has not improved, or has declined further, discontinuation of PERJETA and HERCEPTIN should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks (see DOSAGE AND ADMINISTRATION).

**Immune**

*Infusion-associated reactions, and hypersensitivity reactions/anaphylaxis*

PERJETA has been associated with infusion and hypersensitivity reactions (see ADVERSE REACTIONS). Close observation of the patient for 60 minutes, after the first infusion and for 30 minutes following subsequent infusions is recommended following the administration of PERJETA. If a significant infusion-associated 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).

**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 due to the higher incidence of mucositis and diarrhea in these patients. Symptomatic treatment for mucositis and diarrhea should be considered. In the pivotal trial, WO20698/TOC4129g (CLEOPATRA), no events of febrile neutropenia were reported after cessation of docetaxel. The median total dose of docetaxel was 941.4 mg and 1008.0 mg in the PERJETA-treated and the placebo-treated patients, respectively. Febrile neutropenia occurred in 13.8% 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.

**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.
**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 and for 6 months following the last dose of PERJETA. Male patients with female partners of child bearing potential should also use effective contraception while receiving PERJETA and for 6 months following the last dose.

**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 drug 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):** Of 402 patients who received PERJETA in the randomized trial, 60 patients (15%) were ≥ 65 years of age and 5 patients (1%) were ≥ 75 years of age. No differences in safety and efficacy of PERJETA were observed between adult patients ≥65 and <65 years of age. No dose adjustment is required in the elderly population.

**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 (57.8%) and the placebo-treated group (57.9%). However, the incidence of febrile neutropenia was higher in the PERJETA-treated group (26%) compared with the placebo-treated group (12%). 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 the pivotal trial WO20698/TOC4129g (CLEOPATRA) and in phase I and II trials conducted in more than 1400 patients with various malignancies and predominantly treated with PERJETA in combination with other antineoplastic agents. Table 1 summarises the adverse drug reactions (ADRs) from the pivotal clinical trial 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 1 - Summary of ADRs occurring in ≥1% from the pivotal clinical trial CLEOPATRA

<table>
<thead>
<tr>
<th>Adverse Drug Reaction (ADR) (MedDRA)</th>
<th>System Organ Class</th>
<th>Placebo + HERCEPTIN + docetaxel n=397 Frequency rate %</th>
<th>PERJETA + HERCEPTIN + docetaxel n=407 Frequency rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>36.8</td>
<td>3.3</td>
<td>37.6</td>
</tr>
<tr>
<td>Asthenia</td>
<td>30.2</td>
<td>1.5</td>
<td>26.0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>30.0</td>
<td>0.8</td>
<td>23.1</td>
</tr>
<tr>
<td>Mucosal inflammation/Mucositis</td>
<td>19.9</td>
<td>1.0</td>
<td>27.8</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17.9</td>
<td>0.5</td>
<td>18.7</td>
</tr>
<tr>
<td>Chills</td>
<td>3.8</td>
<td>-</td>
<td>8.1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>60.5</td>
<td>0.3</td>
<td>60.9</td>
</tr>
<tr>
<td>Rash</td>
<td>24.2</td>
<td>0.8</td>
<td>33.7</td>
</tr>
<tr>
<td>Nail disorder</td>
<td>22.9</td>
<td>0.3</td>
<td>22.9</td>
</tr>
<tr>
<td>Adverse Drug Reaction (ADR) (MedDRA) System Organ Class</td>
<td>Placebo + HERCEPTIN + docetaxel n =397 Frequency rate %</td>
<td>PERJETA + HERCEPTIN + docetaxel n =407 Frequency rate %</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10.1</td>
<td>-</td>
<td>14.0</td>
</tr>
<tr>
<td>Erythema</td>
<td>4.8</td>
<td>-</td>
<td>5.4</td>
</tr>
<tr>
<td>Dry skin</td>
<td>4.3</td>
<td>-</td>
<td>10.6</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>2.0</td>
<td>-</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>46.3</td>
<td>5.0</td>
<td>66.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>41.6</td>
<td>0.5</td>
<td>42.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23.9</td>
<td>1.5</td>
<td>24.1</td>
</tr>
<tr>
<td>Constipation</td>
<td>24.9</td>
<td>1.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>15.4</td>
<td>0.3</td>
<td>18.9</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>12.1</td>
<td>-</td>
<td>12.0</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>49.6</td>
<td>45.8</td>
<td>52.8</td>
</tr>
<tr>
<td>Anaemia</td>
<td>18.9</td>
<td>3.5</td>
<td>23.1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>20.4</td>
<td>14.6</td>
<td>18.2</td>
</tr>
<tr>
<td>Febrile neutropenia*</td>
<td>7.6</td>
<td>7.3</td>
<td>13.8</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy peripheral</td>
<td>20.2</td>
<td>1.8</td>
<td>21.1</td>
</tr>
<tr>
<td>Headache</td>
<td>16.9</td>
<td>0.5</td>
<td>20.9</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>15.6</td>
<td>-</td>
<td>18.4</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>14.1</td>
<td>0.3</td>
<td>12.0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12.1</td>
<td>-</td>
<td>12.5</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>23.9</td>
<td>0.8</td>
<td>22.9</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16.1</td>
<td>0.8</td>
<td>15.5</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13.4</td>
<td>-</td>
<td>16.7</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12.8</td>
<td>0.3</td>
<td>11.8</td>
</tr>
<tr>
<td>Paronychia</td>
<td>3.5</td>
<td>0.3</td>
<td>7.1</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>18.6</td>
<td>0.3</td>
<td>21.4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15.6</td>
<td>2.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>5.8</td>
<td>1.3</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>26.4</td>
<td>1.5</td>
<td>29.2</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>13.9</td>
<td>-</td>
<td>14.0</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>13.4</td>
<td>-</td>
<td>13.3</td>
</tr>
<tr>
<td>Adverse Drug Reaction (ADR) (MedDRA) System Organ Class</td>
<td>Placebo + HERCEPTIN + docetaxel n =397 Frequency rate %</td>
<td>PERJETA + HERCEPTIN + docetaxel n =407 Frequency rate %</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td>Grades 3-4</td>
<td>All Grades</td>
<td>Grades 3-4</td>
</tr>
</tbody>
</table>

### Cardiac disorders

| Left ventricular dysfunction\(^1\) | 8.3 | 2.8 | 4.4 | 1.2 |

### Immune system disorders

<table>
<thead>
<tr>
<th>Hypersensitivity</th>
<th>5.0</th>
<th>0.8</th>
<th>6.4</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug hypersensitivity</td>
<td>3.8</td>
<td>1.5</td>
<td>4.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>0.5</td>
<td>0.3</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Infusion Associated Reactions</td>
<td>14.6</td>
<td>-</td>
<td>19.2</td>
<td>-</td>
</tr>
</tbody>
</table>

* 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) (1.0% in the PERJETA-treated group vs. 1.8% in the placebo-treated group)

Table 2 - 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

<table>
<thead>
<tr>
<th>Adverse Event (AE) (MedDRA) System Organ Class</th>
<th>Placebo + HERCEPTIN + docetaxel n =397 (100%) Frequency rate %</th>
<th>PERJETA + HERCEPTIN + docetaxel n =407 (100%) Frequency rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
<td>All Grades %</td>
</tr>
</tbody>
</table>

### General disorders and administration site conditions

| Chills | 3.8 | - | 8.1 | - |
| Influenza like illness | 2.0 | - | 4.9 | 0.2 |

### Gastrointestinal disorders

| Dysphagia | 0.3 | - | 2.9 | 0.2 |

### Musculoskeletal and connective tissue disorders

| Pain in extremity | 11.8 | 0.3 | 15.2 | 0.5 |
| Muscle spasms | 3.8 | - | 7.1 | 0.2 |

### Infections and infestations

| Pharyngitis | 2.0 | 0.3 | 4.2 | 0.2 |
| Cystitis | 1.3 | - | 3.4 | - |
| Rash pustular | - | - | 2.2 | 0.2 |

### Metabolism and nutrition disorders

| Hypokalaemia | 4.8 | 1.3 | 9.1 | 1.2 |
Adverse Event (AE) (MedDRA) Placebo + HERCEPTIN + docetaxel n =397 (100%) Frequency rate %

PERJETA + HERCEPTIN + docetaxel n =407 (100%) Frequency rate %

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Grades %</th>
<th>Grades 3-4 %</th>
<th>All Grades %</th>
<th>Grades 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>1.8</td>
<td>-</td>
<td>3.9</td>
<td>-</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>4.0</td>
<td>0.3</td>
<td>8.4</td>
<td>-</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>2.3</td>
<td>-</td>
<td>5.4</td>
<td>-</td>
</tr>
</tbody>
</table>

Infusion-associated reactions
An infusion reaction was defined in the pivotal trial as any event described 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, 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 13.0% in the PERJETA-treated group, with the majority of reactions being mild or moderate. The most common infusion reactions in the PERJETA-treated group ($\geq$1.0%) were, pyrexia, chills, fatigue, headaches, asthenia, hypersensitivity and vomiting.

During the 2nd cycle when all drugs were administered on the same day, the most common infusion reactions in the PERJETA-treated group ($\geq$1.0%) were fatigue, dysgeusia, hypersensitivity, myalgia and vomiting.

Hypersensitivity reactions/anaphylaxis
In the pivotal trial, the overall frequency of hypersensitivity/anaphylaxis events was 9.1% in the placebo-treated patients and 10.8% in the PERJETA-treated patients, of which 2.5% and 2% 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: Infusion-associated reactions, and hypersensitivity reactions/anaphylaxis).

Overall, the majority of hypersensitivity reactions were mild or moderate in severity and resolved upon treatment.

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

In the pivotal trial, ADRs were reported less frequently after discontinuation of docetaxel treatment. All ADRs in the PERJETA and HERCEPTIN treatment group occurred in <10% of patients with the exception of diarrhea (19.1%), upper respiratory tract infection (12.8%), rash (11.7%), headache (11.4%) and fatigue (11.1%).

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, upper respiratory tract infection, pain in extremity, pruritus, decreased appetite, peripheral neuropathy, peripheral sensory neuropathy, stomatitis, muscle spasms, paronychia, onycholysis and hypokalemia.

Laboratory Abnormalities
The incidence of NCI-CTCAE (version 3) grade 3-4 leukopenia was higher in the PERJETA-treated group (64.5% of PERJETA-treated patients and 60.5% of placebo-treated patients, including 12.4% and 13.2% Grade 4 leukopenia, respectively).

The incidence of NCI-CTCAE (version 3) grade 3-4 neutropenia was balanced in the two treated groups (85.9% of PERJETA-treated patients and 86.6% of placebo-treated patients, including 61.0% and 64.3% Grade 4 neutropenia, respectively).

DRUG INTERACTIONS

Drug-Drug Interactions
A sub-study in 37 patients in the pivotal trial, showed no evidence of drug-drug interaction between PERJETA and HERCEPTIN or between PERJETA and docetaxel.

Four studies have evaluated the effects of PERJETA on the pharmacokinetics of co-administered cytotoxic agents, docetaxel, gemcitabine, erlotinib and capecitabine, respectively. There was no evidence of any pharmacokinetic interaction between PERJETA and any of these agents. The pharmacokinetics of PERJETA in these studies were comparable to those observed in single-agent studies.

Drug-Lifestyle Interactions
No studies on the effects on the ability to drive and to use machines have been performed.

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.

Do not administer as an intravenous push or bolus.
**Recommended Dose and Dose Adjustment**

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

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.

When administered with PERJETA the recommended initial dose of docetaxel is 75 mg/m². The dose may be escalated to 100 mg/m² if the initial dose is well tolerated.

The medicinal products should be administered sequentially. When the patient is receiving docetaxel, the docetaxel should be administered after PERJETA and HERCEPTIN. An observation period of 30 to 60 minutes is recommended after each PERJETA infusion and before commencement of any subsequent infusion of HERCEPTIN or docetaxel (see WARNINGS and PRECAUTIONS: Infusion-associated reactions, hypersensitivity reactions/anaphylaxis).

In the pivotal clinical trial, 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.

**Duration of treatment:**
It is recommended that patients are treated with PERJETA until disease progression or unmanageable toxicity.

**Dose Adjustments:**
Dose reductions are not recommended for PERJETA.

For HERCEPTIN, dose reductions are not recommended, see the HERCEPTIN Product Monograph.

For docetaxel dose modifications, see the docetaxel Product Monograph. A reduction in docetaxel dose was required in approximately 25% of patients in both treatment arms in the pivotal trial.

**Infusion-associated reaction**
The infusion rate of PERJETA may be slowed or interrupted if the patient develops an infusion-associated reaction. The infusion should be discontinued immediately if the patient experiences a serious hypersensitivity reaction (see WARNINGS and PRECAUTIONS: Infusion-associated reactions, hypersensitivity reactions/anaphylaxis).

**Left ventricular dysfunction:**
Withhold PERJETA and HERCEPTIN dosing for at least 3 weeks for either:

- a drop in left ventricular ejection fraction (LVEF) to less than 40%
- a LVEF of 40%-45% associated with a fall of ≥10%-points below pre-treatment value.

PERJETA and HERCEPTIN may be resumed if the LVEF has recovered to >45% or 40-45% associated with <10%-points below pre-treatment value.

If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, discontinuation of PERJETA and HERCEPTIN should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks (see WARNINGS and PRECAUTIONS: Left ventricular dysfunction). The Product Monograph for HERCEPTIN should be referred for further information.

**Missed Dose**

**Delayed or Missed doses**
If the time between two sequential infusions is less than 6 weeks, the 420 mg dose of PERJETA should be administered. Do not wait until the next planned dose. If the time between two sequential infusions is 6 weeks or more, the initial dose of 840 mg PERJETA should be re-administered as a 60 minute intravenous infusion followed every 3 weeks thereafter by a dose of 420 mg administered over 30 to 60 minutes.

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

If docetaxel is discontinued, treatment with PERJETA and HERCEPTIN may continue until disease progression or unmanageable toxicity.

**Administration**

**Instructions for dilution**
PERJETA should be prepared by a health professional using aseptic technique. Withdraw all the PERJETA liquid concentrate from the vial and dilute into the 250 mL PVC or non-PVC polyolefin 0.9% sodium chloride infusion bags. 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, pertuzumab inhibits ligand initiated intracellular signalling through two major signal pathways, mitogen activated protein (MAP) kinase and phosphoinositide 3 kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, 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.

**Absorption:** Pertuzumab is administered as an IV infusion. There have been no studies performed with other routes of administration.

**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 elderly 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. Use established “collection systems”, if available in your location.

**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

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. Breast tumour specimens were required to show HER2 overexpression defined as a score of 3+ by IHC or ISH amplification ratio \( \geq 2.0 \) as determined at a central laboratory. 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 was given intravenously as an initial loading dose of 840 mg, followed every three weeks thereafter by 420 mg. HERCEPTIN was given intravenously as an initial loading dose of 8 mg/kg, followed every three weeks thereafter by 6 mg/kg. 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.

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 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 3 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)].

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 3:

**Table 3: Summary of efficacy from CLEOPATRA study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo + HERCEPTIN + docetaxel (n=406)</th>
<th>PERJETA + HERCEPTIN + docetaxel (n=402)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progression-Free Survival</strong> (IRF review)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with an event</td>
<td>242 (59%)</td>
<td>191 (47.5%)</td>
<td>0.62</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>12.4</td>
<td>18.5</td>
<td>[0.51;0.75]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Secondary Endpoints:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with an event*</td>
<td>154 (37.9%)</td>
<td>113 (28.1%)</td>
<td>0.66</td>
<td>0.0008*</td>
</tr>
<tr>
<td>Median months</td>
<td>37.6</td>
<td>Not reached</td>
<td>[0.49;0.90]#</td>
<td>0.0008*</td>
</tr>
<tr>
<td><strong>Objective Response Rate (ORR)</strong> ^</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with measurable disease</td>
<td>336</td>
<td>343</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (CR+PR)</td>
<td>233 (69.3%)</td>
<td>275 (80.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>14 (4.2%)</td>
<td>19 (5.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>219 (65.2%)</td>
<td>256 (74.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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 ≤ 0.0138). The result was therefore statistically significant.

# adjusted CI presented for OS, to reflect the stopping boundary of p≤ 0.0138. The interval represents the 98.62% CI

^Objective response rate is based on IRF-assessed tumour assessments
Figure 1: Kaplan-Meier curve of IRF-assessed progression-free survival
Figure 2: IRF assessed PFS by patient subgroup

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroup</th>
<th>N</th>
<th>Lower confidence limit</th>
<th>Estimate</th>
<th>Upper confidence limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Treatment Status</td>
<td>De Novo</td>
<td>432</td>
<td>0.49</td>
<td>0.63</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Adjuvant or Neo-Adjuvant Therapy</td>
<td>376</td>
<td>0.46</td>
<td>0.61</td>
<td>0.81</td>
</tr>
<tr>
<td>Region</td>
<td>Europe</td>
<td>306</td>
<td>0.53</td>
<td>0.72</td>
<td>0.97</td>
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<tr>
<td></td>
<td>North America</td>
<td>135</td>
<td>0.31</td>
<td>0.51</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>South America</td>
<td>114</td>
<td>0.27</td>
<td>0.46</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Asia</td>
<td>253</td>
<td>0.48</td>
<td>0.68</td>
<td>0.95</td>
</tr>
<tr>
<td>Age Group</td>
<td>&lt;65 years</td>
<td>681</td>
<td>0.53</td>
<td>0.65</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>&gt;=65 years</td>
<td>127</td>
<td>0.31</td>
<td>0.52</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>&lt;75 years</td>
<td>789</td>
<td>0.53</td>
<td>0.64</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>&gt;=75 years</td>
<td>19</td>
<td>0.12</td>
<td>0.65</td>
<td>2.54</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>480</td>
<td>0.49</td>
<td>0.62</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>30</td>
<td>0.23</td>
<td>0.64</td>
<td>1.79</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>261</td>
<td>0.49</td>
<td>0.68</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>37</td>
<td>0.13</td>
<td>0.39</td>
<td>1.18</td>
</tr>
<tr>
<td>Disease Type</td>
<td>Visceral Disease</td>
<td>630</td>
<td>0.45</td>
<td>0.55</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>Non-Visceral Disease</td>
<td>178</td>
<td>0.61</td>
<td>0.96</td>
<td>1.52</td>
</tr>
<tr>
<td>ER/PgR Status</td>
<td>Positive</td>
<td>388</td>
<td>0.55</td>
<td>0.72</td>
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<tr>
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<td></td>
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<td>12</td>
<td>0.00</td>
<td>179E6</td>
<td>1.36</td>
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<tr>
<td>HER2 IHC Status</td>
<td>3+</td>
<td>721</td>
<td>0.49</td>
<td>0.60</td>
<td>0.74</td>
</tr>
<tr>
<td>FISH Status</td>
<td>FISH Positive</td>
<td>767</td>
<td>0.53</td>
<td>0.64</td>
<td>0.78</td>
</tr>
</tbody>
</table>
Figure 3: Kaplan-Meier curve of overall survival
Study BO17929

BO17929 is a phase II, single arm, non-randomized study with PERJETA and was conducted in patients with HER2 positive MBC that 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 4. 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 4 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 4: Study BO17929: Descriptive Efficacy Data

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

NOTE: >6 months = 8 cycles of therapy

### 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 5.
Table 5: Repeat-Dose Toxicity Studies

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Study Type</th>
<th>Species and Strain</th>
<th>No./Sex/Group</th>
<th>Method of Administration</th>
<th>Pertuzumab Doses (mg/kg) a</th>
<th>Duration of Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>99-520-1820</td>
<td>Repeat-Dose Toxicity</td>
<td>Cynomolgus monkey</td>
<td>2/M, 2/F</td>
<td>IV</td>
<td>10, 50, 100</td>
<td>4 weeks b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>00-377-1821</td>
<td>Repeat-Dose Toxicity</td>
<td>Cynomolgus monkey</td>
<td>4-6/M</td>
<td>IV</td>
<td>15, 50, 150</td>
<td>one dose weekly for 7 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-6/F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>00-604-1560</td>
<td>Repeat-Dose Toxicity</td>
<td>Cynomolgus monkey</td>
<td>3/F</td>
<td>SC</td>
<td>250</td>
<td>one dose weekly for 4 weeks</td>
</tr>
<tr>
<td>01-458-1821</td>
<td>Repeat-Dose Toxicity</td>
<td>Cynomolgus monkey</td>
<td>4-6/M</td>
<td>IV</td>
<td>c 15, 50, 150</td>
<td>one dose weekly for 26 weeks</td>
</tr>
</tbody>
</table>

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.

Comments: Pertuzumab was well tolerated at doses up to 100 mg/kg administered twice weekly.

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.

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.

**Mutagenicity**
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 5 above.

**Teratogenicity**
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 6.

Data from additional toxicology studies are summarized in Table 7.
Table 6: Reproductive and Developmental Toxicity

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Study Type</th>
<th>Species and Strain</th>
<th>No./Sex/Group</th>
<th>Method of Administration</th>
<th>Pertuzumab Doses (mg/kg) (^a)</th>
<th>Duration of Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>07-0925</td>
<td>Reproductive and Developmental Toxicity</td>
<td>Cynomolgus monkey</td>
<td>12/F</td>
<td>IV</td>
<td>(^a) 30/10, 100/33.3, 150/100</td>
<td>Loading: GD19 Maintenance: GD26-50 (twice weekly)</td>
</tr>
</tbody>
</table>

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 7: Other Toxicity Studies

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Type of Study</th>
<th>Species and Strain</th>
<th>No./Sex/Group</th>
<th>Method of Administration</th>
<th>Pertuzumab Doses (mg/kg)</th>
<th>Duration of Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>00-562-1821</td>
<td>Hemolytic Potential &amp; Blood Compatibility</td>
<td>Cynomolgus monkey and human blood, serum, and plasma</td>
<td>NA</td>
<td>In vitro</td>
<td>21.6, 10.8, or 5.4 mg/mL</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Comments:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01-014-1821</td>
<td>Tissue Cross-Reactivity</td>
<td>Human tissue</td>
<td>NA</td>
<td>In vitro</td>
<td>1.0 or 10.0 µg/mL</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Comments:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01-015-1821</td>
<td>Tissue Cross-Reactivity</td>
<td>Cynomolgus monkey tissue</td>
<td>NA</td>
<td>In vitro</td>
<td>1.0 or 10.0 µg/mL</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Comments:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
REFERENCES
PART III: CONSUMER INFORMATION

PRPERJETA™
pertuzumab

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:
- the cancer has spread to other parts of the body (metastasized)
- there are a large number of “HER2-positive” cancer cells involved – your doctor will test for this.

As well as PERJETA you will also receive HERCEPTIN and the chemotherapy medicine docetaxel.

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.

What 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 important 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 important 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 in a single-use vial containing 14 mL preservative-free liquid concentrate, at a concentration of 30 mg/mL for dilution for intravenous infusion.

WARNING AND PRECAUTIONS

Serious Warnings and Precautions

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 and 6 months after the last dose of PERJETA because of the length of time PERJETA can remain in the body.

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.

Infusion reactions
Infusion reactions (including allergic or anaphylactic reactions) can happen. Your healthcare provider will check for side effects during your infusion and for 30 to 60 minutes afterwards. If you get any serious reaction, your doctor may stop treatment with PERJETA. See “Serious side effects” for more details about infusion reactions to look out for during the infusion and thereafter.

Heart problems
Treatment with PERJETA may affect the heart. Therefore, your heart function will be checked before and during treatment with PERJETA. See “Serious side effects” for more details about signs of heart problems to look out for.

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 or during the 6 months after stopping treatment.
- Ask your healthcare provider about whether you can breastfeed during or after treatment with PERJETA.

PERJETA may harm the unborn baby. You should use effective contraception during treatment with PERJETA and for 6 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 for 6 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 6 months for PERJETA 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 6 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.
- PERJETA is given with other cancer treatments (HERCEPTIN and docetaxel).

**The first infusion:**

- you will be given 840 mg of PERJETA over 60 minutes
- you will also be given HERCEPTIN and docetaxel

**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 docetaxel

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

**Overdose:**

In case of drug overdose, contact a healthcare 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 also be given HERCEPTIN and docetaxel.

You will then return to receiving a dose of 420 mg 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.

**Serious side effects**

Tell your healthcare provider immediately, if you notice any of the following side effects:

- The most common side effects are diarrhea, hair loss and a decrease in the number of your white blood cells with or without fever (shown in a blood test)
- Infusion associated, allergic and anaphylactic reactions can happen. These include swelling of your face and throat with difficulty breathing, feeling sick (nausea), fever, chills, feeling tired, headache, loss of appetite, constipation and mouth ulcers.
- Symptoms of heart problems (heart failure) can include cough, shortness of breath when sleeping flat and swelling (fluid retention) in your legs or arms.

Other side effects include:

**Very common (may affect more than 1 in 10 people):**

- feeling dizzy
- loss of, or altered, taste
- producing more tears
- fever
- sore throat, red, sore or runny nose, flu-like symptoms and a fever
- feeling sick or being sick
- having less of an appetite
- shortness of breath
• 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 (bone, neck, chest, abdominal pain)
• inflammation of the lining of your gut (stomatitis)
• swollen ankles or other body parts due to your body holding onto too much water
• decrease in the number of red blood cells – shown in a blood test
• not being able to sleep

Common (may affect up to 1 in 10 people):
• fluid on the lungs causing difficulty in breathing
• inflammation of the nail bed where the nail and skin meet
• reduction in the ability of your heart to pump blood, which may or may not cause other symptoms.

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

<table>
<thead>
<tr>
<th>Symptom / effect</th>
<th>Talk with your doctor or pharmacist</th>
<th>Stop taking drug and call your doctor or pharmacist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only if severe</td>
<td>In all cases</td>
</tr>
<tr>
<td>Very Common</td>
<td>Diarrhea</td>
<td>✓</td>
</tr>
<tr>
<td>Common</td>
<td>Difficulty in breathing</td>
<td>✓</td>
</tr>
</tbody>
</table>

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 www.healthcanada.gc.ca/medeffect
• 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 0701D
    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 www.healthcanada.gc.ca/medeffect.

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

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.rochecanada.com
or by contacting the sponsor, Hoffmann-La Roche Limited, at: 1-888-762-4388

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