CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125409Orig1s109

Trade Name:	PERJETA
Generic or Proper Name:	pertuzumab
Sponsor:	Genentech, Inc.
Approval Date:	March 22, 2016
Indication:	Perjeta is a HER2/neu receptor antagonist indicated for: • Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. • Use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival. Limitation of Use: o The safety of Perjeta as part of doxorubicin-containing regimen has not been established. o The safety of Perjeta administered for greater than 6 cycles for early breast cancer has not been established.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125409/S-109

SUPPLEMENT APPROVAL

Genentech, Inc.
Attention: Ardelle (Jia) Ying, M.D., Ph.D.
Associate Program Director, Global Regulatory Affair (PDR-PM)
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Ying:

Please refer to your Supplemental Biologics License Application (sBLA), dated October 23, 2015, received October 23, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for Perjeta® (pertuzumab).

This Prior Approval supplemental biologics application provides for changes to the USE IN SPECIFIC POPULATIONS, Section 8 of the Full Prescribing Information to comply with the new content and format requirements of the Pregnancy and Lactation Labeling Rule (PLLR). Also, where appropriate, the language and content of Section 8 has been aligned with the Herceptin® and Kadcyla® Full Prescribing Information.

APPROVAL & LABELING

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the package insert and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Amy Tilley, Regulatory Project Manager, at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, M.D.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEOFFREY S KIM
03/22/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s109

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PERJETA safely and effectively. See full prescribing information for PERJETA.

PERJETA® (pertuzumab) injection, for intravenous use
Initial U.S. Approval: 2012

WARNING: LEFT VENTRICULAR DYSFUNCTION and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **Left Ventricular Dysfunction: PERJETA can result in subclinical and clinical cardiac failure manifesting as decreased LVEF and CHF. Evaluate cardiac function prior to and during treatment. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function. (2.2, 5.1, 6.1)**
- **Embryo-fetal Toxicity: Exposure to PERJETA can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception. (5.2, 8.1, 8.3)**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.2) 03/2016

---------- INDICATIONS AND USAGE----------

PERJETA is a HER2/neu receptor antagonist indicated for:

- Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. (1.1)
- Use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival. (1.2, 2.1, 14.2)

  Limitations of Use:
  - The safety of PERJETA as part of a doxorubicin-containing regimen has not been established.
  - The safety of PERJETA administered for greater than 6 cycles for early breast cancer has not been established.

----------DOSAGE AND ADMINISTRATION----------

- **For intravenous infusion only.** Do not administer as an intravenous push or bolus. (2.3)
- The initial PERJETA dose is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by 420 mg administered as a 30 to 60 minute intravenous infusion. (2.1)
- MBC: Administer PERJETA, trastuzumab, and docetaxel by intravenous infusion every 3 weeks. (2.1)
- Neoadjuvant: Administer PERJETA, trastuzumab, and docetaxel by intravenous infusion preoperatively every 3 weeks for 3 to 6 cycles. (2.1)

---------- DOSAGE FORMS AND STRENGTHS----------

- 420 mg/14 mL single-use vial. (3)

---------- CONTRAINDICATIONS ----------

PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Left Ventricular Dysfunction: Monitor LVEF and withhold dosing as appropriate. (5.1, 6.1)
- Infusion-Related Reactions: Monitor for signs and symptoms. If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies. (5.3)
- Hypersensitivity Reactions/Anaphylaxis: Monitor for signs and symptoms. If a severe hypersensitivity reaction/anaphylaxis occurs, discontinue the infusion immediately and administer appropriate medical therapies. (5.4)
- HER2 testing: Perform using FDA-approved tests by laboratories with demonstrated proficiency. (5.5)

---------- ADVERSE REACTIONS ----------

Metastatic Breast Cancer

- The most common adverse reactions (> 30%) with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. (6.1)

Neoadjuvant Treatment of Breast Cancer

- The most common adverse reactions (> 30%) with PERJETA in combination with trastuzumab and docetaxel were alopecia, diarrhea, nausea, and neutropenia. (6.1)
- The most common adverse reactions (>30%) with PERJETA in combination with trastuzumab and docetaxel when given for 3 cycles following 3 cycles of FEC were fatigue, alopecia, diarrhea, nausea, vomiting, and neutropenia. (6.1)
- The most common adverse reactions (>30%) with PERJETA in combination with docetaxel, carboplatin, and trastuzumab (TCH) were fatigue, alopecia, diarrhea, nausea, vomiting, neutropenia, thrombocytopenia, and anemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- USE IN SPECIFIC POPULATIONS ----------

Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of PERJETA. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LEFT VENTRICULAR DYSFUNCTION AND EMBRYO-FETAL TOXICITY

- **Left Ventricular Dysfunction: PERJETA can result in subclinical and clinical cardiac failure manifesting as decreased LVEF and CHF. Evaluate cardiac function prior to and during treatment. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function. (2.2, 5.1, 6.1)**
- **Embryo-fetal Toxicity: Exposure to PERJETA can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception. (5.2, 8.1, 8.3)**

1 INDICATIONS AND USAGE

1.1 Metastatic Breast Cancer (MBC)

PERJETA is indicated for use in combination with 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.

1.2 Neoadjuvant Treatment of Breast Cancer

PERJETA is indicated for use in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival *[see Clinical Studies (14.2) and Dosage and Administration (2.1)]*.

Limitations of Use:

- The safety of PERJETA as part of a doxorubicin-containing regimen has not been established.
- The safety of PERJETA administered for greater than 6 cycles for early breast cancer has not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Doses and Schedules

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

When administered with PERJETA, the recommended initial dose of trastuzumab is 8 mg/kg administered as a 90-minute intravenous infusion, followed every 3 weeks by a dose of 6 mg/kg administered as an intravenous infusion over 30 to 90 minutes.

PERJETA, trastuzumab, and docetaxel should be administered sequentially. PERJETA and trastuzumab can be given in any order. Docetaxel should be administered after PERJETA and trastuzumab. An observation period of 30 to 60 minutes is recommended after each PERJETA infusion and before commencement of any subsequent infusion of trastuzumab or docetaxel *[see Warnings and Precautions (5.3)]*.

Metastatic Breast Cancer (MBC)

When administered with PERJETA, the recommended initial dose of docetaxel is 75 mg/m^2 administered as an intravenous infusion. The dose may be escalated to 100 mg/m^2 administered every 3 weeks if the initial dose is well tolerated.

Neoadjuvant Treatment of Breast Cancer

PERJETA should be administered every 3 weeks for 3 to 6 cycles as part of one of the following treatment regimens for early breast cancer *[see Clinical Studies (14.2)]*:

- Four preoperative cycles of PERJETA in combination with trastuzumab and docetaxel followed by 3 postoperative cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) as given in Study 2
- Three preoperative cycles of FEC alone followed by 3 preoperative cycles of PERJETA in combination with docetaxel and trastuzumab as given in Study 3
- Six preoperative cycles of PERJETA in combination with docetaxel, carboplatin, and trastuzumab (TCH) (escalation of docetaxel above 75 mg/m^2 is not recommended) as given in Study 3

Following surgery, patients should continue to receive trastuzumab to complete 1 year of treatment. There is insufficient evidence to recommend continued use of PERJETA for greater than 6 cycles for early breast cancer. There is insufficient evidence to recommend concomitant administration of an anthracycline with PERJETA, and there are no safety data to support sequential use of doxorubicin with PERJETA.

2.2 Dose Modification

For 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 as an intravenous infusion over 30 to 60 minutes.

PERJETA should be discontinued if trastuzumab treatment is discontinued.

Dose reductions are not recommended for PERJETA.

For docetaxel dose modifications, see relevant prescribing information.

Left Ventricular Ejection Fraction (LVEF):

Withhold PERJETA and trastuzumab dosing for at least 3 weeks for either:

- a drop in LVEF to less than 45% or
- LVEF of 45% to 49% with a 10% or greater absolute decrease below pretreatment values *[see Warnings and Precautions (5.1)]*

PERJETA may be resumed if the LVEF has recovered to greater than 49% or to 45% to 49% associated with less than a 10% absolute decrease below pretreatment values.

If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, PERJETA and trastuzumab should be discontinued, unless the benefits for the individual patient are deemed to outweigh the risks *[see Warnings and Precautions (5.1)]*.

Infusion-Related Reactions

The infusion rate of PERJETA may be slowed or interrupted if the patient develops an infusion-related reaction *[see Warnings and Precautions (5.3)]*.

Hypersensitivity Reactions/Anaphylaxis

The infusion should be discontinued immediately if the patient experiences a serious hypersensitivity reaction *[see Warnings and Precautions (5.4)]*.

2.3 Preparation for Administration

Administer as an intravenous infusion only. Do not administer as an intravenous push or bolus. Do not mix PERJETA with other drugs.

Preparation

Prepare the solution for infusion, using aseptic technique, as follows:

- Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.
- Withdraw the appropriate volume of PERJETA solution from the vial(s).
- Dilute into a 250 mL 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag.
- Mix diluted solution by gentle inversion. Do not shake.
- Administer immediately once prepared.
- If the diluted infusion solution is not used immediately, it can be stored at 2°C to 8°C for up to 24 hours.
- Dilute with 0.9% Sodium Chloride injection only. Do not use dextrose (5%) solution.

3 DOSAGE FORMS AND STRENGTHS

PERJETA (pertuzumab) 420 mg/14 mL (30 mg/mL) in a single-use vial

4 CONTRAINDICATIONS

PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Left Ventricular Dysfunction

Decreases in LVEF have been reported with drugs that block HER2 activity, including PERJETA. In Study 1, for patients with MBC, PERJETA in combination with trastuzumab and docetaxel was not associated with increases in the incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decreases in LVEF compared with placebo in combination with trastuzumab and docetaxel *[see Clinical Studies (14.1)]*. Left ventricular dysfunction occurred in 4.4% of patients in the PERJETA-treated group and 8.3% of patients in the placebo-treated group. Symptomatic left ventricular systolic dysfunction (congestive heart failure) occurred in 1.0% of patients in the PERJETA-treated group and 1.8% of patients in the placebo-treated group *[see Adverse Reactions (6.1)]*. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF.

In patients receiving neoadjuvant treatment in Study 2, the incidence of LVSD was higher in the PERJETA-treated groups compared to the trastuzumab- and docetaxel-treated group. An increased incidence of LVEF declines was observed in patients treated with PERJETA in

combination with trastuzumab and docetaxel. In the overall treatment period, LVEF decline > 10% and a drop to less than 50% occurred in 1.9% of patients treated with neoadjuvant trastuzumab and docetaxel as compared to 8.4% of patients treated with neoadjuvant PERJETA in combination with trastuzumab and docetaxel. Symptomatic LVSD occurred in 0.9% of patients treated with neoadjuvant PERJETA in combination with trastuzumab and no patients in the other 3 arms. LVEF recovered to ≥ 50% in all patients.

In patients receiving neoadjuvant PERJETA in Study 3, in the overall treatment period, LVEF decline > 10% and a drop to less than 50% occurred in 6.9% of patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, 16.0% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, and 10.5% of patients treated with PERJETA in combination with TCH. Symptomatic LVSD occurred in 4.0% of patients treated with PERJETA plus trastuzumab and docetaxel following FEC, 1.3% of patients treated with PERJETA in combination with TCH, and none of the patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel. LVEF recovered to ≥ 50% in all but one patient.

PERJETA has not been studied in patients with a pretreatment LVEF value of ≤ 50%, a prior history of CHF, decreases in LVEF to < 50% during prior trastuzumab therapy, or 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 mg/m^2 of doxorubicin or its equivalent.

Assess LVEF prior to initiation of PERJETA and at regular intervals (e.g., every three months in the metastatic setting and every six weeks in the neoadjuvant setting) during treatment to ensure that LVEF is within the institution's normal limits. If LVEF is < 45%, or is 45% to 49% with a 10% or greater absolute decrease below the pretreatment value, withhold PERJETA and trastuzumab and repeat LVEF assessment within approximately 3 weeks. Discontinue PERJETA and trastuzumab if the LVEF has not improved or has declined further, unless the benefits for the individual patient outweigh the risks *[see Dosage and Administration (2.2)]*.

5.2 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. PERJETA is a HER2/neu receptor antagonist. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported with use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy. In an animal reproduction study, administration of pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death at exposures 2.5 to 20 times the exposure in humans at the recommended dose, based on C_{max}.

Verify the pregnancy status of females of reproductive potential prior to the initiation of PERJETA. Advise pregnant women and females of reproductive potential that exposure to PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception can result in fetal harm, including embryo-fetal death or birth defects. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PERJETA in combination with trastuzumab *[see Use in Specific Populations (8.1, 8.3)]*.

5.3 Infusion-Related Reactions

PERJETA has been associated with infusion reactions *[see Adverse Reactions (6.1)]*. An infusion reaction was defined in Study 1 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. The initial dose of PERJETA was given the day before trastuzumab and docetaxel to allow for the examination of PERJETA-associated reactions. On the first day, when only PERJETA was administered, the overall frequency of infusion reactions was 13.0% in the PERJETA-treated group and 9.8% in the placebo-treated group. Less than 1% were Grade 3 or 4. The most common infusion reactions (≥ 1.0%) were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting.

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

In Study 2 and Study 3, PERJETA was administered on the same day as the other study treatment drugs. Infusion reactions were consistent with those observed in Study 1, with a majority of reactions being National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI - CTCAE v3.0) Grade 1 – 2.

Observe patients closely for 60 minutes after the first infusion and for 30 minutes after subsequent infusions of PERJETA. If a significant infusion-related reaction occurs, slow or interrupt the infusion, and administer appropriate medical therapies. Monitor patients carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in patients with severe infusion reactions *[see Dosage and Administration (2.2)]*.

5.4 Hypersensitivity Reactions/Anaphylaxis

In Study 1, the overall frequency of hypersensitivity/anaphylaxis reactions was 10.8% in the PERJETA-treated group and 9.1% in the placebo-treated group. The incidence of Grade 3 – 4 hypersensitivity/anaphylaxis reactions was 2.0% in the PERJETA-treated group and 2.5% in the placebo-treated group according to NCI - CTCAE v3.0. Overall, 4 patients in PERJETA-treated group and 2 patients in the placebo-treated group experienced anaphylaxis.

In Study 2 and Study 3, hypersensitivity/anaphylaxis events were consistent with those observed in Study 1. In Study 2, two patients in the PERJETA- and docetaxel-treated group experienced anaphylaxis. In Study 3, the overall frequency of hypersensitivity/anaphylaxis was highest in the PERJETA plus TCH treated group (13.2%), of which 2.6% were NCI-CTCAE (version 3) Grade 3 – 4.

Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity, including anaphylaxis, has been observed in clinical trials with treatment of PERJETA *[see Clinical Trials Experience (6.1)]*. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients *[see Contraindications (4)]*.

5.5 HER2 Testing

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for PERJETA therapy because these are the only patients studied and for whom benefit has been shown *[see Indications and Usage (1) and Clinical Studies (14)]*. Patients with breast cancer were required to have evidence of HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 in the clinical studies. Only limited data were available for patients

whose breast cancer was positive by FISH, but did not demonstrate protein overexpression by IHC.

Assessment of HER2 status should be performed by laboratories using FDA-approved tests with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of sub-optimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Left Ventricular Dysfunction *[see Warnings and Precautions (5.1)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.2)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions/Anaphylaxis *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Metastatic Breast Cancer (MBC)

The adverse reactions described in Table 1 were identified in 804 patients with HER2-positive metastatic breast cancer treated in Study 1. Patients were randomized to receive either PERJETA in combination with trastuzumab and docetaxel or placebo in combination with trastuzumab and docetaxel. The median duration of study treatment was 18.1 months for patients in the PERJETA-treated group and 11.8 months for patients in the placebo-treated group. No dose adjustment was permitted for PERJETA or trastuzumab. The rates of adverse events resulting in permanent discontinuation of all study therapy were 6.1% for patients in the PERJETA-treated group and 5.3% for patients in the placebo-treated group. Adverse events led to discontinuation of docetaxel alone in 23.6% of patients in the PERJETA-treated group and 23.2% of patients in the placebo-treated group. Table 1 reports the adverse reactions that occurred in at least 10% of patients in the PERJETA-treated group. The safety profile of PERJETA remained unchanged with an additional 2.75 years of follow-up (median total follow-up of 50 months) in Study 1.

The most common adverse reactions (> 30%) seen with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. The most common NCI - CTCAE v3.0 Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia, and fatigue. An increased incidence of 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, the incidence of febrile neutropenia was higher in the pertuzumab-treated group (26%) compared with the placebo-treated group (12%).

242 **Table 1 Summary of Adverse Reactions Occurring in ≥ 10%**
243 **of Patients on the PERJETA Treatment Arm in Study 1**

Body System/ Adverse Reactions	PERJETA + trastuzumab + docetaxel n=407 Frequency rate %		Placebo + trastuzumab + docetaxel n=397 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions				
Fatigue	37.6	2.2	36.8	3.3
Asthenia	26.0	2.5	30.2	1.5
Edema peripheral	23.1	0.5	30.0	0.8
Mucosal inflammation	27.8	1.5	19.9	1.0
Pyrexia	18.7	1.2	17.9	0.5
Skin and subcutaneous tissue disorders				
Alopecia	60.9	0.0	60.5	0.3
Rash	33.7	0.7	24.2	0.8
Nail disorder	22.9	1.2	22.9	0.3
Pruritus	14.0	0.0	10.1	0.0
Dry skin	10.6	0.0	4.3	0.0
Gastrointestinal disorders				
Diarrhea	66.8	7.9	46.3	5.0
Nausea	42.3	1.2	41.6	0.5
Vomiting	24.1	1.5	23.9	1.5
Constipation	15.0	0.0	24.9	1.0
Stomatitis	18.9	0.5	15.4	0.3
Blood and lymphatic system disorders				
Neutropenia	52.8	48.9	49.6	45.8
Anemia	23.1	2.5	18.9	3.5
Leukopenia	18.2	12.3	20.4	14.6
Febrile neutropenia*	13.8	13.0	7.6	7.3
Nervous system disorders				
Neuropathy peripheral	32.4	3.2	33.8	2.0
Headache	20.9	1.2	16.9	0.5

Dysgeusia	18.4	0.0	15.6	0.0
Dizziness	12.5	0.5	12.1	0.0
Musculoskeletal and connective tissue disorders				
Myalgia	22.9	1.0	23.9	0.8
Arthralgia	15.5	0.2	16.1	0.8
Infections and infestations				
Upper respiratory tract infection	16.7	0.7	13.4	0.0
Nasopharyngitis	11.8	0.0	12.8	0.3
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	14.0	1.0	15.6	2.0
Metabolism and nutrition disorders				
Decreased appetite	29.2	1.7	26.4	1.5
Eye disorders				
Lacrimation increased	14.0	0.0	13.9	0.0
Psychiatric disorders				
Insomnia	13.3	0.0	13.4	0.0

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

The following clinically relevant adverse reactions were reported in < 10% of patients in the PERJETA-treated group in Study 1:

Skin and subcutaneous tissue disorders: Paronychia (7.1% in the PERJETA-treated group vs. 3.5% in the placebo-treated group)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (5.2% in the PERJETA-treated group vs. 5.8% in the placebo-treated group)

Cardiac disorders: Left ventricular dysfunction (4.4% in the PERJETA-treated group vs. 8.3% in the placebo-treated group) including symptomatic left ventricular systolic dysfunction (CHF) (1.0% in the PERJETA-treated group vs. 1.8% in the placebo-treated group)

Immune system disorders: Hypersensitivity (10.1% in the PERJETA-treated group vs. 8.6% in placebo-treated group)

Adverse Reactions Reported in Patients Receiving PERJETA and Trastuzumab after Discontinuation of Docetaxel

In Study 1, adverse reactions were reported less frequently after discontinuation of docetaxel treatment. All adverse reactions in the PERJETA and trastuzumab 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%).

Neoadjuvant Treatment of Breast Cancer (Study 2)

In Study 2, the most common adverse reactions seen with PERJETA in combination with trastuzumab and docetaxel administered for 4 cycles were similar to those seen in the PERJETA-treated group in Study 1. The most common adverse reactions (> 30%) were alopecia,

neutropenia, diarrhea, and nausea. The most common NCI – CTCAE v3.0 Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, leukopenia, and diarrhea. In this group, one patient permanently discontinued neoadjuvant treatment due to an adverse event. Table 2 reports the adverse reactions that occurred in patients who received neoadjuvant treatment with PERJETA for breast cancer in Study 2.

Table 2 Summary of Adverse Reactions Occurring in ≥ 10% in the Neoadjuvant Setting for Patients Receiving PERJETA in Study 2

Body System/ Adverse Reactions	Trastuzumab + docetaxel n=107 Frequency rate %		PERJETA + trastuzumab + docetaxel n=107 Frequency rate %		PERJETA + trastuzumab n=108 Frequency rate %		PERJETA + docetaxel n=108 Frequency rate %	
	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %	All Grades %	Grades 3 – 4 %
General disorders and administration site conditions								
Fatigue	27.1	0.0	26.2	0.9	12.0	0.0	25.5	1.1
Asthenia	17.8	0.0	20.6	1.9	2.8	0.0	16.0	2.1
Edema peripheral	10.3	0.0	2.8	0.0	0.9	0.0	5.3	0.0
Mucosal inflammation	21.5	0.0	26.2	1.9	2.8	0.0	25.5	0.0
Pyrexia	10.3	0.0	16.8	0.0	8.3	0.0	8.5	0.0
Skin and subcutaneous tissue disorders								
Alopecia	66.4	0.0	65.4	0.0	2.8	0.0	67.0	0.0
Rash	21.5	1.9	26.2	0.9	11.1	0.0	28.7	1.1
Gastrointestinal disorders								
Diarrhea	33.6	3.7	45.8	5.6	27.8	0.0	54.3	4.3
Nausea	36.4	0.0	39.3	0.0	13.9	0.0	36.2	1.1
Vomiting	12.1	0.0	13.1	0.0	4.6	0.0	16.0	2.1
Stomatitis	7.5	0.0	17.8	0.0	4.6	0.0	9.6	0.0
Blood and lymphatic system disorders								
Neutropenia	63.6	58.9	50.5	44.9	0.9	0.9	64.9	57.4
Leukopenia	21.5	11.2	9.3	4.7	0.0	0.0	13.8	8.5
Nervous system disorders								
Headache	11.2	0.0	11.2	0.0	13.9	0.0	12.8	0.0
Dysgeusia	10.3	0.0	15.0	0.0	4.6	0.0	7.4	0.0
Peripheral Sensory Neuropathy	12.1	0.9	8.4	0.9	1.9	0.0	10.6	0.0

Musculoskeletal and connective tissue disorders								
Myalgia	22.4	0.0	22.4	0.0	9.3	0.0	21.3	0.0
Arthralgia	8.4	0.0	10.3	0.0	4.6	0.0	9.6	0.0
Metabolism and nutrition disorders								
Decreased appetite	6.5	0.0	14.0	0.0	1.9	0.0	14.9	0.0
Psychiatric disorders								
Insomnia	11.2	0.0	8.4	0.0	3.7	0.0	8.5	0.0

The following adverse reactions were reported in < 10% of patients receiving neoadjuvant treatment and occurred more frequently in PERJETA-treated groups in Study 2: (Ptz=pertuzumab; T=trastuzumab; D=docetaxel)

Blood and lymphatic system disorders: Anemia (6.5% in the T+D arm, 2.8% in the Ptz+T+D arm, 4.6% in the Ptz+T arm and 8.5% in the Ptz+D arm), Febrile neutropenia (6.5% in the T+D arm, 8.4% in the Ptz+T+D arm, 0.0% in the Ptz+T arm and 7.4% in the Ptz+D arm)

Immune system disorders: Hypersensitivity (1.9% in the T+D arm, 5.6% in the Ptz+T+D arm, 5.6% in the Ptz+T arm and 5.3% in the Ptz+D arm)

Nervous system disorders: Dizziness (3.7% in the T+D arm, 2.8% in the Ptz+T+D arm, 5.6% in the Ptz+T arm and 3.2% in the Ptz+D arm)

Infections and infestations: Upper respiratory tract infection (2.8% in the T+D arm, 4.7% in the Ptz+T+D arm, 1.9% in the Ptz+T arm and 7.4% in the Ptz+D arm)

Respiratory, thoracic and mediastinal disorders: Dyspnea (3.7% in the T+D arm, 4.7% in the Ptz+T+D arm, 2.8% in the Ptz+T arm and 2.1% in the Ptz+D arm)

Cardiac disorders: Left ventricular dysfunction (0.9% in the T+D arm, 2.8% in the Ptz+T+D arm, 0.0% in the Ptz+T arm, and 1.1% in the Ptz+D arm) including symptomatic left ventricular dysfunction (CHF) (0.9% in the Ptz+T arm and 0.0% in the T+D arm, Ptz+T+D arm, and Ptz+D arm)

Eye disorders: Lacrimation increased (1.9% in the T+D arm, 3.7% in the Ptz+T+D arm, 0.9% in the Ptz+T arm, and 4.3% in the Ptz+D arm)

Neoadjuvant Treatment of Breast Cancer (Study 3)

In Study 3, when PERJETA was administered in combination with trastuzumab and docetaxel for 3 cycles following 3 cycles of FEC, the most common adverse reactions (> 30%) were diarrhea, nausea, alopecia, neutropenia, vomiting, and fatigue. The most common NCI-CTCAE (version 3) Grade 3 – 4 adverse reactions (> 2%) were neutropenia, leukopenia, febrile neutropenia, diarrhea, left ventricular dysfunction, anemia, dyspnea, nausea, and vomiting.

Similarly, when PERJETA was administered in combination with docetaxel, carboplatin, and trastuzumab (TCH) for 6 cycles, the most common adverse reactions (> 30%) were diarrhea, alopecia, neutropenia, nausea, fatigue, vomiting, anemia, and thrombocytopenia. The most common NCI-CTCAE (version 3) Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, anemia, leukopenia, diarrhea, thrombocytopenia, vomiting, fatigue, ALT increased, hypokalemia, and hypersensitivity.

The rates of adverse events resulting in permanent discontinuation of any component of neoadjuvant treatment were 6.7% for patients receiving PERJETA in combination with trastuzumab and docetaxel following FEC and 7.9% for patients receiving PERJETA in combination with TCH. Table 3 reports the adverse reactions that occurred in patients who received neoadjuvant treatment with PERJETA for breast cancer in Study 3.

Table 3 Summary of Adverse Reactions Occurring in ≥ 10% of Patients Receiving Neoadjuvant Treatment with PERJETA in Study 3

Body System/Adverse Reactions	**PERJETA + trastuzumab + FEC followed by PERJETA + trastuzumab + docetaxel n=72 Frequency rate %**		**PERJETA + trastuzumab + docetaxel following FEC n=75 Frequency rate %**		**PERJETA + TCH n=76 Frequency rate %**	
	All Grades %	**Grades 3 – 4 %**	**All Grades %**	**Grades 3 – 4 %**	**All Grades %**	**Grades 3 – 4 %**
General disorders and administration site conditions						
Fatigue	36.1	0.0	36.0	0.0	42.1	3.9
Asthenia	9.7	0.0	14.7	1.3	13.2	1.3
Edema peripheral	11.1	0.0	4.0	0.0	9.2	0.0
Mucosal inflammation	23.6	0.0	20.0	0.0	17.1	1.3
Pyrexia	16.7	0.0	9.3	0.0	15.8	0.0
Skin and subcutaneous tissue disorders						
Alopecia	48.6	0.0	52.0	0.0	55.3	0.0
Rash	19.4	0.0	10.7	0.0	21.1	1.3
Dry skin	5.6	0.0	9.3	0.0	10.5	0.0
Palmar-Plantar Erythrodysaesthesia Syndrome	6.9	0.0	10.7	0.0	7.9	0.0
Gastrointestinal disorders						
Diarrhea	61.1	4.2	61.3	5.3	72.4	11.8
Dyspepsia	25.0	1.4	8	0.0	22.4	0.0
Nausea	52.8	0.0	53.3	2.7	44.7	0.0
Vomiting	40.3	0.0	36.0	2.7	39.5	5.3

Constipation	18.1	0.0	22.7	0.0	15.8	0.0
Stomatitis	13.9	0.0	17.3	0.0	11.8	0.0
Blood and lymphatic system disorders						
Neutropenia	51.4	47.2	46.7	42.7	48.7	46.1
Anemia	19.4	1.4	9.3	4.0	38.2	17.1
Leukopenia	22.2	19.4	16.0	12.0	17.1	11.8
Febrile neutropenia	18.1	18.1	9.3	9.3	17.1	17.1
Thrombocytopenia	6.9	0.0	1.3	0.0	30.3	11.8
Immune system disorders						
Hypersensitivity	9.7	2.8	1.3	0.0	11.8	2.6
Nervous system disorders						
Neuropathy peripheral	5.6	0.0	1.3	0.0	10.5	0.0
Headache	22.2	0.0	14.7	0.0	17.1	0.0
Dysgeusia	11.1	0.0	13.3	0.0	21.1	0.0
Dizziness	8.3	0.0	8.0	1.3	15.8	0.0
Musculoskeletal and connective tissue disorders						
Myalgia	16.7	0.0	10.7	1.3	10.5	0.0
Arthralgia	11.1	0.0	12.0	0.0	6.6	0.0
Respiratory, thoracic, and mediastinal disorders						
Cough	9.7	0.0	5.3	0.0	11.8	0.0
Dyspnea	12.5	0.0	8.0	2.7	10.5	1.3
Epistaxis	11.1	0.0	10.7	0.0	15.8	1.3
Oropharyngeal pain	8.3	0.0	6.7	0.0	11.8	0.0
Metabolism and nutrition disorders						
Decreased appetite	20.8	0.0	10.7	0.0	21.1	0.0
Eye disorders						
Lacrimation increased	12.5	0.0	5.3	0.0	7.9	0.0
Psychiatric disorders						
Insomnia	11.1	0.0	13.3	0.0	21.1	0.0
Investigations						
ALT increased	6.9	0.0	2.7	0.0	10.5	3.9

316 FEC=5-fluorouracil, epirubicin, cyclophosphamide, TCH=docetaxel, carboplatin, trastuzumab

The following selected adverse reactions were reported in < 10% of patients receiving neoadjuvant treatment in Study 3: (Ptz=pertuzumab; T=trastuzumab; D=docetaxel; FEC= fluorouracil, epirubicin, and cyclophosphamide; TCH=docetaxel, carboplatin, and trastuzumab)

Skin and subcutaneous tissue disorders: Nail disorder (9.7% in the Ptz+T+FEC/Ptz+T+D arm, 6.7% in the FEC/Ptz+T+D arm, and 9.2% in the Ptz+TCH arm), Paronychia (0% in the Ptz+T+FEC/Ptz+T+D and 1.3% in both the FEC/Ptz+T+D and Ptz+TCH arms), Pruritis (2.8% in the Ptz+T+FEC/Ptz+T+D arm, 4.0% in the FEC/Ptz+T+D arm, and 3.9% in the Ptz+TCH arm)

Infections and infestations: Upper respiratory tract infection (8.3% in the Ptz+T+FEC/Ptz+T+D arm, 4.0% in the FEC/Ptz+T+D arm, and 2.6% in the Ptz+TCH arm), Nasopharyngitis (6.9% in the Ptz+T+FEC/Ptz+T+D arm, 6.7% in the FEC/Ptz+T+D arm, and 7.9% in the Ptz+TCH arm)

Respiratory, thoracic, and mediastinal disorders: Pleural effusion (1.4% in the Ptz+T+FEC/Ptz+T+D arm and 0% in the FEC/Ptz+T+D and Ptz+TCH arm)

Cardiac disorders: Left ventricular dysfunction (5.6% in the Ptz+T+FEC/PTZ+T+D arm, 4.0% in the FEC/Ptz+T+D arm, and 2.6% in the Ptz+TCH arm) including symptomatic left ventricular systolic dysfunction (CHF) (2.7% in the FEC/Ptz+T+D arm and 0% in the Ptz+T+FEC/Ptz+T+D and Ptz+TCH arms)

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response to PERJETA.

Patients in Study 1 were tested at multiple time-points for antibodies to PERJETA. Approximately 2.8% (11/386) of patients in the PERJETA-treated group and 6.2% (23/372) of patients in the placebo-treated group tested positive for anti-PERJETA antibodies. Of these 34 patients, none experienced anaphylactic/hypersensitivity reactions that were clearly related to the anti-therapeutic antibodies (ATA). The presence of pertuzumab in patient serum at the levels expected at the time of ATA sampling can interfere with the ability of this assay to detect anti-pertuzumab antibodies. In addition, the assay may be detecting antibodies to trastuzumab. As a result, data may not accurately reflect the true incidence of anti-pertuzumab antibody development.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication, and the underlying disease. For these reasons, comparison of the incidence of antibodies to PERJETA with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No drug-drug interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry and Pharmacovigilance Program

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to PERJETA during pregnancy. Encourage women who receive PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception, to enroll in the MotHER

Pregnancy Registry by contacting 1-800-690-6720 or visiting http://www.motherpregnancyregistry.com/.

In addition, there is a pregnancy pharmacovigilance program for PERJETA. If PERJETA is administered during pregnancy, or if a patient becomes pregnant while receiving PERJETA or within 7 months following the last dose of PERJETA in combination with trastuzumab, health care providers and patients should immediately report PERJETA exposure to Genentech at 1-888-835-2555.

Risk Summary

Based on its mechanism of action and findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. There are no available data on the use of PERJETA in pregnant women. However, in post-marketing reports, use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. In an animal reproduction study, administration of pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal deaths at clinically relevant exposures that were 2.5 to 20-fold greater than exposures in humans receiving the recommended dose, based on C_{max} *[see Data]*. Apprise the patient of the potential risks to a fetus. There are clinical considerations if PERJETA in combination with trastuzumab is used during pregnancy or within 7 months prior to conception *[see Clinical Considerations]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Animal Data

Pregnant cynomolgus monkeys were treated on Gestational Day (GD)19 with loading doses of 30 to 150 mg/kg pertuzumab, followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in clinically relevant exposures of 2.5 to 20-fold greater than exposures in humans receiving the recommended dose, based on C_{max}. Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-fetal death between GD25 to GD70. The incidences of embryo-fetal loss were 33, 50, and 85% for dams treated with bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (2.5 to 20-fold greater than the recommended human dose, based on C_{max}). 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. Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

8.2 Lactation

Risk Summary

There is no information regarding the presence of pertuzumab in human milk, the effects on the breastfed infant or the effects on milk production. Published data suggest that human IgG is present in human milk but does not enter the neonatal and infant circulation in substantial amounts. Consider the developmental and health benefits of breast feeding along with the mother's clinical need for PERJETA treatment and any potential adverse effects on the breastfed child from PERJETA or from the underlying maternal condition. This consideration should also take into account the elimination half-life of pertuzumab and the trastuzumab wash out period of 7 months.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of PERJETA.

Contraception

Females

Based on the mechanism of action and animal data, PERJETA can cause embryo-fetal harm when administered during pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PERJETA in combination with trastuzumab *[see Use in Specific Populations (8.1)]*.

8.4 Pediatric Use

The safety and effectiveness of PERJETA have not been established in pediatric patients.

8.5 Geriatric Use

Of 402 patients who received PERJETA in Study 1, 60 patients (15%) were ≥ 65 years of age and 5 patients (1%) were ≥ 75 years of age. No overall differences in efficacy and safety of PERJETA were observed between these patients and younger patients.

Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of pertuzumab between patients < 65 years (n=306) and patients ≥ 65 years (n=175).

8.6 Renal Impairment

Dose adjustments of PERJETA are not needed in patients with mild (creatinine clearance [CLcr] 60 to 90 mL/min) or moderate (CLcr 30 to 60 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min) because of the limited pharmacokinetic data available *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of pertuzumab.

10 OVERDOSAGE

No drug overdoses have been reported with PERJETA to date.

11 DESCRIPTION

Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2). Pertuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture containing the antibiotic, gentamicin. Gentamicin is not detectable in the final product. Pertuzumab has an approximate molecular weight of 148 kDa.

PERJETA is a sterile, clear to slightly opalescent, colorless to pale brown liquid for intravenous infusion. Each single use vial contains 420 mg of pertuzumab at a concentration of 30 mg/mL in 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pertuzumab 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 EGFR, HER3, and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signal pathways, mitogen-activated protein (MAP) kinase, and phosphoinositide 3-kinase (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

While pertuzumab alone inhibited the proliferation of human tumor cells, the combination of pertuzumab and trastuzumab augmented anti-tumor activity in HER2-overexpressing xenograft models.

12.3 Pharmacokinetics

Pertuzumab demonstrated linear pharmacokinetics at a dose range of 2 – 25 mg/kg. Based on a population PK analysis that included 481 patients, the median clearance (CL) of pertuzumab was 0.24 L/day and the median half-life was 18 days. With an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks thereafter, the steady-state concentration of pertuzumab was reached after the first maintenance dose.

The population PK analysis suggested no PK differences based on age, gender, ethnicity (Japanese vs. non-Japanese), or disease status (neoadjuvant versus metastatic setting). Baseline serum albumin level and lean body weight as covariates only exerted a minor influence on PK parameters. Therefore, no dose adjustments based on body weight or baseline albumin level are needed.

No drug-drug interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel in a sub-study of 37 patients in Study 1.

No dedicated renal impairment trial for PERJETA has been conducted. Based on the results of the population pharmacokinetic analysis, pertuzumab exposure in patients with mild (CLcr 60 to 90 mL/min, n=200) and moderate renal impairment (CLcr 30 to 60 mL/min, n=71) were similar to those in patients with normal renal function (CLcr greater than 90 mL/min, n=200). No relationship between CLcr and pertuzumab exposure was observed over the range of observed CLcr (27 to 244 mL/min).

12.6 Cardiac Electrophysiology

The effect of pertuzumab with an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks on QTc interval was evaluated in a subgroup of 20 patients with

HER2-positive breast cancer in Study 1. No large changes in the mean QT interval (i.e., greater than 20 ms) from placebo based on Fridericia correction method were detected in the trial. A small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded because of the limitations of the trial design.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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 months duration in cynomolgus monkeys.

14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer

Study 1 was a multicenter, double-blind, placebo-controlled trial of 808 patients with HER2-positive metastatic breast cancer. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were randomly allocated 1:1 to receive placebo plus trastuzumab and docetaxel or PERJETA plus trastuzumab and docetaxel. Randomization was stratified by prior treatment (prior or no prior adjuvant/neoadjuvant anti-HER2 therapy or chemotherapy) 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 greater than 12 months before trial enrollment.

PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every 3 weeks thereafter. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks thereafter. Patients were treated with PERJETA and trastuzumab until progression of disease, withdrawal of consent, or unacceptable toxicity. Docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for at least 6 cycles. The docetaxel dose 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 administered was 16.2 in the placebo-treated group and 19.9 in the PERJETA-treated group.

The primary endpoint of Study 1 was progression-free survival (PFS) as assessed by an independent review facility (IRF). PFS was 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 tumor assessment. Additional endpoints included overall survival (OS), PFS (investigator-assessed), objective response rate (ORR), and duration of response.

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. Tumor 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 tumors, 45% received prior adjuvant hormonal therapy and 11% received

hormonal therapy for metastatic disease. Eleven percent of patients received prior adjuvant or neoadjuvant trastuzumab.

Study 1 demonstrated a statistically significant improvement in IRF-assessed PFS in the PERJETA-treated group compared with the placebo-treated group [hazard ratio (HR)=0.62 (95% CI: 0.51, 0.75), $p < 0.0001$] and an increase in median PFS of 6.1 months (median PFS of 18.5 months in the PERJETA-treated group vs. 12.4 months in the placebo-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 hormone receptor-negative disease (n=408), the hazard ratio was 0.55 (95% CI: 0.42, 0.72). In the subgroup of patients with hormone receptor-positive disease (n=388), the hazard ratio was 0.72 (95% CI: 0.55, 0.95). 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).

At the time of the final PFS analysis, 165 patients had died, and more deaths had occurred in the placebo-treated group (23.6%) compared with the PERJETA-treated group (17.2%); OS was not mature and interim OS analysis results did not meet the pre-specified stopping boundary for statistical significance. The final analysis of OS (Table 4, Figure 2) was performed when 389 patients had died (221 in the placebo-treated group and 168 in the PERJETA-treated group). A statistically significant OS improvement in favor of the PERJETA-treated group was demonstrated [HR=0.68 (95% CI; 0.56, 0.84), p=0.0002] with an increase in median OS of 15.7 months (median OS of 56.5 months in the PERJETA-treated group vs. 40.8 months in the placebo-treated group). OS results in patient subgroups were consistent with those observed for IRF-assessed PFS with the exception of the subgroup of patients with disease limited to non-visceral metastasis [HR=1.11 (95% CI: 0.66, 1.85)].

Table 4 Summary of Efficacy from Study 1

Parameter	PERJETA + trastuzumab + docetaxel n=402	Placebo + trastuzumab + docetaxel n=406	HR (95% CI)	p-value
Progression-Free Survival (independent review)				
No. of patients with an event	191 (47.5%)	242 (59.6%)	0.62	
Median months	18.5	12.4	(0.51, 0.75)	< 0.0001
Overall Survival* (final analysis)				
No. of patients who died	168 (41.8%)	221 (54.4%)	0.68	
Median months	56.5	40.8	(0.56, 0.84)	0.0002
Objective Response Rate	343	336		

(ORR, independent review)	275 (80.2%)	233 (69.3%)		
No. of patients analyzed	19 (5.5%)	14 (4.2%)		
Objective response (CR + PR)	256 (74.6%)	219 (65.2%)		
Complete response (CR)	20.2	12.5		
Partial Response (PR)				
Median Duration of Response (months)				
Difference in ORR	10.8%			
95% CI	(4.2%, 17.5%)			0.0011

566

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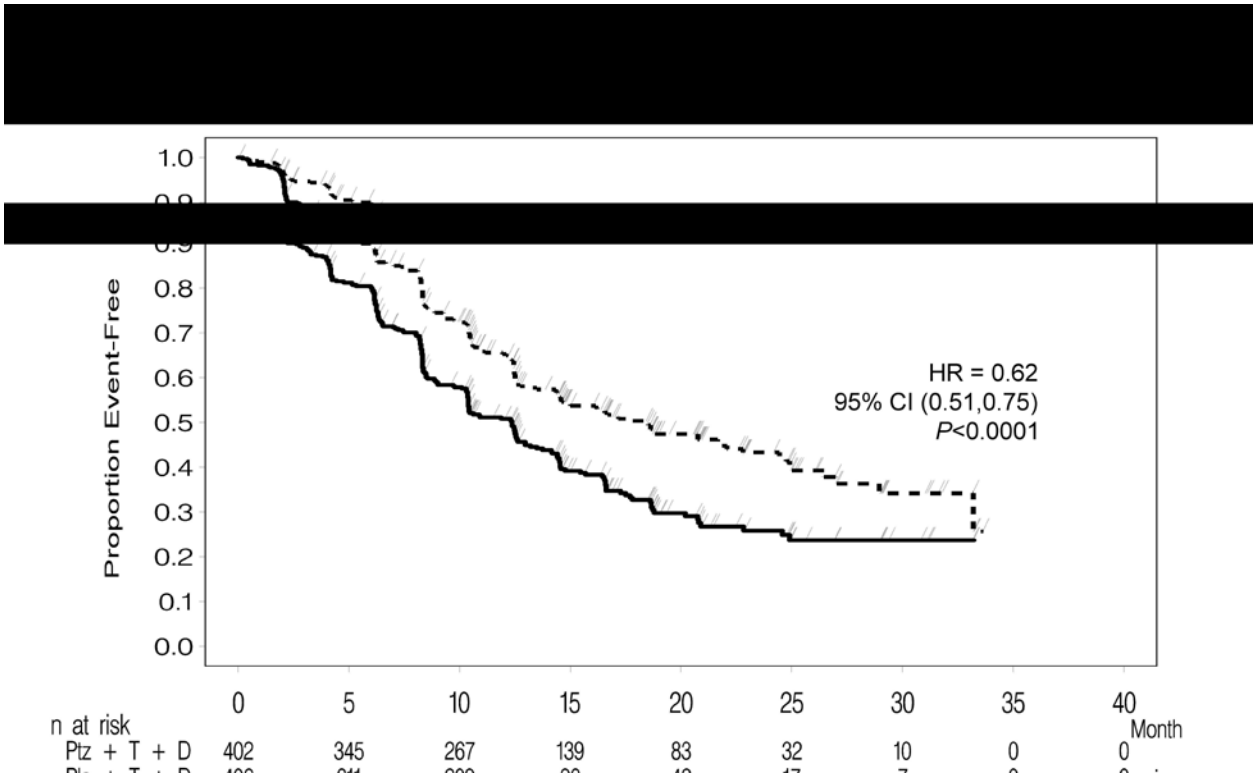
568 * Final analysis of overall survival, cutoff date Feb 2014

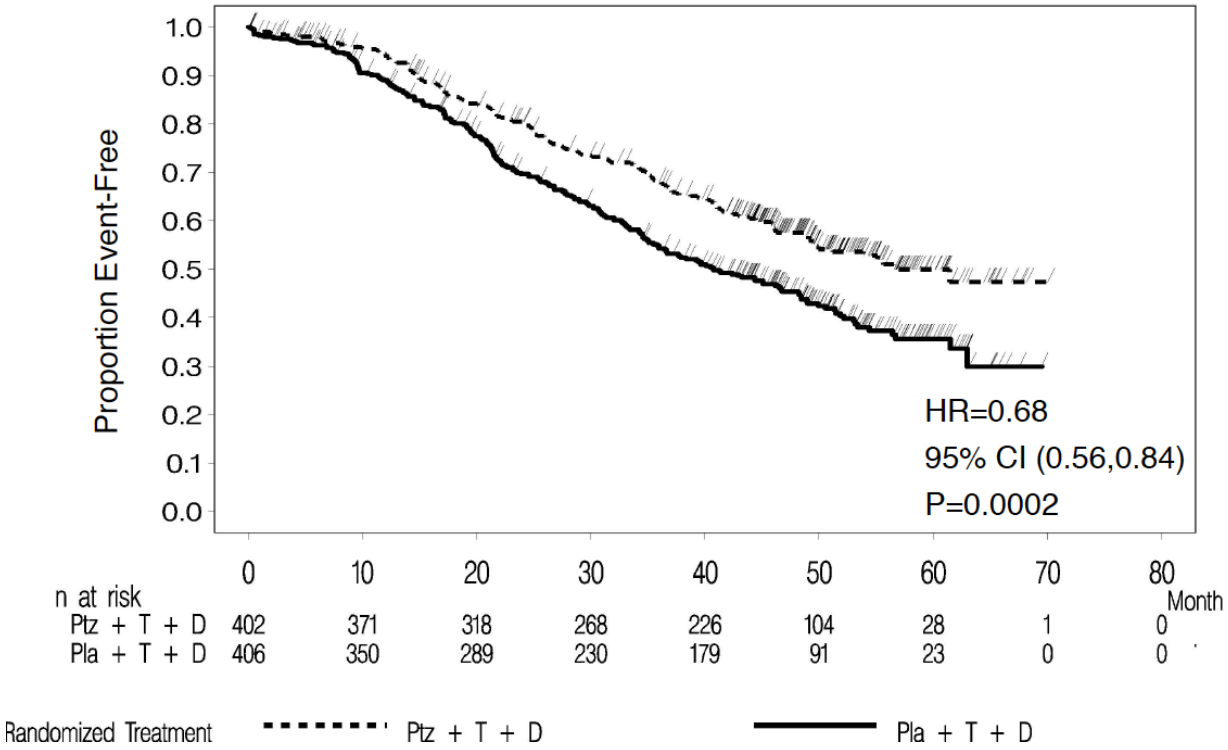
569 CI=Confidence Interval

570 **Figure 1 Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival for Study 1**



571

Figure 2 Kaplan-Meier Curve of Overall Survival for Study 1 (Final Analysis)



14.2 Neoadjuvant Treatment of Breast Cancer

Study 2

Study 2 was a multicenter, randomized trial conducted in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d) who were scheduled for neoadjuvant therapy. HER2 overexpression was defined as a score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory. Patients were randomly allocated to receive 1 of 4 neoadjuvant regimens prior to surgery as follows: trastuzumab plus docetaxel, PERJETA plus trastuzumab and docetaxel, PERJETA plus trastuzumab, or PERJETA plus docetaxel. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen receptor (ER) or progesterone receptor (PgR) positivity.

PERJETA was given intravenously at an initial dose of 840 mg, followed by 420 mg every 3 weeks for 4 cycles. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks for 4 cycles. Docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for 4 cycles. The docetaxel dose could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. Following surgery all patients received 3 cycles of 5-fluorouracil (600 mg/m^2), epirubicin (90 mg/m^2), and cyclophosphamide (600 mg/m^2) (FEC) given intravenously every 3 weeks and trastuzumab administered intravenously every 3 weeks to complete 1 year of therapy. After surgery, patients in the PERJETA plus trastuzumab arm received docetaxel every 3 weeks for 4 cycles prior to FEC.

The primary endpoint of the study was pathological complete response (pCR) rate in the breast (ypT0/is). The FDA-preferred definition of pCR is the absence of invasive cancer in the breast and lymph nodes (ypT0/is ypN0).

Demographics were well balanced (median age was 49 – 50 years old, the majority were Caucasian (71%) and all were female. Overall, 7% of patients had inflammatory cancer, 32% had locally advanced cancer, and 61% had operable cancer. Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as ER-positive and/or PgR-positive).

The efficacy results are summarized in Table 5. Statistically significant improvements in pCR rates by both the study and FDA-preferred definitions were observed in patients receiving PERJETA plus trastuzumab and docetaxel compared to patients receiving trastuzumab plus docetaxel. The pCR rates and magnitude of improvement with PERJETA were lower in the subgroup of patients with hormone receptor-positive tumors compared to patients with hormone receptor-negative tumors.

Table 5 Summary of Efficacy from Study 2

Endpoint/Study Population	**H+T**	**Ptz+H+T**	**Ptz+H**	**Ptz+T**
Overall ITT	**N=107**	**N=107**	**N=107**	**N=96**
pCR[1], n **(%)** **[95% CI][2]**	23 (21.5%) [14.1, 30.5]	42 (39.3%) [30.0, 49.2]	12 (11.2%) [5.9, 18.8]	17 (17.7%) [10.7, 26.8]
p-value (with Simes correction for CMH test)[3]		0.0063 (vs. H+T)	0.0223 (vs. H+T)	0.0018 (vs. Ptz+H+T)
Hormone receptor-positive subgroup	N=50	N=50	N=51[4]	N=46
pCR[1], n **(%)** **[95% CI][2]**	6 (12.0%) [4.5, 24.3]	11 (22.0%) [11.5, 36.0]	1 (2.0%) [0.1, 10.5]	4 (8.7%) [2.4, 20.8]
Hormone receptor-negative subgroup	N=57	N=57	N=55[4]	N=50
pCR[1], n **(%)** **[95% CI][2]**	17 (29.8%) [18.4, 43.4]	31 (54.4%) [40.7, 67.6]	11 (20.0%) [10.4, 33.0]	13 (26.0%) [14.6, 40.3]

T=docetaxel, Ptz=PERJETA, H=trastuzumab

CI=Confidence Interval

[1] ypT0/is ypN0 (absence of invasive cancer in the breast and lymph nodes)

[2] 95% CI for one sample binomial using Pearson-Clopper method.

[3] p-value from Cochran-Mantel-Haenszel (CMH) test, with Simes multiplicity adjustment

[4] One patient had unknown hormone receptor status. The patient did not achieve a pCR.

Study 3

An additional phase 2 neoadjuvant study was conducted in 225 patients with HER2-positive locally advanced, operable, or inflammatory (T2-4d) breast cancer designed primarily to assess cardiac safety in which all arms included PERJETA. HER2 overexpression was defined as a

score of 3+ IHC or FISH amplification ratio of 2.0 or greater as determined by a central laboratory.

Patients were randomly allocated to receive 1 of 3 neoadjuvant regimens prior to surgery as follows: 3 cycles of FEC followed by 3 cycles of docetaxel all in combination with PERJETA and trastuzumab, 3 cycles of FEC alone followed by 3 cycles of docetaxel and trastuzumab in combination with PERJETA, or 6 cycles of docetaxel, carboplatin, and trastuzumab (TCH) in combination with PERJETA. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER and/or PgR positivity.

PERJETA was given by intravenous infusion at an initial dose of 840 mg, followed by 420 mg every 3 weeks. Trastuzumab was given by intravenous infusion at an initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks. 5-Fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (600 mg/m^2) were given intravenously every 3 weeks for 3 cycles. In the PERJETA plus trastuzumab, docetaxel, and FEC arms, docetaxel was given as an initial dose of 75 mg/m^2 by intravenous infusion every 3 weeks for 3 cycles with the option to escalate to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. However, in the PERJETA plus TCH arm, docetaxel was given intravenously at 75 mg/m^2 (no escalation was permitted) and carboplatin (AUC 6) was given intravenously every 3 weeks for 6 cycles. Following surgery all patients received trastuzumab to complete 1 year of therapy, which was administered intravenously every 3 weeks.

Demographics were well balanced (median age was 49-50 years old, the majority were Caucasian (76%)) and all were female. Overall 6% of patients had inflammatory cancer, 25% had locally advanced cancer and 69% had operable cancer, with approximately half the patients in each treatment group having ER-positive and/or PgR-positive disease.

The pCR (ypT0/is ypN0) rates were 56.2% (95% CI: 44.1%, 67.8%), 54.7% (95% CI: 42.7%, 66.2%), and 63.6% (95% CI: 51.9%, 74.3%) for patients treated with PERJETA plus trastuzumab and FEC followed by PERJETA plus trastuzumab and docetaxel, PERJETA plus trastuzumab and docetaxel following FEC, or PERJETA plus TCH, respectively. The pCR rates were lower in the subgroups of patients with hormone receptor-positive tumors: 41.0% (95% CI: 25.6%, 57.9%), 45.7% (95% CI: 28.8%, 63.4%), and 47.5% (95% CI: 31.5%, 63.9%) than with hormone receptor-negative tumors: 73.5% (95% CI: 55.6%, 87.1%), 62.5% (95% CI: 45.8%, 77.3%), and 81.1% (95% CI: 64.8%, 92.0%), respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PERJETA is supplied as a 420 mg/14 mL (30 mg/mL) single-use vial containing preservative-free solution. NDC 50242-145-01.

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use.

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

DO NOT FREEZE. DO NOT SHAKE.

17 PATIENT COUNSELING INFORMATION

Left Ventricular Dysfunction

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness [*see Warnings and Precautions (5.1)*].

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential that exposure to PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.
- Advise women who are exposed to PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception that there is a pregnancy exposure registry and a pregnancy pharmacovigilance program that monitors pregnancy outcomes. Encourage these patients to enroll in the MotHER Pregnancy Registry and report their pregnancy to Genentech *[see Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PERJETA in combination with trastuzumab *[see Use in Specific Populations (8.3)]*.

PERJETA® (pertuzumab)

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No. 1048

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s109

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Oncology Products 1

Application Number: BLA 125409/S-109

Name of Drug/Product: Perjeta® (pertuzumab)

Sponsor: Genentech, Inc.

Material Reviewed

Submission Date: October 23, 2015

Receipt Date: October 23, 2015

Background and Summary

BLA 125409 Perjeta® is a HER2/neu receptor antagonist indicated for use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease and for use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer..

This supplement provides for revisions to update the USE IN SPECIFIC POPULATIONS, Section 8 of the Full Prescribing Information to comply with the new content and format requirements of the Pregnancy and Lactation Labeling Rule (PLLR). Also, where appropriate, the language and content of Section 8 has been aligned with the Herceptin® and Kadcyla® Full Prescribing Information.

This supplement has been reviewed by Laleh Amiri-Kordestani, M.D., Acting Clinical Team Leader; William Pierce, Pharm.D., Associate Director for Labeling/Clinical Reviewer; Todd Palmby, Ph.D., Pharmacology Toxicology Supervisor, DHOT; Kimberly Ringgold, Ph.D., Pharmacologist, DHOT; Christos Mastroyannis, M.D., Reviewer, DPMH; and Tamara Johnson, M.D., Team Leader, DPMH.

Recommendations for Regulatory Action

The attached agreed to labeling should be approved.

_____

Amy Tilley
Regulatory Project Manager

_____
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff

_____
William Pierce, Pharm.D.
Associate Director for Labeling/Clinical Reviewer

_____
Laleh Amiri-Kordestani, M.D.
Acting Clinical Team Leader

Review

Package Insert

The attached labeling is the agreed upon labeling between FDA and Genentech, Inc. and contains the FDA review comments on the proposed labeling.

29 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY R TILLEY
03/15/2016

ALICE KACUBA
03/15/2016

WILLIAM F PIERCE
03/16/2016

LALEH AMIRI KORDESTANI
03/16/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
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Division of Pediatric and Maternal Health Review

Date: March 9, 2016

From: Christos Mastroyannis, M.D.
Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., M.S.
Team Leader, Maternal Health Team (MHT)
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Division Director,
Division of Pediatric and Maternal Health

To: OHOP/DOP1

Drug product: Perjeta (pertuzumab)

BLA: 125409 S-109

Subject: Pregnancy and Lactation Labeling Rule Recommendations

Applicant: Genentech, Inc.

Indications:

- Use in combination with pertuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease
- Use in combination with pertuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast

cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.

Materials Reviewed:

- December 1, 2015, Genentech's response to the Division's information request of November 4, 2015
- November 3, 2015, OHOP/DOP1's request to DPMH-MHT for labeling review
- October 23,2015 last labeling submission
- October 23, 2015, Genentech's Supplement submission S-5109
- April 27, 2015 Applicant's submission for existing PMR/PMC for Herceptin
- DPMH previous reviews in DARRTS dated: 4/25/2014, 9/16/2013, 1/14/2013 and 8/27/2012.

INTRODUCTION

On October 23, 2015, Genentech submitted to Office of Hematology and Oncology Products /Division of Oncology Products 1 (OHOP/DOP1) the labeling supplement BLA 125409 S-109 for Perjeta (pertuzumab). The purpose of this submission is to provide revised labeling to update the USE IN SPECIFIC POPULATIONS section of the Perjeta United States Prescribing Information (USPI) in compliance with the new content and format requirements of the Pregnancy and Lactation Labeling Rule (PLLR). Additionally, where appropriate, language/content of the USE IN SPECIFIC POPULATIONS section has been aligned with that of the Herceptin® (trastuzumab) and Kadcyla® (ado-trastuzumab emtansine) USPIs. An update to the Herceptin USPI per PLLR was submitted on September 3, 2015. An updated Kadcyla USPI was submitted on October 29, 2015.

DOP1 consulted the Division of Pediatric and Maternal Health (DPMH) on November 3, 2015, to review the Pregnancy and Lactation subsections of labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule formatting requirements and to provide comments to be included in the labeling that will be sent to the applicant.

This review provides recommended revisions and structuring of information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with PLLR regulatory requirements.

BACKGROUND

Drug Description

Trastuzumab is a recombinant humanized monoclonal antibody (mAb) that selectively targets the extracellular domain of human epidermal growth factor receptor 2 (HER2), a transmembrane tyrosine kinase receptor.
Trastuzumab is a monoclonal antibody that targets the extracellular domain of the HER2 protein. Pertuzumab is an IgG1 (k) humanized monoclonal antibody (human mouse monoclonal 2C4 heavy chain) with Fc framework identical to trastuzumab. Pertuzumab binds to a different epitope on HER2 and has been shown to complement trastuzumab activity when the two are used in combination with docetaxel.

Pertuzumab 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 EGFR, HER3, and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signal pathways, mitogen-activated protein (MAP) kinase, and phosphoinositide 3-kinase (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

While pertuzumab alone inhibited the proliferation of human tumor cells, the combination of pertuzumab and trastuzumab augmented anti-tumor activity in HER2-overexpressing xenograft models (see current labeling).

The half-life of trastuzumab has been updated to 38 days based on an updated population PK model that included additional trials, and it is expected that would require 7 months for the drug to be cleared from the body as opposed to 6 months. [1,2] Similar studies have not been conducted for pertuzumab. Since both trastuzumab and pertuzumab are mAbs and target the extracellular domain of the HER2 protein, the same half-life update should apply to pertuzumab too, e.g., it requires 7 months for the drug to be cleared from the body.

Disease Epidemiology
Human epidermal growth factor receptor 2 (HER2) gene amplification or protein overexpression occurs in approximately 20% of patients with breast cancer and has been associated with more aggressive disease and poorer clinical outcomes compared with breast cancer patients with normal HER2[3].

Regulatory History
On June 8, 2012, Perjeta was approved for:

- Use in combination with pertuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease
- Use in combination with pertuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.

Perjeta and Pregnancy Registry
The letter of approval for Herceptin (trastuzumab), the first HER2 receptor antagonist approved (in 2006), included a postmarketing requirement (PMR). This PMR required the establishment of a pregnancy registry because exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. The approval letter for pertuzumab issued on June 8, 2012, also required a PMR for a prospective pregnancy registry. The pregnancy registry protocol (MotHER) submitted by the sponsor expanded to include Perjeta and

[1] Clinical Pharmacology review in DARRTS. IND 9900, June 18, 2014
[2] Ceresa, C DPMH Consult Review in DARRTS, March 12, 2015
[3] PSUR submitted by Applicant, November 27, 2015

Kadcyla after their marketing approvals and was reviewed by the PMHS-MHT and Office of Pharmacovigilance and Epidemiology, Division of Epidemiology - I (DEPI) and recommendations were provided to the Applicant.

Pregnancy and Lactation Labeling Rule

On December 4, 2014, the Food and Drug Administration (FDA) published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling", also known as the Pregnancy and Lactation Labeling Rule (PLLR).[4] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential (if applicable). Specifically, the pregnancy categories (A, B, C, D and X) have been removed from all prescription drug and biological product labeling and a new format is required for all drug products that are subject to the 2006 Physician Labeling Rule (PLR),[5] to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR took effect on June 30, 2015.

Existing Label Information of Perjeta on Pregnancy

There is no human data regarding Perjeta use in pregnant women. The effects of Perjeta are likely to be present during all trimesters of pregnancy.

In an animal reproduction study, administration of pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death at exposures 2.5 to 20 times the exposure in humans at the recommended dose. Pertuzumab was found in offsprings at levels of 29% to 40% of maternal serum levels at gestational day 100.[6]

Perjeta and Oligohydramnios

Oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death has been reported after exposure to trastuzumab during pregnancy. To date, there have been no reports of oligohydramnios after exposure to pertuzumab in pregnancy. However, pertuzumab has a similar mechanism of action as trastuzumab and in an embryofetal development study in cynomolgus monkeys there was embryofetal loss, low amniotic fluid volume and evidence of delayed renal development at all doses tested. The reader is referred to the DPMH reviews in DARRTS by C. Mastroyannis[7] and M. Tassinari. [8,9,10] Oligohydramnios and its adverse reactions are stated in the Perjeta labeling.

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[4] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

[5] Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006)

[6] Existing Perjeta labeling

[7] Mastroyannis, Christos: DPMH Consult Review in DARRTS, February 2016

[8] Tassinari, M: PMHS Consult reviews in DARRTS, May 24, 2012,

[9] Tassinari, M, Yao, L PMHS Pregnancy Registry-Protocol Review in DARRTS, August 27, 2012

[10] Tassinari, M, Yao, L PMHS Pregnancy Registry-Protocol Review in DARRTS, January 14, 2013

REVIEW OF DATA

Pregnancy Registry (MotHER study)

As of January 31, 2015, the cut-off point for the latest interim report of the MotHER pregnancy registry, and October 14, 2015, the last database review in response to the Information Request from the Agency of November 4, 2015, cumulatively (over the last 7 years) 15 patients have enrolled (14 Herceptin-exposed and 1 Herceptin plus Perjeta-exposed).

Eleven patients have completed registry follow-up, 3 patients discontinued early (i.e., were lost to follow-up) and 1 patient is ongoing pending the 12-month follow-up visit for the infant. Among the 3 patients who discontinued early, 1 discontinued after 6 months of post-delivery follow-up, 1 discontinued after 2 months of post-delivery follow-up, and 1 discontinued, with pregnancy outcome available but no additional follow-up. The only Perjeta plus Herceptin-exposed patient has completed the registry study (see Table 1). No other clinical information in regards to Perjeta-exposed pregnant patients is available from the MotHER registry.

Reviewer Comment:

There is only one subject who was exposed to Perjeta between June 2012 to June 2015. This subject delivered a normal newborn, . This enrollment rate remains low despite the sponsor's attempt to increase enrollment based on recommendations by DPMH/DEPI I and the DOP1. One possible reason for this low enrollment may be the fact that pregnancy occurs infrequently in women undergoing active treatment for breast cancer. The boxed warning in the labeling may be a contributing factor. This enrollment rate finding is in contrast to pharmacovigilance (PV) reports (32 reports -3 from spontaneous sources and the rest from clinical trials).

Global Postmarketing Information from Company's Safety Database

The applicant has implemented a Global Enhanced Pharmacovigilance (PV) Pregnancy Program which aims to collect additional maternal and fetal/infant information on all reports of women exposed to Perjeta, Herceptin or Kadcyla during pregnancy, or within seven months prior to conception, and are received spontaneously by the Applicant.

Cumulatively[11], since initial marketing of Perjeta, up to and including October 31, 2015, a total of 32 reports (including two twin pregnancies) were retrieved from the Global Safety database under the SMQ "Pregnancy and neonatal topics - wide". They are summarized in Table 2 below. The 32 cases include 1 non-pregnancy-related report of a benign hydatidiform mole from a clinical trial on metastatic breast cancer and 7 pregnancies with an LMP / estimated conception date of > 7 months after the last doses of blinded pertuzumab and trastuzumab, reported from another clinical trial where per protocol, pregnancies have to be reported up to 10 years after discontinuation of study

[11] The event term 'normal newborn' (or 'normal baby') is used when it is known that the baby was born and was reported to be a normal, healthy baby (no birth defects or other disorders). The term 'live born' is used when it is known that the baby was born but it is not known whether the baby was healthy (no birth defects or other disorders). If the event term of 'pregnancy' is reported and it is also reported that there are no adverse effects detected in the fetus and it is a normal pregnancy, then the event term of 'no adverse effect' is added to the case to show that this is a normal pregnancy. This is used only when the pregnancy is ongoing. If follow-up information is received, which reports the pregnancy term has been completed, the outcome is reported as 'normal newborn' (or 'normal baby'), 'live birth' etc., as appropriate. All reported cases of birth defects and abortion were medically reviewed individually in terms of primary reporter type (medically confirmed or consumer cases).

medication. The outcomes of these 7 pregnancies were: Pregnancy ongoing (n=4), Normal birth (n=2), and Premature twin birth (n=1).

Of the remaining 24 cases of pertuzumab-exposed pregnancies, 17 were reported from clinical trials, 1 from the US pregnancy registry MotHER and 6 from spontaneous sources. The outcomes of the 24 pertuzumab exposed pregnancies were: Abortion spontaneous (n=4), induced abortion (n=8), patients who had normal new-born (n=6), patients who had premature births (n=2) (one of which was a premature twin birth), patients still pregnant (n=5), and patients with unknown pregnancy outcome (n=3).

No cases involving pregnancy complications, including oligohydramnios, and no birth defects or fetal abnormalities have been reported to date.

Table 2: Summary of Cumulative Pregnancy Outcomes from Pertuzumab-Exposed Patients

	Prospective Cases					Retrospective Cases				
	Timing of pertuzumab exposure in pregnancy					Timing of pertuzumab exposure in pregnancy				
	1st Trimester	2nd Trimester	3rd Trimester	Within 7 mths Before Conception	>7 mths Before Conception	1st Trimester	2nd Trimester	3rd Trimester	Within 7 mths Before Conception	>7 mths Before Conception
Pregnancy Outcome										
Ectopic pregnancy	0	0	0	0	0	0	0	0	0	0
Spontaneous abortion	3	0	0	0	0	1	0	0	0	0
Therapeutic abortion -	0	0	0	0	0	0	0	0	0	0
Therapeutic abortion - no defects reported	6[a]	0	0	1	0	1	0	0	0	0
Stillbirth – defects	0	0	0	0	0	0	0	0	0	0
Stillbirth - no known	0	0	0	0	0	0	0	0	0	0
Live birth – abnormal	0	0	0	0	0	0	0	0	0	0
Live birth – normal	1[b]	0	0	4	2	0	0	0	1[b]	0
Live birth – premature	1[c]	0	0	1	1[c]	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0	0	0	0	0
Unknown	1[e]	2[f]	0	0	0	0	0	0	0	0
Not reported	0	0	0	0	0	0	0	0	0	0
Ongoing	1	0	0	0	4	0	0	0	0	0
Other	1[d]	0	0	0	0	0	0	0	0	0
Total	**14**	**2**	**0**	**6**	**7**	**2**	**0**	**0**	**1**	**0**

a In one case, the mother was lost to follow-up after the therapeutic abortion

b This includes one case received from H4621g (MotHER) in which the mother was lost to follow-up after the reported outcome of a normal live birth. There was one additional case from MAP-BR-7853 in which insufficient details are available after reported outcome of a live birth. Pertuzumab exposure might have been during lactation (will be queried).

c Premature twin birth

d Benign hydatidiform mole

e Unknown if exposed to pertuzumab

f One might be a duplicate

From Applicant's submission December 1, 2015, Table 1, P 4.

Literature Case Reports
As of June 7, 2015, there was no published literature regarding the use of Perjeta in pregnant or lactating women.

DISCUSSION

A. Perjeta and Lactation

No lactation studies have been conducted to determine whether pertuzumab may be present in human milk, the effects on the breast-fed infant or the effects on milk production. No confirmed cases of exposure during lactation were identified in the applicant's postmarketing safety database or in the published literature. The Drugs and Lactation Database (LactMed)[12] and the Medications & Mother's Milk by Thomas Hale, an expert in lactation, were searched for available lactation data on with the use of Perjeta. No entries were found. Perjeta, being an IgG, is expected as per published literature to be present in human milk but it does not enter the neonatal and infant circulation in substantial amounts.

The current Perjeta labeling states that: "it is not known whether Perjeta is secreted in human milk, but human IgG is excreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from Perjeta, a decision should be made whether to discontinue nursing, or discontinue drug, taking into account the elimination half-life of Perjeta and the importance of the drug to the mother." However, following discussion with DOP1, additional consideration must be given to information known about the drug class. DOP1 has concluded that if there is no data to support the recommendation "advice not to breastfeed", then a statement should be placed about the benefits of breastfeeding and risks from the underlying maternal condition. DPMH agreed that no potential safety concerns have been identified to recommend against use of drug while breastfeeding.

Reviewer Comment:
This reviewer recommends the following breastfeeding benefit-risk statement:

> *The developmental and health benefits of breastfeeding along with the mother's clinical need for Perjeta treatment and any potential adverse effects on the breastfed child from Perjeta or from the underlying maternal condition.*

B. Females and Males of Reproductive Potential

Infertility
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 months duration in cynomolgus monkeys.

[12] United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed)*. http://toxnet nlm.nih.gov/cgi-bin/sis/htmlgen?LACT.
The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding

CONCLUSION
The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling were structured to be consistent with the PLLR. Review of the existing data from different sources revealed no additional information on risks with Perjeta use in pregnant or lactating women except for the already known risk of oligohydramnios and its potential complications in the developing fetus. There is no new information about Perjeta and Females and Males of Reproductive Potential.

DPMH LABELING RECOMMENDATION

DPMH has the following recommendations for Perjeta labeling. The reader is referred to the final NDA action for final labeling.

BOXED WARNING
Embryo-Fetal Toxicity
Embryo-Fetal Toxicity: Exposure to PERJETA during pregnancy can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception. (5.2, 8.1, 8.3)

Full Prescribing Information

HIGHLIGHTS
USE IN SPECIFIC POPULATIONS
- Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of Perjeta.

5 WARNINGS AND PRECAUTIONS
5.2 Embryo-Fetal Toxicity
Perjeta can cause fetal harm when administered to a pregnant woman. PERJETA is a HER2/neu receptor antagonist. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported with use during pregnancy of another HER2/neu receptor antagonist (trastuzumab). In animal reproduction studies, administration of pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis and at exposures 2.5 to 20 times the recommended human dose resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Verify the pregnancy status of females of reproductive potential prior to the initiation of PERJETA. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with PERJETA and for 7 months following the last dose of PERJETA in combination with trastuzumab *[see Use in Specific Populations (8.1, 8.3*

***[DPMH rationale**:*
The language regarding the MotHER pregnancy registry and Genentech Adverse Event line are more appropriately placed in sections 8.1 and 17.]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry and Pharmacovigilance Program

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to PERJETA during pregnancy. Encourage women who receive PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception, to enroll in the MotHER Pregnancy Registry by contacting 1-800-690-6720 or visiting http://www.motherpregnancyregistry.com/.

In addition, there is a pregnancy pharmacovigilance program for PERJETA. If PERJETA is administered during pregnancy, or if a patient becomes pregnant while receiving PERJETA or within 7 months following the last dose of PERJETA in combination with trastuzumab, health care providers and patients should immediately report PERJETA exposure to Genentech at 1-888-835-2555.

Risk Summary

Based on its mechanism of action and findings in animal reproduction studies, PERJETA can cause fetal harm when administered to a pregnant woman. There are no available data on the use of PERJETA in pregnant women. However, in post-marketing reports, use of another HER2 receptor antagonist during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. In animal reproduction studies administration of pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis, resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal deaths at clinically relevant exposures of 2.5 to 20 fold greater than the recommended human dose [*see Data*]. (b) (4)

The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received PERJETA in combination with trastuzumab during or within 7 months of a pregnancy for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care. The efficacy of IV hydration in management of oligohydramnios due to HER2 receptor antagonist exposure is not known.

Data

Animal Data

Reproductive toxicology studies have been conducted in cynomolgus monkeys. Pregnant monkeys were treated on Gestational Day (GD)19 with loading doses of 30 to 150 mg/kg pertuzumab, followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based on C_{max}. Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-fetal death between

GD25 to GD70. The incidences of embryo-fetal loss were 33, 50, and 85% for dams treated with bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (2.5 to 20-fold greater than the recommended human dose, based on C_{max}). 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. Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

8.2 Lactation

Risk Summary

There is no information regarding the presence of pertuzumab in human milk, the effects on the breastfed infant or the effects on milk production. Published data suggest that human IgG is present in human milk, but does not enter the neonatal and infant circulation in substantial amounts. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for PERJETA treatment and any potential adverse effects on the breastfed child from PERJETA or from the underlying maternal condition. This consideration should also take into account the elimination half-life of pertuzumab *[see Clinical Pharmacology (12.3)]*.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of PERJETA.

Contraception

Females

Based on the mechanism of action and animal data, PERJETA can cause embryo-fetal harm when administered during pregnancy. Advise females of reproductive potential to use effective contraception during treatment with PERJETA and for 7 months following the last dose of PERJETA in combination with trastuzumab.

17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity *[see Use in Specific Populations (8.1, 8.3)]*

- Advise pregnant women and females of reproductive potential that exposure to PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy.

- Advise women who are exposed to PERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception that there is a pregnancy exposure registry and a pregnancy pharmacovigilance program that monitors pregnancy outcomes. Encourage these patients to enroll in the MotHER Pregnancy Registry and report their pregnancy to Genentech *[see Use in Specific Populations (8.1)]*.

- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PERJETA in combination with trastuzumab *[see Use in Specific Populations (8.3)]*.

APPEARS THIS WAY ON ORIGINAL

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/s/

CHRISTOS MASTROYANNIS
03/10/2016

TAMARA N JOHNSON
03/10/2016

LYNNE P YAO
03/14/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Labeling Review and Rationale for Changes

Application number:	125409 (S-109)
Supporting document/s:	739, 754, 781
Sponsor's letter date:	October 23, 2015
CDER stamp date:	October 23, 2015
Product:	Pertuzumab (Perjeta)
Indication:	In combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease In combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early breast cancer
Sponsor:	Genentech, Inc. South San Francisco, CA
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology Products 1)
Reviewer:	Tiffany K. Ricks, PhD
Supervisor/Team Leader:	Todd Palmby, PhD
Division Director:	John Leighton, PhD, DABT (DHOT) Geoffrey Kim, MD (DOP1)
Project Manager:	Amy Tilley

Introduction

Perjeta (pertuzumab) is a HER2/neu receptor antagonist indicated for use in combination with trastuzumab and docetaxel for 1) treatment of patients with HER2-positive metastatic breast cancer and 2) neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer. The Applicant submitted a labeling supplement to update the approved package insert to be in compliance with the content and formatting of the Pregnancy and Lactation Labeling Rule (PLLR). Changes were also made to harmonize language and content in the package inserts of two other HER2-directed therapies, Herceptin and Kadcyla, which are also held by the Applicant. The Applicant did not submit new nonclinical data for this labeling supplement. The majority of changes in the label were made to comply with 21 CFR 201 on PLLR content and formatting.

In Section 8.1 Pregnancy, the approved Perjeta label only included data from an animal reproductive and developmental toxicity study, which demonstrated that administration of pertuzumab to pregnant Cynomolgus monkeys during the period of organogenesis caused oligohydramnios, delayed fetal kidney development, and embryo-fetal death. There are no available data on the use of Perjeta in pregnant women; however, use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy resulted in cases of oligohydramnios. Because the risk of oligohydramnios is a class effect of HER2/neu receptor antagonists, the Division recommended adding a new statement in sections 5.2 Embryo-Fetal Toxicity and 8.1 Pregnancy to describe cases of oligohydramnios reported following administration of trastuzumab during pregnancy. In addition, the Boxed Warning clearly informs of the risk of embryo-fetal death and birth defects. The Division recommended removing animal data in the Boxed Warning describing the reproductive and developmental effects in monkeys. The similar mechanisms of action of pertuzumab and trastuzumab and adverse effects in the postmarketing setting in patients treated with trastuzumab during pregnancy were the reasons that embryo-fetal toxicity was included in the Boxed Warning for Perjeta, not the findings in the reproductive and developmental toxicity study in monkeys administered pertuzumab.

In section 8.2 Lactation, the Applicant proposed the following statement in the Risk Summary section, which is in compliance with the PLLR draft guidance: “Consider the developmental and health benefits of breast feeding along with the mother’s clinical need for Perjeta treatment and any potential adverse effects on the breastfed child from Perjeta or from the underlying maternal condition.” The Pharmacology/ Toxicology team agreed that the recommendation was appropriate as published data suggest that human IgG is present in human milk, but does not enter the neonatal and infant circulation in substantial amounts.

Recommendations

The Perjeta labeling supplement is recommended for approval from the Pharmacology/Toxicology perspective.

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/s/

TIFFANY RICKS
03/08/2016

TODD R PALMBY
03/09/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125409Orig1s109

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From:	Tilley, Amy
To:	"ying.ardelle@gene.com"
Bcc:	Amiri Kordestani, Laleh (FDA); Pierce, William (CDER)
Subject:	TIME SENSITIVE BLA 125409-S-109 Perjeta - FDA Revised PI 3-10-16
Date:	Thursday, March 10, 2016 2:18:00 PM
Attachments:	FDA rev PI Perjeta S-109 3-10-16.doc
Importance:	High

Ying,

Please see the attached FDA Revised PI regarding S-109 for Perjeta. We request your response **no later than 9 am, tomorrow Mar 11, 2016.**

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone)● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

25 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

AMY R TILLEY
03/10/2016

From:	Tilley, Amy
To:	"ying.ardelle@gene.com"
Cc:	Miu Chau (chau.miu-fun@gene.com)
Bcc:	Amiri Kordestani, Laleh (FDA)
Subject:	TIME SENSITIVE BLA 125409-S-109 Perjeta - FDA Revised PI
Date:	Friday, March 04, 2016 4:41:14 PM
Attachments:	Perjeta S-109 FDA Revised PI 3-4-16.doc
Importance:	High

Ying,

Please see the attached FDA Revised PI. Please respond via email **by 10:00 am Tuesday, March 8, 2016**, and then follow up with an official submission to the BLA.

Kindly confirm receipt of this email.

Regards.
Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

25 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

AMY R TILLEY
03/07/2016

From: Tilley, Amy
To: "Miu Chau"
Bcc: Pierce, William (CDER)
Subject: RE: TIME SENSITIVE sBLA 125409 S-109 Perjeta - FDA Revised PI
Date: Friday, February 12, 2016 4:42:44 PM
Importance: High

Miu, the 22nd is in 2 weeks not next Tuesday. Please confirm you can respond with your edits on Feb 22nd or propose a new date.

I apologize as I forgot to send the following information in my original email.

A comprehensive, multi-disciplinary, cross-divisional review of the Pregnancy, Lactation, and Reproductive labeling (PLLR) information for Herceptin, Perjeta, and Kadcyla was conducted by the Division of Oncology Products 1 (DOP1). The revised PLLR labeling represents a collaborative effort, and includes best labeling practices, from DOP1, the Division of Pediatric and Maternal Health (DPMH), the Division of Hematology, Oncology, Toxicology (DHOT), and the OND Labeling Development Team (formerly SEALD).

We carefully considered the data supporting the PLLR labeling revisions for each product; and carefully reviewed the PLLR information across all three HER2/neu receptor antagonists for consistency. We believe the resultant PLLR labeling provides effective dissemination of the PLLR risks related to HER2/neu receptor antagonists, while maintaining scientific accuracy, and not being false or misleading. We believe the labeling (and comments in the labeling) adequately describes our review conclusions and key considerations, but can also provide additional clarification on specific issues if required.

Regards.
Amy

From: Miu Chau [mailto:chau.miu-fun@gene.com]
Sent: Friday, February 12, 2016 4:35 PM
To: Tilley, Amy
Subject: Re: TIME SENSITIVE sBLA 125409 S-109 Perjeta - FDA Revised PI

Dear Amy,

Thanks for the draft USPI. We will only be able to get back to you next Tuesday on the response timeline as most of our team is in Switzerland and Monday is a Swiss holiday.

Hope this is ok with you.

Thanks,
Miu

Sent from my iPhone

On Feb 12, 2016, at 11:21 AM, Tilley, Amy <Amy.Tilley@fda.hhs.gov> wrote:

Miu,

Attached is the FDA revised PI regarding sBLA 125409 S-109 Perjeta.

We request your response **no later than 12 Noon on February 22, 2016.**

Kindly confirm receipt of this email.

Regards.
Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

<PERJETA FDA revd label 2-12-16.doc>

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/s/

AMY R TILLEY
02/12/2016

From:	Tilley, Amy
To:	Miu Chau (chau.miu-fun@gene.com)
Bcc:	Pierce, William (CDER); Amiri Kordestani, Laleh (FDA); Kacuba, Alice; Venugopal, Rajesh; Balcazar, Pamela
Subject:	TIME SENSITIVE sBLA 125409 S-109 Perjeta - FDA Revised PI
Date:	Friday, February 12, 2016 2:21:05 PM
Attachments:	PERJETA FDA revd label 2-12-16.doc
Importance:	High

Miu,

Attached is the FDA revised PI regarding sBLA 125409 S-109 Perjeta.

We request your response **no later than 12 Noon on February 22, 2016.**

Kindly confirm receipt of this email.

Regards.
Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
02/12/2016

From:	Tilley, Amy
To:	"Miu Chau"
Bcc:	Mastroyannis, Christos; Johnson, Tamara
Subject:	RE: TIME SENSITIVE re sBLA 125409-109 Perjeta - DPMH IR
Date:	Thursday, November 05, 2015 9:48:29 AM

Miu, you can respond to the IR on Nov 30th. Please email me your response (if possible) and then follow up with an official submission. This allows us to review the information quicker.

Amy

From: Miu Chau [mailto:chau.miu-fun@gene.com]
Sent: Wednesday, November 04, 2015 7:42 PM
To: Tilley, Amy
Subject: Re: TIME SENSITIVE re sBLA 125409-109 Perjeta - DPMH IR

Dear Amy,

Thanks for your email.

After discussion with our team we respectfully request an extension of the submission timeline to Nov 30th, 2015 in order to prepare a thorough response.

Please let me know if our proposal is acceptable to the Agency or not.

Best regards,
Miu

On Wed, Nov 4, 2015 at 7:57 AM, Tilley, Amy <Amy.Tilley@fda.hhs.gov> wrote:
Miu,

On December 4, 2014, the Food and Drug Administration published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR went into effect on June 30, 2015. According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

Together with submission of the proposed labeling for PLLR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).

During our preliminary review of your submitted labeling you did not provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling (if you have, please direct us where to find them). Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made.

Submit the following information both via email and as an official submission to the BLA regarding Perjeta's use in pregnant and lactating women **by November 16, 2015.** If the information below was already submitted to

the BLA please direct us to where it can be located.

- a review and summary of all available published literature regarding Perjeta,
- a review and summary from your pharmacovigilance database,
- interim ongoing or final report on a closed pregnancy registry .
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Regards.
Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/05/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125409/S-109

PRIOR APPROVAL SUPPLEMENT - ACKNOWLEDGEMENT & FILING

Genentech, Inc.
Attention: Miu Chau
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Chau:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

BLA SUPPLEMENT NUMBER: 125409/S-109

PRODUCT NAME: Perjeta® (pertuzumab) liquid single use vial, 20 mL vial contains 420 mg (nominal)

DATE OF SUBMISSION: October 23, 2015

DATE OF RECEIPT: October 23, 2015

This supplemental application proposes the following changes: UPDATES TO THE USE IN SPECIFIC POPULATIONS Section 8 of the Prescribing Information to comply with the new content and format requirements of the Pregnancy and Lactation Labeling Rule. Also, where appropriate, the language and content of Section 8 has been aligned with the Herceptin® and Kadcyla® Prescribing Information.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 23, 2015, in accordance with 21 CFR 601.2(a).

If the application is filed, the goal date will be April 22, 2016.

CONTENT OF LABELING

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

If you have questions, contact me at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Amy R. Tilley
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

AMY R TILLEY
11/04/2015

From:	Tilley_Amy
To:	"miuc@gene.com"
Bcc:	Mastroyannis_Christos; Johnson_Tamara
Subject:	TIME SENSITIVE re sBLA 125409-109 Perjeta - DPMH IR
Date:	Wednesday, November 04, 2015 10:57:22 AM

Miu,

On December 4, 2014, the Food and Drug Administration published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR went into effect on June 30, 2015. According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

Together with submission of the proposed labeling for PLLR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).

During our preliminary review of your submitted labeling you did not provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling (if you have, please direct us where to find them). Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made.

Submit the following information both via email and as an official submission to the BLA regarding Perjeta's use in pregnant and lactating women **by November 16, 2015.** If the information below was already submitted to the BLA please direct us to where it can be located.

- a review and summary of all available published literature regarding Perjeta,
- a review and summary from your pharmacovigilance database,
- interim ongoing or final report on a closed pregnancy registry .
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format
(
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf
). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Regards.

Amy Tilley

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/s/

AMY R TILLEY
11/04/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**DIVISION OF PEDIATRIC AND MATERNAL HEALTH REQUEST FOR CONSULTATION**	
TO: CDER Pediatric and Maternal Health Staff *(please check)* Pediatrics ☐ Maternal Health ☒ Both ☐			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Amy Tilley/OHOP/DOP1/301-796-3994	
DATE November 3, 2015	IND NO.	NDA/BLA NO. sBLA 125409/109 Sequence No. 280 SDN 739	TYPE OF DOCUMENT SLR PAS PLLR	DATE OF DOCUMENT October 23, 2015
NAME OF DRUG Perjeta (pertuzumab)	NAME OF FIRM Genentech		CLASSIFICATION OF DRUG	PDUFA Goal Date 4-22-16
Requested Consult Completion Date: Prior to 1-14-16 label meeting	☐ Urgent* (< 14 days)		☐ Priority (14-29 days)	☒ Routine ≥ 30 days

*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.

REASON FOR REQUEST

Pediatrics:	Maternal Health Team:
☐ Labeling Review ☐ Written Request/PPSR ☐ PREA PMR/General Regulatory Question ☐ SPA ☐ Action Letter Review ☐ 30-day IND Review ☐ Other Protocol Review ☐ Meeting Attendance ☐ PeRC Preparation Assistance ☐ Other (please explain):	☒ Labeling Review ☐ Pregnancy Exposure Registry (protocol or report) ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ 30-day IND Review ☐ Risk Management – Pregnancy Prevention and Planning ☐ Evaluation of possible safety signal ☐ Guidance development ☐ Other (please explain):
Link to electronic submission (if available): EDR Location: \\CDSESUB1\evsprod\BLA125409\125409.enx	Materials to be reviewed: PLLR Conversion with revisions to USE IN SPECIFIC POPULATIONS of the PI.

1. Please briefly describe the submission including drug's indication(s):

The purpose of this submission is to provide revised labeling to update the USE IN SPECIFIC POPULATIONS section of the Perjeta United States Prescribing Information (USPI) in compliance with the new content and format requirements of the Pregnancy and Lactation Labeling Rule. Additionally, where appropriate, language/content of the USE IN SPECIFIC POPULATIONS section has been aligned with that of the Herceptin® (trastuzumab) and Kadcyla® (ado-trastuzumab emtansine) USPIs. An update to the Herceptin USPI per PLLR was submitted on September 3, 2015 (Sequence No. 0169 and SDN 1512). An updated Kadcyla USPI was submitted on October 29, 2015 (Sequence No. 253 and SDN 608).

2. Describe in detail the reason for your consult. Include specific questions:

The DOP1 Perjeta Review Team is requesting the Reviewer as Christos Mastroyannis and Team Leader Tamara Johnson to be assigned to review this PLLR as they also are reviewing both the Herceptin and Kadcyla PLLRs noted above.

The PT Review Team needs to consider consistency with the Herceptin and Kadcyla labels while trying to update the Perjeta PI to comply with PLLR as much as possible. MH please review the Section USE IN SPECIFIC POPULATIONS of the PI and give us your input on formatting and where to place certain information within the Perjeta PI.

3. Meeting dates: January 14, 2016

4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years): Reference ID: 3134509 5/24/12; Reference ID: 3180728 8/27/12; Reference ID: 3244903 1/14/13; Reference ID: 3375070 9/17/13; Reference ID: 3495585 4/25/14

Review Team: Project Manager: Amy Tilley Clinical reviewer & Team Leader: Laleh Amiri Kordestani / Julia Beaver Pharmacology/Toxicology reviewer & Team Leader: Tiffany Ricks / Todd Palmby Clinical Pharmacology reviewer & Team Leader: Other:	
PRINTED NAME or SIGNATURE OF REQUESTOR: Amy Tilley	METHOD OF DELIVERY (Please check) ☒ DARRTS ☒ EMAIL ☐ HAND ☐ OTHER

Version: DARRTS 10/14/2014

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/s/

AMY R TILLEY
11/03/2015