# THE EU RISK MANAGEMENT PLAN FOR PERJETA® / PERTUZUMAB

RMP version to be assessed as part of this application: 14.1

RMP Version number: 14.1

Data lock point for this RMP: 20 December 2023

Date of final sign off: Please see dates in the signature panel below

| Date and Time (UTC) | Reason for Signing | Name |
|---|---|---|
| 30-Jan-2024 08:18:57 | Deputy QPPV | PPD |
| 30-Jan-2024 16:15:56 | Company Signatory (PV) | |

# Table of Contents - Core Report

# List of Tables

# List of Annexes

## Rationale for submitting an updated risk management plan (RMP):

In version 14.1 of the European Union Risk Management Plan (EU-RMP), there is a modification in the commitment timeline for the BO25126 (APHINITY) study. The revised commitment indicates that the submission of the final Clinical Study Report (CSR) should occur within 12 months from the Clinical Cutoff Date (CCOD),.

## Summary of significant changes in this RMP

- Table 1 within Part I (Product Overview) has been updated with the latest Anatomical Therapeutic Chemical (ATC) code for Perjeta.
- Part IV (Plans for Post–Authorization Efficacy Studies) has been updated for BO25126 (APHINITY) study in Table 25 to reflect change in the due date for submission of the final CSR from 2024 to within 12 months from CCOD.
- Table 2 (for Completed studies) within Annex 2 has been updated with date of final study report submission for BERENICE study. The word ‘COMPLETED’ and a footnote against PERUSE study is removed from Table 2 within Annex 2.
- Protocol for Study MO28047 (PERUSE) has been removed from Annex 3.
- Annex 8 was updated to reflect all changes made to the RMP.

## Other RMP versions under evaluation: None

RMP Version number: N/A

Submitted on: N/A

Procedure number: N/A

### Details of Currently Approved RMP

Version number: 14.0

Approved with procedure: EMEA/H/C/002547/II/0059 Date of approval (Commission Decision date): 2 September 2021

See page 1 for signature and date

| | |
|---|---|
| Dr. Birgitt Gellert (QPPV) (Delegate: PPD [Deputy QPPV]) | Date |

See page 1 for signature and date

| | |
|---|---|
| (Clinical Safety Team Leader) | Date |

## PART I: PRODUCT OVERVIEW

| | |
|---|---|
| Active Substance(s)<br>(INN or common name) | Pertuzumab |
| Pharmacotherapeutic group(s) (ATC Code) | L01FD02 |
| Marketing Authorization Holder (or Applicant) | Roche Registration GmbH |
| Medicinal products to which this RMP refers | One |
| Invented name(s) in the European Economic Area (EEA) | Perjeta® |
| Marketing authorization procedure | Centrally authorized procedure |
| Brief description of the product including: | Chemical Class: Anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody. |
| | Summary of mode of action: Perjeta is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), and thereby blocks ligand-dependent heterodimerisation of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, Perjeta inhibits ligand-initiated intracellular signalling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, respectively. In addition, Perjeta mediates antibody-dependent cell-mediated cytotoxicity (ADCC).While Perjeta alone inhibited the proliferation of human tumor cells, the combination of Perjeta and trastuzumab significantly augmented antitumor activity in HER2-overexpressing xenograft models. |
| | Important information about its composition: Pertuzumab is a humanised IgG1 monoclonal antibody produced in mammalian (Chinese |

| | |
|---|---|
| | hamster ovary) cells by recombinant DNA technology. |
| Hyperlink to the Product Information | Product Information |
| Indication(s) in the EEA | Current:<br>**Early breast cancer**<br>Perjeta is indicated for use in combination with trastuzumab and chemotherapy in:<br>• the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence<br>• the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence<br>**Metastatic breast cancer**<br>Perjeta is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. |
| | • Proposed: Not applicable |
| Dosage in the EEA | Current:<br>The recommended initial loading dose of Perjeta is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes.<br>Perjeta and trastuzumab should be administered sequentially and can be given in any order. When administered with Perjeta the recommended initial loading dose of trastuzumab is 8 mg/kg body weight administered as an intravenous infusion followed every 3 weeks thereafter by a maintenance dose of 6 mg/kg body weight.<br>In patients receiving a taxane, Perjeta and trastuzumab should be administered prior to the taxane.<br>When administered with Perjeta the recommended initial dose of docetaxel is |

| | |
|---|---|
| | 75 mg/m$^2$ administered thereafter on a 3 weekly schedule.<br>In patients receiving an anthracycline-based regimen, Perjeta and trastuzumab should be administered following completion of anthracycline (see section 4.4 of the SmPC).<br>**Metastatic Breast Cancer**<br>Perjeta should be administered in combination with trastuzumab and docetaxel until disease progression or unmanageable toxicity. Treatment with Perjeta and trastuzumab may continue even if treatment with docetaxel is discontinued.<br>**Early breast cancer**<br>**Neoadjuvant Treatment of Breast Cancer**<br>In the neoadjuvant setting, Perjeta should be administered for 3 to 6 cycles in combination with trastuzumab and chemotherapy, as part of a complete treatment regimen for early breast cancer (see Section 5.1 of the SmPC).<br>**Adjuvant Treatment of Breast Cancer**<br>In the adjuvant setting, Perjeta should be administered in combination with trastuzumab for a total of one year (up to 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first) as part of a complete regimen for early breast cancer and regardless of the timing of surgery. Treatment should include standard anthracycline- and/or taxane-based chemotherapy. Perjeta and trastuzumab should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued. |
| | Proposed: Not applicable |
| Pharmaceutical form(s) and strengths | Current:<br>Concentrate solution for infusion.<br>One 14 ml vial of concentrate contains 420 mg of pertuzumab at a concentration of 30 mg/ml. |
| | Proposed: Not applicable |
| Is or will the product be subject to additional monitoring in the EU? | No |

EEA=European economic area; EU=European Union; HER2=Human epidermal growth factor receptor 2; SmPC=Summary of Product Characteristics.

# GLOSSARY OF ABBREVIATIONS

| Abbreviations | Definition |
|---|---|
| AEGT | Adverse Event Grouped Term |
| AEs | Adverse events |
| ADAs | anti-drug antibodies |
| ALK | Alkaline phosphatase |
| ATAs | anti-therapeutic antibodies |
| CBR | clinical benefit rate |
| CHF | Congestive heart failure |
| CHMP | Final Committee of Medicinal Products for Human Use |
| CSR | Clinical Study Report |
| CVD | Cerebrovascular disease |
| EBC | Early breast cancer |
| EU-RMP | European Union Risk Management Plan |
| FEC | 5 fluorouracil, epirubicin and cyclophosphamide |
| GD | gestation day |
| H | trastuzumab (Herceptin) |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HER | Human epidermal growth factor receptor |
| HIV | Human immunodeficiency virus |
| IHD | ischemic heart disease |
| IRF-PFS | independent review facility-assessed progression-free survival |
| IRR | infusion-related reactions |
| ITT | intent-to-treat |
| IV | intravenous |
| LVD | left ventricular dysfunction |
| LVEF | left ventricular ejection fraction |
| LVSD | left ventricular systolic dysfunction |
| MBC | Metastatic breast cancer |
| NYHA | New York Heart Association |
| ORR | overall response rate |
| OS | overall survival |
| PFS | Progression-free survival |
| Pla | Placebo |
| Pla+H+D | Placebo + trastuzumab + docetaxel |

| Abbreviations | Definition |
|---|---|
| Ptz+H+D | pertuzumab + trastuzumab + docetaxel |
| PK | Pharmacokinetics |
| PSUR | Periodic Safety Update Report |
| PT | Preferred Term |
| Ptz | Pertuzumab |
| RMP | Risk Management Plan |
| RSI | Reference Safety Information |
| SAEs | Serious adverse events |
| SEER | Surveillance Epidemiology and End Results |
| SmPC | Summary of Product Characteristics |
| SMQ | Standard MedDRA Query |
| TEE | thromboembolic events |

# PART II: SAFETY SPECIFICATION

# PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

## SI.1 METASTATIC BREAST CANCER

### Incidence

The epidemiologic evidence specific to the human epidermal growth receptor 2 (HER2)-positive metastatic breast cancer (MBC) patient population is limited; we therefore present data from the general breast cancer population to supplement our findings.

Breast cancer was the second most commonly diagnosed cancer in the world and the most commonly diagnosed cancer among women with 2.09 million new cases and approximately 630,000 deaths in 2018 (IARC Breast Cancer 2018). In the more developed nations, it is the second most common cause of cancer death. This is a disease affecting 10 – 12% of women (Benson 2009). In 2018, it was estimated that there were 522,513 new cases of breast cancer in Europe, which represents 26% of all reported cases of cancer in women. (IARC Breast Cancer 2018. Since HER2-positive disease accounts for approximately 15% – 20% of cases of breast cancer (Wolff et al, 2007; Chia et al, 2008, Ross et al, 2009). It is estimated that approximately 264,000 new cases of HER2-positive breast cancer occur each year globally and 92,620 cases in the EU. Of these, around 94 – 95% would be non-metastatic at diagnosis and therefore potentially eligible for adjuvant or neoadjuvant treatment.

Depending on stage, tumor biology and the treatments utilized, between 20% and 85% of women with early breast cancer (EBC) develop distant metastases. The overall incidence of MBC (i.e., including patients initially presenting with early disease who subsequently relapse) is probably best indicated by annual mortality rates (refer to the mortality section below) since most patients who die from breast cancer die from metastatic disease.

There is limited data on the secular trends associated with the incidence of HER2-positive breast cancer. Köninki et al, 2009 reported the results from three cohorts (years 1982 to 1986 [n = 310], 1989 to 1992 [n = 108], and 2004 to 2005 [n = 713]) to estimate time trends of HER2-positive breast cancer: the age-adjusted incidence of HER2-positive breast cancer increased only slightly from 1982 to 2005 (12.2 per 100,000 to 13.0 per 100,000, respectively), whereas the incidence of HER2-negative breast cancer doubled over the same period (44.1 per 100,000 to 82.3 per 100,000, respectively). Numbers for incidence of HER2 positive breast cancer may vary as other factors like demographic parameters, histology/type of breast cancer and/or HER2 testing quality have an impact on positivity rates (Ruschoff et al, 2017; Wolff et al, 2007).

## Prevalence

In 2008, the 5-year limited duration prevalence (i.e., breast cancer cases diagnosed between 2004 and 2008 who were still alive at the end of 2008) in the EU-27 was estimated to be 1,329,950 (Bray et al, 2013). To our knowledge, there have been no epidemiologic studies reporting on the prevalence of HER2-positive MBC. However, based on the prevalence of breast cancer in general, the 5-year limited duration prevalence of HER2-positive v is estimated to be 266,000 (or ~20% of all breast cancer cases) in the EU-27. It was suggested that improvements in treatment and aging of the population could lead to increased prevalence of MBC (Mariotto et al, 2017).

## Demographics:

The incidence rate of BC rises rapidly between 35 and 39 years of age and then levels off to a plateau after 80 years of age (Benson et al. 2009, Smigal et al. 2006). From US Surveillance Epidemiology and End Results (SEER) data 2005-2009, the median age at diagnosis for cancer of the breast was 61 years. HER2-positive BC tends to occur in the mid-50s (around 5 years younger than the general BC population (Neven et al. 2008, Kwan et al. 2009). Among patients newly diagnosed with BC, 28% of those aged 20-29 years were HER2-positive, while only about 10% of those aged >75 years were HER2-positive (Clarke et al. 2012).

The average age of diagnosis of breast cancer for men is 67 years, which is 5 – 10 years later than the average age of diagnosis for women. Estimation of HER2-positive breast cancer in men varies in the literature and may be as high as 5% – 56% (Onami et al, 2010; Barh 2009). Racial differences in the incidence of different breast cancer sub-types have been described (Kwan et al, 2009), notably for triple-negative breast cancer, but no particular racial differences have been described for HER2-positive disease.

## The main existing treatment options:

The treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and systemic treatment of disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy, including HER2-targeted therapies, or combinations of these.

## Risk factors for the disease:

Major risk factors for developing breast cancer (of all types) include age, sex and biomarker status (Hennigs et al, 2016; Ngyugen et al, 2008). It was reported that the number of involved lymph nodes at the time of breast cancer diagnosis are significant risk factors for distant metastases. The incidence rate rises rapidly after around 35 years of age, the increase slows around 50 years and then levels off to a plateau after 80 years of age (Benson et al 2009; Smigal et al 2006). HER2-positive breast cancer tends to occur in the mid-50s (around 5 years younger than the general breast cancer population (Neven et al, 2008; Kwan et al, 2009). Breast cancer is rare in men, accounting for less than 1% of all malignancies in men (Fentiman et al, 2006).

## Natural history of the indicated condition in the untreated population:

*Mortality:* Approximately 630,000 deaths due to breast cancer were recorded worldwide in 2018. Of these, 46,000 deaths in North America. and 138,000 deaths in the EU due to breast cancer were reported (IARC Breast Cancer 2018). According to Surveillance Epidemiology and End Results (SEER) database, from 2010 to 2014, the age-adjusted mortality due to breast cancer was reported to be 21.2 per 100,000 women per year (SEER website). According to an analysis of the SEER data (n = 1800), stage IV breast cancer is associated with a 27-fold increase in mortality compared to stage I disease (Yancik et al, 2001).

*Discussion of the possible stages of disease progression to be treated:* Most breast cancers in the Western world (around 94% – 95% of patients in the U.S. and Europe) are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread (Howlader et al, 2016; Sant et al, 2003) i.e. only around 5% – 6% of new cases are metastatic at diagnosis. Hence, around 94 – 95% would be non-metastatic at diagnosis and therefore potentially eligible for adjuvant or neoadjuvant treatment.

*Outcome of the (untreated) target disease*: MBC is almost always fatal. Five-year relative survival for newly diagnosed patients with distant disease is 24%, as compared to 99% for localized patients (Howlader et al, 2016). Depending on stage, tumor biology and the treatments utilized, between 20% and 85% of women with EBC develop distant metastases.

## Important co-morbidities:

Diabetes, Obesity, Thromboembolic events (TEE), Cerebrovascular disease (CVD), Congestive Heart failure (CHF), Ischemic heart disease (IHD), Hypertension.

## SI.2 EARLY BREAST CANCER

- Incidence:

The epidemiologic evidence has been limited in the HER2-positive EBC patient population; therefore the data is presented from the general breast cancer population to supplement our findings. Refer to Section SI.1 for information regarding the incidence of overall BC and HER2-positive disease.

As mentioned in Section SI.1, most breast cancers in the Western world (around 94% – 95% of patients in the U.S. and Europe) are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread (Howlader et al, 2016; Sant et al, 2003) (i.e., EBC at diagnosis).

The age adjusted incidence rate of EBC among white women in the U.S. aged ≥ 20 years, from 2005 to 2009, was reported to be 163.2 per 100,000 person-years, while among non-white women, it was reported to be 56.6 per 100,000 person-

years (Crabbe et al, 2015).The incidence of diagnosis of EBC increases with advanced age (De Glas et al, 2014).

- Prevalence:

The prevalence of HER-2 positive breast cancers in 12 population-based SEER registries was estimated at 19% (95% confidence interval [CI]: 13; 25%) of women aged 49 years or younger and 15% (95%CI: 9; 21%) of women aged 50 years or older with early stage breast cancer. The overall prevalence estimate for the SEER population was 16% (95%CI: 12; 21%) for stage I, II, and IIIa breast cancer among women diagnosed in the year 2005 (Cronin et al, 2010).

- Demographics:

The demographic profile of EBC is similar to that in MBC (refer to Section SI.1), although patients tend to be a few years younger. The incidence of breast cancer increases with age, and is higher in females than males and in Caucasians compared with other racial groups (Howlader et al, 2010; Anderson WF et al, 2009; Crabbe et al, 2015; Iqbal et al, 2015).

- The main existing treatment options:

The treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and systemic treatment of disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy, including HER2-targeted therapies, or combinations of these. Data from recent observational studies using very large, prospectively collected, population-based studies suggested a detrimental impact for delayed time to surgery (Bleicher et al, 2015), or delayed initiation of adjuvant chemotherapy (Chavez-MacGregor et al, 2016).

- Risk factors for the disease:

Major risk factors for developing breast cancer are described in Section SI.1.

*Mortality:* Mortality from breast cancer is typically due to metastatic disease. According to the SEER database, the mortality among patients with EBC due to breast cancer, from 2004 to 2012, was found to be 1.9% (3889/206,625) (Iqbal et al, 2017). Based on SEER data (2010), approximately 57% of deaths from breast cancer occur in those aged $>$65 years, and the median age at death from breast cancer is 68 years. Stage 4 breast cancer is associated with a 27-fold increase in mortality compared to stage I disease (Yancik et al, 2001).

- *Outcome of the (untreated) target disease*: Based on a review of 107 published studies, Ross et al, 2009 reported that the relative risk for adverse clinical outcome of untreated HER2-positive breast cancer is 2.74 (range, 1.39 – 6.93). It is estimated that up to 1 in 4 patients will experience recurrence within 10 – 11 years of diagnosis (Slamon et al, 2015; Cameron et al, 2017; Perez et al, 2014).

- Important co-morbidities:
- Important co-morbidities for EBC are similar to those for MBC and are described in Section SI.1.

# PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

## SII.1 GENERAL SAFETY PHARMACOLOGY

### SII.1.1 GENERAL FINDINGS

**Relevance to human usage**: Yes

**Discussion**: The pharmacokinetics (PK) of pertuzumab were consistent with trastuzumab and other IgG1 monoclonal antibodies that share the same Fc region as characterized by a distribution phase of less than 1 day, a terminal half-life of approximately 10 days, and volume of distribution of the central compartment of 30 to 50 mL/kg approximating the serum volume.

### SII.1.2 DOSE ESCALATION

**Relevance to human usage**: Yes

**Discussion**:

In cynomolgus monkeys, weekly intravenous (IV) administration of pertuzumab at doses up to 150 mg/kg/dose were generally well tolerated. With doses of 15 mg/kg and higher intermittent mild treatment-associated diarrhea was noted. In a subset of monkeys chronic dosing (7 to 26 weekly doses) resulted in episodes of diarrhea-related dehydration which were managed with IV fluid replacement therapy. Diarrhea was observed in clinical trials.

### SII.1.3 MECHANISMS FOR DRUG INTERACTIONS

**Relevance to human usage**: Yes

**Discussion**:

No PK interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel in a sub-study of 37 patients in the randomized, pivotal trial CLEOPATRA in MBC. In addition, no evidence of drug-drug interactions has been shown between pertuzumab and trastuzumab or between pertuzumab and docetaxel, paclitaxel, gemcitabine, capecitabine, carboplatin, or erlotinib. The absence of drug-drug interactions was confirmed by PK data from the NEOSPHERE trial in the neoadjuvant setting and by PK data from the APHINITY trial in the adjuvant setting.

## SII.2 TOXICITY

### SII.2.1 DEVELOPMENT TOXICITY

Placental transfer of pertuzumab was confirmed in cynomolgus monkeys. Systemic maternal and fetal exposure at clinically relevant pertuzumab concentrations was confirmed. Fetal to maternal pertuzumab serum concentration ratios were similar across a 10-fold range of doses at clinically relevant concentrations (20-fold greater than human clinical dose). Pertuzumab-related embryo-fetal lethality, oligohydramnios, and microscopic evidence of delayed renal development occurred in a study when pertuzumab was administered intravenously from Gestation Day 19 (GD19) through GD50 to pregnant cynomolgus monkeys, the period of organogenesis in this species (GD20–50). In addition, consistent with fetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 30 mg/kg and 1 of 2 100 mg/kg), ventricular septal defects (1 of 6 30 mg/kg), thin ventricular wall 1 of 2 100 mg/kg) and minor skeletal defects (external - 3 of 6 30 mg/kg) were also noted.

**Relevance to human usage**: Yes

**Discussion**:

No clinical studies have been performed in pregnant women.

Women of childbearing potential and female partners of male patients of childbearing potential should use effective contraception while receiving pertuzumab and for 6 months following the last dose of pertuzumab (7 months after the last dose of trastuzumab, which is generally given concurrently with pertuzumab in clinical studies and routine practice).

### SII.2.2 CARCINOGENICITY

**Relevance to human usage**: Yes

**Discussion**:

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of pertuzumab. In accordance with ICH guidance S6(R1) carcinogenicity tests are not required for the safety evaluation of monoclonal antibodies or recombinant human proteins such as pertuzumab.

### SII.2.3 MUTAGENICITY

**Relevance to human usage**: Yes

**Discussion**:

Studies have not been performed to evaluate the mutagenic potential of pertuzumab. In accordance with ICH guidance S6(R1) standard mutagenicity tests are not required for

the safety evaluation of monoclonal antibodies or recombinant human proteins such pertuzumab.

### SII.2.4 OTHER TOXICITY-RELATED INFORMATION OR DATA

**Relevance to human usage**: Yes

**Discussion**:

Since Perjeta is a biological medicine, general pharmacology, nephrotoxicity and hepatotoxicity were not studied.

## PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Clinical trial exposure data are presented below for each indication by duration of exposure, age group, dose and racial origin in Table 1 to Table 9.

The clinical safety data presented are derived primarily from the following trials:

- **MBC indication:** The pivotal, randomized, double-blind, placebo-controlled Phase III MBC study, WO20698/TOC4129g (CLEOPATRA), an exploratory Phase II study, BO17929 and Phase III MO28047 (PERUSE).
- **EBC indications:** Three neoadjuvant treatment studies, WO20697 (NEOSPHERE, the pivotal, randomized, Phase II neoadjuvant study), BO22280 (TRYPHAENA) and WO29217 (BERENICE); and the pivotal, randomized, double-blind, placebo-controlled Phase III adjuvant study, BO25126 (APHINITY).

# Table 1 Duration of Exposure to Perjeta in the PERUSE study

Duration of Exposure to Perjeta in the PERUSE study

| | Pertuzumab + Trastuzumab + Chemotherapy (N=1435) |
|---|---|
| **Total Patient cycles of Pertuzumab exposure** | |
| n | 1435 |
| Mean (SD) | 37.6 (33.6) |
| Median | 24.0 |
| Range | 1, 126 |
| **Duration of Exposure** | |
| n | 1435 |
| <= 1 months | 40 ( 2.8%) |
| > 1 - <= 3 months | 62 ( 4.3%) |
| > 3 - <= 6 months | 161 (11.2%) |
| > 6 - <= 12 months | 319 (22.2%) |
| > 12 - <= 24 months | 292 (20.3%) |
| > 24 months | 561 (39.1%) |
| **Patient exposure duration (months per patient)** | |
| n | 1435 |
| Mean (SD) | 26.3 (23.9) |
| Median | 16.2 |
| Range | 0, 86 |

Months = (days/365.25)x12

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dur_per.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dur_per_SE.out
24JUN2020 10:25

## Table 2 **Duration of Exposure to Perjeta by Indication**

Duration of Exposure to Perjeta by Indication

| | EBC (N=3282) | MBC (N=1983) | Total (N=5265) |
|---|---|---|---|
| Total Patient cycles of Pertuzumab exposure | | | |
| Mean (SD) | 14.4 (5.7) | 34.8 (31.6) | 22.1 (22.2) |
| Median | 17.0 | 22.0 | 18.0 |
| Range | 1, 22 | 1, 140 | 1, 140 |
| Duration of Exposure | | | |
| n | 3282 | 1983 | 5265 |
| <= 1 months | 110 ( 3.4%) | 77 ( 3.9%) | 187 ( 3.6%) |
| > 1 - <= 3 months | 428 (13.0%) | 109 ( 5.5%) | 537 (10.2%) |
| > 3 - <= 6 months | 210 ( 6.4%) | 228 (11.5%) | 438 ( 8.3%) |
| > 6 - <= 12 months | 2178 (66.4%) | 420 (21.2%) | 2598 (49.3%) |
| > 12 - <= 24 months | 356 (10.8%) | 438 (22.1%) | 794 (15.1%) |
| > 24 months | 0 | 711 (35.9%) | 711 (13.5%) |
| Patient exposure duration (months per patient) | | | |
| Mean (SD) | 9.6 (4.1) | 24.2 (22.6) | 15.1 (15.9) |
| Median | 11.7 | 15.2 | 11.7 |
| Range | 0, 17 | 0, 98 | 0, 98 |

Months = (days/365.25)x12

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dur.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dur_AP.out
24JUN2020 10:33

## Table 3 Exposure to Perjeta by Dose and Indication

Exposure to Perjeta by Dose and Indication

| | EBC (N=3282) | MBC (N=1983) | Total (N=5265) |
|---|---|---|---|
| Total pertuzumab exposure (mg) | | | |
| Mean (SD) | 6516.9 (2429.53) | 15083.5 (13324.51) | 9743.4 (9368.05) |
| Median | 7980.0 | 9660.0 | 7980.0 |
| Range | 300, 9660 | 420, 59640 | 300, 59640 |
| Number of Patients Receiving Planned Dose Level | n (%) Person months | n (%) Person months | n (%) Person months |
| 420mg (840mg loading dose) | 3282(100.0)[33711.8] | 1983(100.0)[49390.3] | 5265(100.0)[83102.1] |

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25 )*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dose.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dose_AP.out
24JUN2020 10:48 Page 1 of 1

## Table 4 Exposure to Perjeta by Dose and Age-Group: Metastatic Breast Cancer

Exposure to Perjeta by Dose and Age-Group: Metastatic Breast Cancer

| | Age 18-39 (N=252) | Age 40-64 (N=1354) | Age 65-74 (N=293) | Age >=75 (N=84) |
|---|---|---|---|---|
| Total pertuzumab exposure (mg) | | | | |
| Mean (SD) | 15347.7 (13616.21) | 15650.1 (13507.18) | 12928.0 (12186.68) | 12675.4 (12437.78) |
| Median | 10080.0 | 10500.0 | 7980.0 | 6930.0 |
| Range | 840, 51249 | 420, 53340 | 420, 59640 | 840, 48774 |
| Number of Patients Receiving Planned Dose Level | n (%) Person months | n (%) Person months | n (%) Person months | n (%) Person months |
| 420mg (840mg loading dose) | 252(100.0)[6360.1] | 1354(100.0)[35015.7] | 293(100.0)[6251.6] | 84(100.0)[1762.9] |

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25 )*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dose.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dose_AGEGRP_MBC_AP.out
24JUN2020 10:54 Page 1 of 1

## Table 5 Exposure to Perjeta by Dose and Age-Group: Early Breast Cancer

| | Age 18-39 (N=495) | Age 40-64 (N=2394) | Age 65-74 (N=352) | Age >=75 (N=41) |
|---|---|---|---|---|
| Total pertuzumab exposure (mg) | | | | |
| Mean (SD) | 6590.2 (2367.69) | 6544.2 (2414.54) | 6430.1 (2481.56) | 4781.9 (2974.56) |
| Median | 7980.0 | 7980.0 | 7980.0 | 3780.0 |
| Range | 420, 8400 | 300, 9660 | 420, 8400 | 420, 7980 |
| Number of Patients Receiving Planned Dose Level | n (%) Person months | n (%) Person months | n (%) Person months | n (%) Person months |
| 420mg (840mg loading dose) | 495(100.0)[5154.4] | 2394(100.0)[24668.7] | 352(100.0)[3580.3] | 41(100.0)[308.4] |

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25 )*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: /opt/BIOSTAT/prod/cd11450w/t_ex_dose.sas / Output: /opt/BIOSTAT/prod/cd11450w/reports/t_ex_dose_AGEGRP_EBC_AP.out
03MAY2017 12:04 Page 1 of 1

## Table 6 Exposure to Perjeta by Dose and Age-Group: Metastatic and Early Breast cancer

Exposure to Perjeta by Dose and Age-Group: Metastatic and Early Breast cancer

| | Age 18-39 (N=747) | Age 40-64 (N=3748) | Age 65-74 (N=645) | Age >=75 (N=125) |
|---|---|---|---|---|
| Total pertuzumab exposure (mg) | | | | |
| Mean (SD) | 9544.5 (9124.69) | 9833.8 (9420.19) | 9381.8 (9009.96) | 10086.3 (10965.71) |
| Median | 7980.0 | 7980.0 | 7980.0 | 6720.0 |
| Range | 420, 51249 | 300, 53340 | 420, 59640 | 420, 48774 |
| Number of Patients Receiving Planned Dose Level | n (%) Person months | n (%) Person months | n (%) Person months | n (%) Person months |
| 420mg (840mg loading dose) | 747(100.0) [11514.5] | 3748(100.0) [59684.4] | 645(100.0) [9831.9] | 125(100.0) [2071.3] |

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25 )*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dose.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dose_AGEGRP_AP.out
24JUN2020 11:01 Page 1 of 1

## Table 7 Exposure to Perjeta by Dose and Race: Metastatic Breast Cancer

Exposure to Perjeta by Dose and Race: Metastatic Breast Cancer

| | Asian (N=243) | Black (N=22) | White (N=1388) | Other (N=329) | Missing (N=1) |
|---|---|---|---|---|---|
| Total pertuzumab exposure (mg) | | | | | |
| Mean (SD) | 14574.0 (11713.09) | 11798.2 (9757.26) | 14992.0 (13480.94) | 16110.1 (13941.00) | 420.0 |
| Median | 10920.0 | 9030.0 | 9500.0 | 10500.0 | 420.0 |
| Range | 840, 45780 | 840, 34860 | 420, 59640 | 840, 52500 | 420, 420 |
| Number of Patients Receiving Planned Dose Level | n (%) Person months | n (%) Person months | n (%) Person months | n (%) Person months | n (%) Person months |
| 420mg (840mg loading dose) | 243(100.0)[5805.2] | 22(100.0)[426.9] | 1388(100.0)[34383.5] | 329(100.0)[8773.9] | 1(100.0)[0.7] |

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25 )*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dose.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dose_RACEGR1_MBC_AP.out
24JUN2020 11:09 Page 1 of 1

## Table 8 Exposure to Perjeta by Dose and Race: Early Breast Cancer

| | Asian (N=700) | Black (N=58) | White (N=2380) | Other (N=89) | Missing (N=55) |
|---|---|---|---|---|---|
| Total pertuzumab exposure (mg) | | | | | |
| Mean (SD) | 6814.2 (2283.97) | 5257.2 (2836.87) | 6446.3 (2458.17) | 6418.0 (2577.41) | 7277.5 (1381.34) |
| Median | 7980.0 | 6300.0 | 7980.0 | 7980.0 | 7560.0 |
| Range | 420, 8400 | 840, 8400 | 300, 9660 | 840, 7980 | 1680, 7980 |
| Number of Patients Receiving Planned Dose Level | n (%) Person months | n (%) Person months | n (%) Person months | n (%) Person months | n (%) Person months |
| 420mg (840mg loading dose) | 700(100.0)[7447.8] | 58(100.0)[480.3] | 2380(100.0)[24236.4] | 89(100.0)[896.4] | 55(100.0)[651.0] |

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25 )*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: /opt/BIOSTAT/prod/cd11450w/t_ex_dose.sas / Output: /opt/BIOSTAT/prod/cd11450w/reports/t_ex_dose_RACEGR1_EBC_AP.out
03MAY2017 12:05 Page 1 of 1

## Table 9 Exposure to Perjeta by Dose and Race: Metastatic and Early Breast cancer

Exposure to Perjeta by Dose and Race: Metastatic and Early Breast cancer

| | Asian (N=943) | | Black (N=80) | | White (N=3768) | | Other (N=418) | | Missing (N=56) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Total pertuzumab exposure (mg) | | | | | | | | | | |
| Mean (SD) | 8813.8 (7116.68) | | 7056.0 (6304.92) | | 9594.2 (9366.26) | | 14046.5 (13040.45) | | 7155.0 (1647.16) | |
| Median | 7980.0 | | 7140.0 | | 7980.0 | | 7980.0 | | 7560.0 | |
| Range | 420, 45780 | | 840, 34860 | | 300, 59640 | | 840, 52500 | | 420, 7980 | |
| Number of Patients Receiving Planned Dose Level | n (%) | Person months | n (%) | Person months | n (%) | Person months | n (%) | Person months | n (%) | Person months |
| 420mg (840mg loading dose) | 943(100.0) | [13253.0] | 80(100.0) | [907.2] | 3768(100.0) | [58619.9] | 418(100.0) | [9670.3] | 56(100.0) | [651.7] |

Person months = SUM(((date of last dose+21 days)-date of first dose)/365.25 )*12
In each of the trials a loading dose of 840mg was administered at Cycle 1 followed by a maintenance dose of 420mg starting at Cycle 2

Program: root/clinical_studies/RO4368451/share/pool_RMP/prod/program/t_ex_dose.sas
Output: root/clinical_studies/RO4368451/share/pool_RMP/prod/output/t_ex_dose_RACEGR1_AP.out
24JUN2020 11:18 Page 1 of 1

## Special Population Exposure (by Indication)

There are currently no specific exposure data available for special population groupings, which are, by definition, excluded from the clinical trial program. As of 7 June 2020, it is estimated that 784 male patients have been exposed to Perjeta in the clinical trial program.

# PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS
## SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

## Table 10 Important Exclusion Criteria in Pivotal Studies in the Development Program

| Criterion | Reason for Exclusion | Is it to be included as missing information? (Yes/No) | Rationale |
|---|---|---|---|
| Hypersensitivity | Patients with known hypersensitivity to pertuzumab or to any of its excipients were excluded from clinical trials to avoid risk of anaphylactic shock/reaction. | No | Patient with hypersensitivity to the active substance or to any of the excipients is contraindicated as per EU SmPC. A statement regarding severe hypersensitivity, including anaphylaxis and events with a fatal outcome, have been observed with Perjeta has been added in Section 4.4 of the EU SmPC. In addition, a statement regarding permanent discontinuation of pertuzumab for any patient who experiences a NCI CTCAE Grade 4 reaction, will remain in Section 4.4 of the EU SmPC. |
| Pregnancy | Pregnant patients were excluded in clinical trials as Studies in animals have shown reproductive related toxicity (see Module II-Toxicity). | Yes<br>Please refer to section SVII.3 for additional details on the missing information “Use during pregnancy and lactation”. | Not applicable |
| Patients with poor performance status | Such patients are unlikely to be able to tolerate taxane- or anthracycline-based therapy | No | No warning or exclusion included in the EU SmPC for Perjeta. Assessment of a patient’s fitness for chemotherapy is part of routine oncology practice |

| Criterion | Reason for Exclusion | Is it to be included as missing information? (Yes/No) | Rationale |
|---|---|---|---|
| Patients with known Central nervous system metastases | Pertuzumab and trastuzumab are monoclonal antibodies and therefore are thought to cross the blood-brain barrier poorly. Such patients also tend to have aggressive disease and may have insufficient time to benefit from treatment in a trial setting | No | Section 5.1 of the EU SmPC for Perjeta indicates that patients with brain metastases were excluded from the CLEOPATRA trial and that no data are available on Perjeta activity on brain metastases. |
| Patients exposed to cumulative doses of doxorubicin >360 mg/m$^2$ (or equivalent cumulative doses of other anthracyclines) or prior radiotherapy to the chest area. | Such patients are thought to be at increased risk of cardiac toxicity associated with HER2-targeted agents. | No | Included in Section 4.4, Special Warnings and Precautions for Use, in the EU SmPC for Perjeta |
| Patients with uncontrolled hypertension, a history of congestive heart failure, a serious cardiac arrhythmia requiring treatment (other than atrial fibrillation or paroxysmal supraventricular tachycardia), angina requiring anti-angina medication, clinically significant valvular heart disease, or a myocardial infarction within the last 6 months | Such patients are thought to be at increased risk of cardiac toxicity associated with HER2-targeted agents. | No | Not applicable |
| Patients with low left ventricular ejection fraction (<50% or <55%, depending on the patient population) | Such patients are thought to be at increased risk of cardiac toxicity associated with HER2-targeted agents | Yes. | Not applicable |

| Criterion | Reason for Exclusion | Is it to be included as missing information? (Yes/No) | Rationale |
|---|---|---|---|
| | | Please refer to section SVII.3 for additional details on the missing information “Cardiac impairment”. | |
| Patients with inadequate renal or hepatic function or with impaired bone marrow reserve (manifest as anemia, neutropenia or thrombocytopenia) | Such patients are unlikely to be able to tolerate taxane- or anthracycline-based therapy | No | EU SmPC for Perjeta indicates that there is no information on patients with severe renal impairment<br><br>EU SmPC for Perjeta indicates that Perjeta has not been studied in patients with hepatic impairment.<br><br>EU SmPCs for cytotoxic agents commonly used in patients with breast cancer (e.g. docetaxel, paclitaxel, doxorubicin and epirubicin) indicate that clearance may be reduced and/or toxicity increased in patients with hepatic impairment. EU SmPCs for docetaxel and paclitaxel do not include information on patients with severe renal impairment; for doxorubicin and epirubicin, SmPCs indicate that dose reductions may be required for renal impairment. The SmPCs for these agents also clearly indicate the high risk of myelosuppression and the need to monitor blood counts before and during therapy |

| Criterion | Reason for Exclusion | Is it to be included as missing information? (Yes/No) | Rationale |
|---|---|---|---|
| Patients with other severe, uncontrolled systemic diseases or known to be infected with HIV, HBV or HCV | Such patients may not be able to tolerate taxane- or anthracycline-based therapy and are at increased risk of infectious complications associated with myelosuppression | No | No specific warning or exclusion included in the EU SmPC for Perjeta since assessment of a patient's fitness for chemotherapy is part of routine oncology practice. This concern is not considered by the MAH to be a sufficient reason to limit physician options in treatment of patients with active infections with Perjeta.<br>However, Section 4.4 of the Perjeta SmPC indicates that patients treated with Perjeta, trastuzumab and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, trastuzumab and docetaxel.<br><br>The SmPCs of cytotoxic agents commonly used in patients with breast cancer (e.g., docetaxel, paclitaxel, doxorubicin and epirubicin) provide extensive warnings about the risks of neutropenia and its complications. |
| Patients with current dyspnea at rest due to advanced malignancy or other diseases that require continuous oxygen therapy | Such patients may not be able to tolerate the infusion reactions associated with pertuzumab, trastuzumab, docetaxel and paclitaxel | No | No specific warning or exclusion included in the EU SmPC for Perjeta since this is considered part of routine assessment of a patient's fitness for treatment (part of routine oncology practice). The EU SmPC for Perjeta, Herceptin, docetaxel and paclitaxel all include details of infusion reactions in Section 4.4, Special Warnings and Precautions for Use. |

| Criterion | Reason for Exclusion | Is it to be included as missing information? (Yes/No) | Rationale |
|---|---|---|---|
| Patients requiring chronic daily treatment with corticosteroids (other than inhaled or topical steroids) | Such patients may not be able to tolerate taxane- or anthracycline--based therapy and are at increased risk of infectious complications associated with myelosuppression | No | No specific warning or exclusion included in the EU SmPC since this is considered part of routine assessment of a patient's fitness for treatment (part of routine oncology practice). |
| Patients who have had recent major surgical procedures or significant traumatic injury | Such patients may not be able to tolerate taxane- or anthracycline-based therapy and may be at increased risk of infectious complications associated with myelosuppression | No | No specific warning or exclusion included in the EU SmPC since this is considered part of routine assessment of a patient's fitness for treatment (part of routine oncology practice). |
| Patients with other malignancies in the last 5 years (other than curatively-treated non-melanomatous skin cancer or in situ carcinomas treated with curative intent) | Such patients were excluded from clinical trials because relapse or progression of the other malignancy could confound interpretation of trial efficacy data. | No | Such patients should still benefit from treatment with Perjeta, Herceptin and chemotherapy. No warning or exclusion included in the EU SmPC. |
| Patients receiving other investigational treatments | Such patients were excluded from clinical trials because the other investigational agent could confound interpretation of trial safety and efficacy data. | No | No warning or exclusion included in the EU SmPC. Co-administration of investigational agents is beyond the scope of the EU SmPC. |

EU=European Union; HER2=Human epidermal growth factor receptor 2; HIV=Human immunodeficiency virus; HBV=Hepatitis B virus; HCV=Hepatitis C virus; LVEF= Left ventricular ejection fraction; MAH=Marketing authorization holder; SmPC=Summary of Product Characteristics.

## SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAM

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

## SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

### Table 11 Exposure of special populations included or not in clinical trial development program

| Type of special population | Exposure |
|---|---|
| Pregnant women | Not included in the clinical development program |
| Breastfeeding women | Not included in the clinical development program |
| **Patients with relevant comorbidities** | |
| Patients with hepatic impairment | Not included in the clinical development program, including:<br>• Patients with known severe hepatic impairment;<br>• Patients with current known infection with HIV, HBV or HCV were excluded. |
| Patients with renal impairment | Patients with a serum creatinine > 2.0 mg/dL or 177 µmol/L or > 1.5 × upper limit of normal were not included in the clinical development program. |
| Patients with cardiovascular impairment | • Not included in the clinical development program, including following groups: Patients with a left ventricular ejection fraction < 50 % or 55 % in history or at screening.<br>• Patients with a clinically significant cardiovascular disease, such as uncontrolled hypertension, unstable angina, a history of CHF or serious cardiac arrhythmias.<br>Patients with a cumulative dose of prior anthracyclines > 360 mg/m$^2$ of doxorubicin or equivalent. |
| Subpopulations carrying relevant genetic polymorphisms | Not applicable. |
| **Other** | |
| Children: | Children and adolescents below the age of 18 years were not included in the clinical development program. |
| Elderly aged ≥75 years : | These patients were not excluded from the clinical trial program for Perjeta. The number of patients aged > 75 years exposed via participation in clinical trials remains small (refer to Table 6), however the data regarding use of Perjeta in patients aged 75 years or older is growing. . |

| Type of special population | Exposure |
|---|---|
| Male breast cancer patients | Male breast cancer patients were not excluded from the clinical trial program for Perjeta. However, the number of male breast cancer patients exposed via participation in clinical trials remains relatively small as compared to female breast cancer patients..<br>Refer to Part II-Module SIII-clinical trial exposure–Special Population Exposure for male patients' exposure.<br>Of note, a considerable number of male patients have now been exposed to Perjeta in the post-marketing setting (Table 12). |

CHF= congestive heart failure; HBV= Hepatitis B virus; HCV= Hepatitis C virus HIV = Human immunodeficiency virus.

# PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

## SV.1 Post-authorization exposure

### SV.1.1 Method used to calculate exposure

**Worldwide Exposure from Marketing Experience (Excluding the United States)**

Exposure is based on Roche internal data on the number of commercial product vials shipped to each country and Roche market research with oncologists to estimate patients receiving therapy.

In keeping with the methodology, data by sex and age are only shown for the five largest European countries.

Exposure in the EBC setting is currently estimated based on projected adoption and verification of usage from Roche market research with oncologists.

**Patient Exposure from Marketing Experience in the United States**

The patient exposure data presented are based on a patient model that assumes U.S. sales are split such that 65% of usage was in patients with EBC and 35% in the MBC setting. Patient exposure is calculated from actual vials sold, divided by estimated historical vials per patient from the patient model.

According to data obtained via patient tracking activities, approximately 25% of patients receiving Perjeta for EBC and 41% of patients receiving Perjeta for MBC in the U.S. are aged 65 years or older. Epidemiology data indicates 0.8% of patients with breast cancer are male.

No estimates of pediatric exposure are provided but exposure is expected to be very low in view of the rarity of breast cancer in the pediatric age group.

**Patient Exposure from Marketing Experience in Japan**

The estimated exposure in Japan was calculated using the following algorithm:

1) the ratio of the total dose for each indication was calculated from 2018 Sales Assumption data,

2) the total dose for the indication being studied was calculated using the ratio of each indication (calculated in “(1)” above) and total sales data during the period,

3) the dose per patient per indication was calculated from 2018 Sales Assumption data, and

4) the patient exposure for indication was then calculated by dividing the results in “(2)” by the results in “(3)”.

## SV.1.2 Exposure

From the international birth date (IBD: 8 June 2012) up to 7 June 2020, an estimated total of 475,041patients have received Perjeta from marketing experience (Perjeta PBRER Report 1101895 [Reporting interval: 8 June 2019 to 7 June 2020]). The estimated cumulative exposure to Perjeta is presented in Table 12.

## Table 12 Cumulative Exposure to Perjeta from Marketing Experience

| Indication | Sex | | | Age (years) | | | | Region | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M | F | Unk | 0 to ≤ 16 | > 16 to ≤ 65 | > 65 | Unk | EEA | U.S. | RoW | Japan | |
| **EBC** | 1,943 | 232,037 | 65,306 | 0 | 174,767 | 59,215 | 65,306 | 71,942 | 162,039 | 56,886 | 8,420 | 299,287 |
| **MBC** | 944 | 110,034 | 64,776 | 0 | 73,871 | 37,107 | 64,776 | 55,959 | 55,019 | 33,573 | 31,203 | 175,754 |
| **Total** | 2,887 | 342,072 | 130,082 | 0 | 248,638 | 96,322 | 130,082 | 127,901 | 217,058 | 90,459 | 39,623 | 475,041 |
| **Grand Total**[a] | 475,041 | | | 475,041 | | | | 475,041 | | | | |

EBC = early breast cancer; EEA = European Economic Area; F = female; M = male; MBC = metastatic breast cancer; n/a = Not applicable; RoW = Rest of World; Unk = unknown.

[a] Sum of exposure numbers in each category may not equal the totals due to rounding errors.

## PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

### SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Drugs that have potential for misuse for illegal purposes are expected to share some general characteristics, such as psychoactive effects or, less commonly, anabolic effects or enhancement of hemoglobin levels. There is no evidence that Perjeta has such effects which makes it highly unlikely that Perjeta will be misused for illegal purposes.

## PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

### SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

#### SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

#### SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

### SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No new safety concerns have been identified since this module of the RMP was last submitted.

.

### SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

#### SVII.3.1. Presentation of important identified risks and important potential risks

**1. INFORMATION ON IMPORTANT IDENTIFIED RISKS**

**1.1 INFUSION-RELATED REACTIONS, HYPERSENSITIVITY REACTIONS/ANAPHYLAXIS**

MedDRA Terms:

*Infusion-related reactions (IRRs):*

In Study WO20698 (CLEOPATRA), a conservative definition was initially used to identify potential infusion-associated events. IRR was subsequently defined as any event in the MedDRA SMQ “Anaphylactic reaction (wide)”, Roche Standard Adverse Event Grouped Term (AEGT) “Anaphylaxis and hypersensitivity” and, the Roche Standard AEGT “Infusion Related Reactions + Hypersensitivity” that occurred on the day of a Perjeta (or

placebo) infusion, irrespective of Investigator causality. This definition was also used for the NEOSPHERE, TRYPHAENA, APHINITY and PERUSE studies (see Table 14).

*Hypersensitivity reactions/Anaphylaxis*:

Identified using the Roche standard AEGT, 'Anaphylaxis and Hypersensitivity', containing the MedDRA SMQ (narrow) 'Anaphylactic reaction' plus all MedDRA Preferred Terms containing the term, 'hypersensitivity.'

Note that analysis of hypersensitivity reactions/anaphylaxis is not time-restricted (i.e., includes events occurring at any time) or restricted to events considered related to study treatment. Thus, the figures include occasional unrelated events such as hypersensitivity reactions to other medication (e.g. antibiotics) or food.

Potential mechanisms:

IRRs are thought to be due to release of cytokines and/or other chemical mediators. Anaphylactic or hypersensitivity reactions to the IV administration of protein may also play a part in some patients, for example monoclonal antibodies. Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms of these reactions overlap (Lenz 2007).

Evidence source(s) and strength of evidence:

Randomized clinical trial data

Based on safety results from WO20698 (CLEOPATRA), WO20697 (NEOSPHERE), BO22280 (TRYPHAENA), BO25126 (APHINITY) and MO28047 (PERUSE).

Characterization of the risk:

**Background Incidence/Prevalence**

Infusion-associated reactions are known to occur with monoclonal antibodies. The frequency of infusion-associated reactions is variable depending on the molecule and the definition used for an infusion-associated reaction, the time window reviewed and whether the first or later cycles are assessed. These differences mean that comparison of incidence figures for different antibodies should be interpreted with caution.

In general antibody infusion-associated AEs are more frequent and severe with the first infusion, and decrease in number and severity over time, and the majority of AEs resolve fully.

Infusion-associated reactions typically occur during or shortly after infusions of monoclonal antibodies but may also show a delayed onset. The true relation of an event

to infusion of study treatment is therefore difficult to ascertain, particularly when treatment regimens involve combination therapy. The potential incidence of infusion-associated reactions has been considered using a number of approaches in studies involving Perjeta. A conservative approach was initially used in the CLEOPATRA study, in which all events occurring on the day of the infusion and the day following Perjeta infusion were presented as infusion-associated AEs, whether considered related or unrelated to Perjeta by the investigator. This definition is likely to result in inclusion of events that are not truly Perjeta infusion-related. Therefore, the definition was revised to include any event in the AEGT/SMQ for 'Anaphylactic Reactions (wide)', 'Roche Standard AEGT Anaphylaxis and Hypersensitivity', 'AEGT - Rituximab-Specific AEGT Hypersensitivity Infusion Reaction (MabThera RA), plus the Preferred Term (PT) Cytokine Release Syndrome 'occurring on the day of the Perjeta (or placebo), whether considered related or unrelated to Perjeta by the investigator.

Hypersensitivity reactions to trastuzumab are described as common (≥1/100 to <1/10 patients).

Although not a monoclonal antibody, taxanes are also associated with infusion-related reactions, hypersensitivity reactions and anaphylaxis, and these reactions also typically start during the first or second infusion. The incidence of hypersensitivity reactions with 75 mg/m$^2$ of docetaxel alone is described as common (≥1/100 to <1/10 patients). With 100 mg/m$^2$, such reactions are described as very common (≥1/10) and include Grade ≥3 reactions in 5.3% of cases (Docetaxel SmPC).

**Frequency with 95% CI:**

The great majority of patients included received Ptz+H+chemotherapy. The details are provided in Table 13 below:

## Table 13 Summary of Infusion-Related Reactions in Early and Metastatic Breast Cancer

| | EBC (N=3282) | MBC (N=548) | Total (N=3830) |
|---|---|---|---|
| Infusion-associated reaction n(%) | 208 (6.3%) | 34 (6.2%) | 242 (6.3%) |
| 95% Clopper-Pearson Confidence Interval | [5.5; 7.2] | [4.3; 8.6] | [5.6; 7.1] |

Program: /opt/BIOSTAT/prod/cd11450w/t_ae_risks.sas
Output: /opt/BIOSTAT/prod/cd11450w/reports/t_ae_risks_RMPIR_NADJ_AP.out
03MAY2017 12:06 Page 1 of 1

**Seriousness / Outcomes**

Please refer to Table 14, Table 15 and Table 16 below in clinical trials.

*Events with a fatal outcome in clinical trials*: There have been no infusion reactions with a fatal outcome.

## Table 14 Summary of Infusion-Related Reactions (AEGT/SMQ) Occurring on the Day of a Pertuzumab Infusion in the NEOSPHERE, TRYPHAENA, and APHINITY Studies

### Early Breast Cancer

| Cycle | NEOSPHERE | | | | | | TRYPHAENA | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ptz+H+D (n=107) | | Ptz+H (n=108) | | Ptz+D (n=94) | | Ptz+H+FEC/ Ptz+H+D (n=72) | | FEC/Ptz+H+D (n=75) | | Ptz+TCH (n=76) | |
| | All | Gr ≥ 3 | All | Gr ≥ 3 | All | Gr ≥ 3 | All | Gr ≥ 3 | All | Gr ≥ 3 | All | Gr ≥ 3 |
| All | 38.3% | 0 | 38.0% | 2.8% | 35.1% | 0 | 37.5% | 1.4% | 25.3% | 4.0% | 46.1% | 3.9% |
| 1[a] | 23.4% | 0 | 33.3% | 1.9% | 8.5% | 0 | 25.0% | 1.4% | 18.6% | 4.3% | 23.7% | 3.9% |
| 2[a] | 12.4% | 0 | 7.4% | 0.9% | 17.2% | 0 | 12.7% | 0 | 13.6% | 0 | 17.6% | 0 |

| Cycle | APHINITY | | | |
|---|---|---|---|---|
| | Ptz+H+Chemo n=2364 | | Pla+H+Chemo n=2405 | |
| | All | Gr ≥ 3 | All | Gr ≥ 3 |
| All | 54.7% | 2.7% | 51.3% | 2.1% |
| 1 | 20.9% | 1.2% | 18.0% | 0.7% |
| 2 | 13.3% | 0.3% | 12.6% | 0.4% |

Pla+H+D=placebo+Herceptin+docetaxel; Ptz+H+D= Perjeta+Herceptin+docetaxel; TCH=docetaxel (Taxotere), carboplatin, Herceptin, Ptz+H+FEC: Perjeta+Herceptin + 5-fluorouracil, epirubicin, cyclophosphamide

Shaded columns show incidence of AEs (all Grades) in the AEGT/SMQ for anaphylactic reactions, hypersensitivity reactions and infusion reactions that occurred on the day of a Perjeta infusion. [a]Cycle 1 and 2 indicate the first and second cycle at which Perjeta was scheduled (ie. Cycle 4 and 5 for patients in the FEC/Ptz+H+D arm).

Sources: Tables 66 and 69 in the Summary of Clinical Safety (neoadjuvant); APHINITY Primary CSR, t_ae_ppinf_TRT1A_IREA_SE. Data cut off dates WO20697 NEOSPHERE (12 July 2012), BO22280/TRYPHAENA (04 July 2012), APHINITY (19 Dec 2016).

## Table 15 Summary of Infusion-Related Reactions (AEGT/SMQ) Occurring on the Day of a Pertuzumab Infusion in the CLEOPATRA and PERUSE Studies

### Metastatic Breast Cancer

| Cycle | CLEOPATRA | | | | PERUSE | |
|---|---|---|---|---|---|---|
| | Ptz+H+D (n=408) | | Pla+H+D (n=396) | | Ptz+H+Taxane N=1436 | |
| | All | Gr ≥ 3 | All | Gr ≥ 3 | All | Gr ≥ 3 |
| All | 63.0% | 5.1% | 53.5% | 4.0% | 73.1% | 7.9% |
| 1 | 13.7% | 0.2% | 10.1% | 0.3% | 30.7% | 2.3% |
| 2 | 14% | 0.3% | 15.9% | 1.0% | 19.3% | 0.9% |

Pla+H+D=placebo+Herceptin+docetaxel; Ptz+H+D= Perjeta+Herceptin+docetaxel

Shaded columns show incidence of AEs (all Grades) in the AEGT/SMQ for anaphylactic reactions, hypersensitivity reactions and infusion reactions that occurred on the day of a Perjeta infusion. Source: Table 23 of final CSR and t_fae1_iar_hday_ua_aepr_s. Data cut-off date WO20698 CLEOPATRA (23 Nov 2018).

## Table 16 Summary of Anaphylaxis/Hypersensitivity Reactions

### Early Breast Cancer

| Safety parameter | Patients experiencing event | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | NEOSPHERE | | | | TRYPHAENA | | | APHINITY | |
| | T+D n=107 | Ptz+H+D n=107 | Ptz+H n=108 | Ptz+D n=94 | Ptz+H+FEC/ Ptz+H+D (n=72) | FEC/Ptz+H +D (n=75) | Ptz+TCH (n=76) | Ptz+H+Chemo n=2364 | Pla+H+Chemo n=2405 |
| Anaphylaxis/ hypersensitivity All Grades | 1.9% | 5.6% | 5.6% | 7.4% | 9.7% | 1.3% | 13.2% | 4.9% | 3.6% |
| Anaphylaxis/ hypersensitivity Grade ≥ 3[a] | 0 | 0.9% | 1.9% | 0 | 2.8% | 0 | 2.6% | 0.8% | 0.7% |

Pla+H+D=placebo+Herceptin+docetaxel; Ptz+H+D= Perjeta+Herceptin+docetaxel; TCH=docetaxel (Taxotere), carboplatin, Herceptin, Ptz+H+FEC: Perjeta+Herceptin + 5-fluorouracil, epirubicin, cyclophosphamide

## Metastatic Breast Cancer

| Safety parameter | Patients experiencing event | | |
|---|---|---|---|
| | CLEOPATRA | | PERUSE |
| | Ptz+H+D n=408 | Pla+H+D n=396 | Ptz+H+Taxane N=1436 |
| Anaphylaxis/ hypersensitivity All Grades | 11.8% | 9.3% | 8.6% |
| Anaphylaxis/ hypersensitivity Grade ≥ 3[a] | 2.0% | 2.5% | 1.3% |

Pla+H+D=placebo+Herceptin+docetaxel; Ptz+H+D= Perjeta+Herceptin+docetaxel

Sources: Tables 19 and 23 of the Summary of Clinical Safety (neoadjuvant); APHINITY Primary CSR. Table 44; CLEOPATRA Final CSR Table 32. Data cut off dates WO20697 NEOSPHERE (09 March 2012), BO22280/TRYPHAENA (04 July 2012), APHINITY (19 Dec 2016) and WO20698 CLEOPATRA (23 Nov 2018, , ROCHE\PERTUZUMAB\XSA84478_QSTR\BIOSTATISTICS\PRODUCTION\TABLES\ADHOC\T_AE_HYP_ADHOC.SAS] IQVIA 30APR2020.

[a] No Grade 5 events occurred

**Severity and Nature of Risk:**

*Infusion-related reactions (IRRs):*

Perjeta has been associated with IRRs, including events with fatal outcomes. Overall, the incidence and severity of IRRs was similar across treatment arms and studies. Less than 5% of patients in any treatment arm experienced Grade ≥ 3 reactions. The incidence of IRRs was generally highest in the first cycle of therapy and declined thereafter, as is typical of infusion reactions with monoclonal antibodies.

*Hypersensitivity and Anaphylaxis:*

The incidence and severity of events was similar in Study WO20698 in MBC and in studies in the neoadjuvant treatment of EBC (NEOSPHERE/ TRYPHENA), and in the adjuvant setting (APHINITY), with the majority of events being Grade 1 – 2 in severity.

Hypersensitivity reactions are typically associated with pre-formed antibodies and therefore require prior exposure to the drug or a cross reacting agent. Thus hypersensitivity reactions would be expected to worsen with repeated doses (Lenz 2007). This distinguishes them from infusion-associated events, which are typically worst with the first dose and become less severe with repeated doses. However, symptoms overlap, and in practice it can be difficult to distinguish between infusion-associated events and hypersensitivity reactions in individual patients.

**Impact on quality of life:**

Patients may experience considerable discomfort during a reaction (e.g., chills, rigors, flushing, breathing difficulty, vomiting, itching, headache), although symptoms are likely to resolve completely following the infusion. Hence, such reactions are likely to have no long-term impact on quality of life.

On the other hand, although severe infusion reactions, hypersensitivity and anaphylactic reactions to pertuzumab are rare events, such reactions would prevent the patient from continuing treatment.

Risk factors and risk groups:

There are currently no reliable predictors of patients who may or may not be susceptible to infusion-associated reactions, hypersensitivity or anaphylaxis to pertuzumab. Patients with a history of asthma, eczema or hay fever (atopy) had a slightly increased risk of developing an IRR (on the day of or the day after a Perjeta infusion) than patients who did not have a history of atopy but the number of patients with a history of atopy was too small for any firm conclusions to be drawn. Moreover, patients with a history of atopy did not appear to be at increased risk of anaphylaxis or hypersensitivity reactions. Importantly, prior and concomitant trastuzumab exposure did not appear to reduce or exacerbate the infusion-associated events seen with Perjeta.

*Anti-Drug Antibodies (ADA) in Study WO20698*

Serum samples were assayed for ADAs to pertuzumab, also known as anti-therapeutic antibodies (ATAs) or human anti-human antibodies (HAHA). The incidence of ADA was calculated from the total number of patients who tested positive for ADA against pertuzumab after dosing, divided by the total number of patients who had post dose ADA samples available for the ADA analysis. A conservative approach was taken for calculating the incidence of ADA so that any patient confirmed to have an ADA positive sample after dosing was considered positive for ADA, regardless of baseline status.

Since trastuzumab and pertuzumab share the same framework structure, differing only in the complementarity-determining region, it is possible that the positive ADA findings in patients treated with Placebo + trastuzumab (Herceptin) + docetaxel (Pla + H + D) were due to antibodies directed toward the common framework portion of pertuzumab and trastuzumab.

In Study WO20698, at the second clinical data cutoff (14 May 2012), 6.7% (25/372 patients) of placebo-treated patients and 3.3% (13/389 patients) of Perjeta-treated patients tested positive for ADA. Of these 38 patients, none experienced anaphylactic/ hypersensitivity reaction that was clearly related to the ADA. Most patients with detectable ADA were able to continue study treatment, sometimes for prolonged periods.

Preventability:

Infusion reactions, hypersensitivity and anaphylactic reactions to pertuzumab cannot be reliably predicted or prevented. However, the incidence and severity of infusion reactions may be reduced by premedication and appropriate monitoring of the patient during infusions, with slowing or discontinuation of the infusion if needed.

Impact on the benefit-risk balance of the product:

The impact of infusion- associated reactions to the benefit-risk balance of Perjeta is considered to be low since the symptoms generally resolve completely once the infusion has been discontinued, slowed or completed. IRRs are commonplace in oncology practice and patients are already at higher risk of reactions due to the concomitant administration of taxanes and trastuzumab. Due to this increased risk, oncology patients are routinely monitored for the typical symptoms of an infusion related event.

Current pharmacovigilance plans and product labels include guidance for patient management in the event of a hypersensitivity or infusion related reaction (Section 4.4 of the EU SmPC, “Infusion reactions” and “Hypersensitivity reactions/anaphylaxis” provides recommendations on risk management approach) and these measures are considered adequate to manage the risk.

Public health impact:

The potential public health impact of Perjeta-related IRRs is considered low. Patients receiving trastuzumab or taxanes are already at risk of IRRs and monitoring and treatment of IRRs is a routine part of oncology clinical practice.

In studies in MBC and EBC, the incidence of events coded to the AEGT “Anaphylaxis and Hypersensitivity” Grade ≥3 was low. Therefore, the potential public health impact associated with this safety concern is considered to be low.

## 1.2 CONGESTIVE HEART FAILURE/LEFT VENTRICULAR DYSFUNCTION

MedDRA Terms:

Serious adverse events (SAEs) in the MedDRA SMQ Cardiac failure-wide

LVEF declines (significant LVEF declines were defined as any LVEF decline of ≥10%-points from baseline to an absolute value of <50%). Note that reporting of cardiac dysfunction is based on a single LVEF decline, which is a conservative approach, as many LVEF declines are not confirmed at the next assessment.

Potential mechanisms:

Since pertuzumab targets HER2, like trastuzumab, there is a potential risk of cardiac dysfunction, particularly in patients who have received prior anthracycline treatment. HER2 signaling is required for the growth, repair and survival of cardiomyocytes. These repair mechanisms involve HER2-HER4 heterodimeric receptors which trigger the myocyte survival pathways required during the activation of acute stress signals mainly by anthracyclines (Crone et al, 2002; Swayer et al, 2002; Negro et al, 2004). Available clinical evidence to date from studies in MBC and EBC suggests a similar or only slightly increased risk of cardiotoxicity with the addition of Perjeta to trastuzumab. It is possible that the maximum effect on cardiomyocytes is already exerted by trastuzumab and that the addition of Perjeta does not add to this (Stortecky & Suter 2010; Zuppinger & Suter 2010; Carver 2010).

Evidence source(s) and strength of evidence:

Clinical trial data

Based on safety results from WO20697 (NEOSPHERE), WO20698 (CLEOPATRA), BO22280 (TRYPHAENA), WO29217 (BERENICE), BO25126 (APHINITY), and MO28047 (PERUSE).

Characterization of the risk:

**Background Incidence / Prevalence:**

First-line HER2-positive MBC:

The incidence of symptomatic CHF (Grades 3 or 4) for:

- Non-trastuzumab containing regimens:
  - Without anthracyclines: 0.3% to 1% (Slamon et al, 2001, Johnston 2009)
  - With anthracyclines: 3% to 4.7% (Slamon et al, 2001, O'Brien 2004).
- Trastuzumab containing regimens:
  - Without anthracyclines: 2% to 4% (Slamon et al, 2001, Seidman et al, 2002)
  - With anthracyclines: 16% (Slamon et al, 2001).

Long-term trastuzumab therapy: Among 173 patients who received ≥1 year of trastuzumab-based therapy (median length of treatment was 21.3 months), 10.9% experienced Grade 3 cardiac toxicity (85% were exposed to anthracyclines).

Second-line HER2-positive MBC:

Based on three lapatinib studies, the incidence of symptomatic CHF (Grades 3 or 4) was <1% for non-trastuzumab containing regimens (Blackwell 2010, Capri at al. 2010, Burstein at al. 2003). In a pooled analysis of 3689 lapatinib patients enrolled in clinical trials, the incidence of symptomatic cardiac toxicity by prior treatment was:

- Anthracyclines: 0.5%
- Trastuzumab: 0.1%
- Neither anthracyclines nor trastuzumab: 0.1%.

Based on data from Study MO22324 (PHEREXA), the most common AE that led to withdrawal of all study treatment was left ventricular dysfunction (LVD):

- Treatment Arm A (Herceptin+capecitabine): 0.9%
- Treatment Arm B (Perjeta+Herceptin+capecitabine): 3.1%.

The incidence of AEs reported during the study in the SOC 'Cardiac Disorders' was higher in treatment Arm B (8.7% vs. 14.0%), with LVD being the most commonly reported and occurred more frequently in treatment Arm B (3.2% vs. 7.5%). The proportion of patients that experienced cardiac disorders as SAEs was low in both treatment arms but higher in treatment Arm B (2.3% vs. 6.1%). Grade ≥3 LVD was also reported more frequently in treatment Arm B (0.9% vs. 2.2%).

The incidence of event to monitor LVD (both asymptomatic and symptomatic left ventricular systolic dysfunction [LVSD] New York Heart Association [NYHA class

II/III/IV]) was higher in treatment Arm B (asymptomatic: 3.2% in Arm A and 6.6% in Arm B; symptomatic: 0 in Arm A and 2.2% in Arm B); however, these findings were consistent when compared to prior experience with Perjeta. All five events of symptomatic LVSD in Arm B were considered as possibly related to study treatment by the investigator. Of the five patients with symptomatic LVSD, three had central LVEF assessment at baseline lower than 50% however, their local LVEF readings were all above 50%, making them eligible for the study. Four of the five patients reported cardiac medical history, all five received anthracycline therapy, and three received radiotherapy to the chest. At the time of the clinical cut-off date, four of the five symptomatic LVSD events had resolved. The mean LVEF at baseline was balanced between the two treatment arms (60.8% in Arm A and 60.0% in Arm B). The incidence of asymptomatic LVEF-drops reported as AEs was low (2.3% of patients in Arm A vs. 5.3% in Arm B).

Based on a review of three adjuvant trastuzumab trials (NASBP B-31, NCCTG N9831, HERA) with anthracycline and non-anthracycline containing regimens, the incidence of symptomatic CHF (defined as NYHA Class III or IV) was:

- 0.6% to 3.8% for trastuzumab containing regimens
- 0% to 0.9% for non-trastuzumab containing regimens.

In a meta-analysis of eight randomized clinical trials (B31, BCIRG006, Buzdar, FinHer, HERA, NOAH, N9831, PACS-04) involving 10,281 patients, 2.5% of patients treated with a trastuzumab containing regimen and 0.4% of patients treated with a non-trastuzumab containing regimen experienced CHF. In a Phase III trial of 615 women with HER2-positive operable or locally advanced breast cancer (median age = 50 years) treated with epirubicin, cyclophosphamide, and docetaxel with lapatinib (n = 308) or trastuzumab (n = 307) (Untch et al, 2012), the incidence of Grade 3 – 4 CHF (NCI-CTC version 3) was 0% with trastuzumab containing regimens and 0.3% with lapatinib containing regimens.

In a randomized, open label multi-centre Phase III study comparing the activity of lapatinib alone versus trastuzumab alone versus trastuzumab followed by lapatinib versus lapatinib concomitantly with trastuzumab in the adjuvant treatment of patients with ErbB2 overexpressing and/or amplified breast cancer (ALTTO), although approximately 90% of patients received anthracycline-based chemotherapy, which has raised concerns regarding cardiotoxicity, congestive heart failure occurred in less than 1% across all arms (Piccart-Gebhart et al, 2014).

The incidence of CHF was reported to be 3.3% in HER2-positive EBC patients treated with anthracycline prior to trastuzumab (Anthony et al, 2015).

Refer to Table 17 below:

## Table 17 Summary of Congestive Heart Failure in Early and Metastatic Breast Cancer

| | EBC (N=3282) | MBC (N=548) | Total (N=3830) |
|---|---|---|---|
| Congestive Heart Failure n(%) | 76 (2.3%) | 7 (1.3%) | 83 (2.2%) |
| 95% Clopper-Pearson Confidence Interval | [1.8; 2.9] | [0.5; 2.6] | [1.7; 2.7] |

Program: /opt/BIOSTAT/prod/cd11450w/t_ae_risks.sas
Output: /opt/BIOSTAT/prod/cd11450w/reports/t_ae_risks_RMPIR_CARD_AP.out
03MAY2017 12:08 Page 1 of 1

Note: Congestive Heart Failure is defined by SAEs in the SMQ (wide) Cardiac Failure.

### Seriousness/Outcomes

Please refer to Table 18 and Table 19 below.

Events with a fatal outcome in clinical trials: There were two fatal CHF events in Study BO25126 (APHINITY): an event of cardiogenic shock in the Ptz + H + Chemo arm and an event of cardiac failure in the Pla + H + Chemo arm.

## Table 18 Key Cardiac Safety Data from the NEOSPHERE, TRYPHAENA, APHINITY, BERENICE, CLEOPATRA and PERUSE Studies

### Early Breast Cancer

| | Patients Experiencing Event | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | NEOSPHERE (overall treatment period) | | | | TRYPHAENA (overall treatment period) | | | APHINITY (overall treatment period) | | BERENICE (overall study period) | |
| | H+D n=107 | Ptz+H+D n=107 | Ptz+H n=108 | Ptz+D n=94 | Ptz+H+FEC/ Ptz+H+D n=72 | FEC/ Ptz+H+D n=75 | Ptz+TCH n=76 | Ptz+H+Chemo n=2364 | Pla+H+Chemo n=2405 | ddAC, T+PH n=199 | FEC, D+PH n=198 |
| Any cardiac AE[a] | 7.5% | 20.6% | 14.8% | 12.8% | 15.3% | 16.0% | 21.1% | 11.4% | 10.6% | 18.6% | 13.1% |
| LVD/EFD/CF[b] (PT) | 1.9% | 7.5% | 0 | 5.3% | 8.3% | 9.3% | 6.6% | 6.4%[e] | 6.8%[e] | 15.1% | 14.1% |
| Gr ≥ 3 LVD/EFD/CF (PT) | 0 | 0.9%[c] | 0 | 0 | 0 | 2.7% | 1.3% | 2.3%[f] | 2.0%[f] | 6.0% | 4.0% |
| LVEF decline[c] | 1.9% | 7.5% | 0.9% | 5.3% | 6.9% | 13.3% | 7.9% | 5.7%[g] | 7.0%[g] | 13.6% | 12.1% |
| CHF SAE | 0 | 2.8%[d] | 0.9% | 0 | 1.4% | 2.7% | 1.3% | 1.8% | 1.1% | 4.5% | 4.0% |
| Grade 5 CHF | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.04 | 0.04 | 0 | 0 |

## Table 18 Key Cardiac Safety Data from the NEOSPHERE, TRYPHAENA, APHINITY, BERENICE, CLEOPATRA and PERUSE Studies (cont.)

### Metastatic Breast Cancer

| Safety Parameter | Patients Experiencing Event | | |
|---|---|---|---|
| | CLEOPATRA (overall treatment period) | | PERUSE |
| | Ptz+H+D n=408 | Pla+H+D n=396 | Ptz+H+Taxane N=1436 |
| Any cardiac AE[a] | 17.9% | 17.4% | 15.2% |
| LVD/EF (PT)[b] | 7.8% | 8.6% | 13.6% |
| Gr ≥ 3 LVD (PT) | 1.5% | 3.3% | 2.9% |
| LVEF decline[c] | 7.1% | 7.4% | 9.4% |
| CHF SAE | 2.0% | 2.0% | 2.4% |
| Grade 5 CHF | 0 | 0 | 0.2% |

AE=adverse event; CF=cardiac failure; CHF=congestive heart failure (symptomatic left ventricular dysfunction) SAEs analyzed by SMQ (wide) 'Cardiac failure'; EFD=ejection fraction decrease; FEC=5-fluorouracil, epirubicin, cyclophosphamide; LVEF=left ventricular ejection fraction; LVD=left ventricular dysfunction; Pla+H+D=placebo+Herceptin+docetaxel; PT=preferred term; Ptz+H+D= Perjeta+Herceptin+docetaxel; SAE=serious adverse event.

Pla+H+D=placebo+Herceptin+docetaxel; Ptz+H+D= Perjeta+Herceptin+docetaxel; TCH=docetaxel (Taxotere), carboplatin, Herceptin; Ptz+H+FEC: Perjeta+Herceptin + 5-fluorouracil, epirubicin, cyclophosphamide; ddAC= dose-dense doxorubicin and cyclophosphamide; T+PH=paclitaxel+Perjeta+Herceptin; FEC=5-fluorouracil, epirubicin, cyclophosphamide; D+PH=docetaxel+ Perjeta+Herceptin

[a] Any AE in the Cardiac Disorder SOC.

[b] APHINITY based on PTs 'cardiac failure' and 'ejection fraction decreased'. BERENICE based on selected AE 'heart failure' and PT 'ejection fraction decreased'. All other studies based on LVD PT only, due to differences in MedDRA coding.

[c] LVEF decline of ≥ 10% from baseline to an absolute value <50%.

[d] Reported as an SAE suggestive of CHF, however, events were asymptomatic.

[e] APHINITY based on PTs 'cardiac failure' and 'ejection fraction decreased'.

[f] Based on grade ≥ 3 gevents of 'cardiac failure' and 'ejection fraction decreased'. Note that a primary cardiac event (defined as either Heart Failure [NYHA Class III or IV] and a drop in LVEF of at least 10 EF points from baseline AND to below 50%, or Cardiac Death) was reported in 0.7% of patients in the Ptz+H+Chemo arm and 0.3% of patients in the Pla+H+Chemo arm.

[g] Rate for the whole study period, not just the treatment period.

## Table 18 Key Cardiac Safety Data from the NEOSPHERE, TRYPHAENA, APHINITY, BERENICE, CLEOPATRA and PERUSE Studies (cont.)

Source: Tables 34, 35, 37, and 39 and t_ae11_345 in the Update CSR for NEOSPHERE; Tables 7, 14, 15, and 17 in the Update CSR for TRYPHAENA; APHINITY Primary CSR, Table 56, t_ae_TRT1A_SE, t_ae_TRT1A_CFEFD_SE, t_ae_TRT1A_CFEFD_CTC3_SE, t_ae_TRT1A_CFN_SER_SE and t_saf_lvefc_TRT1A_SE and Tables 27, 30, 32, 34 and t_ae11_345_pr in the final CSR for CLEOPATRA. Data cut off dates WO20697 NEOSPHERE (12 July 2012), BO22280 TRYPHAENA (04 July 2012), APHINITY (19 Dec 2016) and WO20698 CLEOPATRA (23 Nov 2018),ROCHE\PERTUZUMAB\XSA84478_QSTR\BIOSTATISTICS\PRODUCTION\TABLES\ADHOC\T_AE_CARDIAC_CI_ADHOC.SAS] IQVIA 30APR2020. WO29217 BERENICE source: program: root/clinical_studies/RO4368451/CDPT3497/WO29217/data_analysis/Final_CSR/prod/program/ah_sa2003_t_ae_risks.sas, output: root/clinical_studies/RO4368451/CDPT3497/WO29217/data_analysis/Final_CSR/prod/output/ah_sa2003_t_ae_risks_SE.out 19Mar2021 12:52. Program: root/clinical_studies/RO4368451/CDPT3497/WO29217/data_analysis/Final_CSR/prod/program/ah_sa2003_t_saf_lvef_ov.sas. Output: root/clinical_studies/RO4368451/CDPT3497/WO29217/data_analysis/Final_CSR/prod/output/ah_sa2003_t_saf_lvef_ov_SIGDL_SE.out 18MAR2021 14:33.

## Table 19 Cardiac Events, LVD/EFD and LVEF Declines with Confidence Intervals in the NEOSPHERE, TRYPHAENA, APHINITY, BERENICE, CLEOPATRA and PERUSE Studies

### Early Breast Cancer

| Safety Parameter | Patients Experiencing Event | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | NEOSPHERE (overall treatment period) | | | | TRYPHAENA (overall treatment period) | | | APHINITY (overall treatment period) | | BERENICE (overall study period) | |
| | H+D n=107 | Ptz+H+D n=107 | Ptz+H n=108 | Ptz+D n=94 | Ptz+H+FEC/ Ptz+ H+D n= 72 | FEC/ Ptz+H+D n=75 | Ptz+TCH n=76 | Ptz+H+ Chemo n=2364 | Pla+H+Chemo n=2405 | ddAC, T+PH n=199 | FEC, D+PH n=198 |
| **Cardiac Disorder AE**[a] | | | | | | | | | | | |
| Incidence (% pts) | 7.5 | 20.6 | 14.8 | 12.8 | 15.3 | 16.0 | 21.1 | 11.4 | 10.6 | 18.6 | 13.1 |
| 95% CI | 3.3;14.2 | 13.4;29.5 | 8.7;22.9 | 6.8;21.2 | 7.9;25.7 | 8.6;26.3 | 12.5;31.9 | 10.1; 12.7 | 9.4; 11.9 | 13.4;24.7 | 8.8;18.6 |
| **LVD/EFD/CF**[b] | | | | | | | | | | | |
| Incidence (% pts) | 1.9 | 7.5 | 0.9 | 5.3 | 8.3 | 9.3 | 6.6 | 6.4[d] | 6.8[d] | 15.1 | 14.1 |
| 95% CI | 0.2;6.6 | 3.3;14.2 | 0.0;5.1 | 1.7;12.0 | 3.1;17.3 | 3.8;18.3 | 2.2;14.7 | 5.4; 7.5 | 5.8; 7.9 | 10.4;20.8 | 9.6; 19.8 |
| **LVEF Decline**[c] | | | | | | | | | | | |
| Incidence (% pts) | 1.9 | 8.4 | 0.9 | 7.4 | 6.9 | 14.7 | 10.5 | 5.7[e] | 7.0[e] | 13.6 | 12.1 |
| 95% CI | 0.2;6.6 | 3.9;15.4 | 0.0;5.1 | 3.0;14.7 | 2.3;15.5 | 7.6;24.7 | 4.7;19.7 | 4.8; 6.7 | 6.0; 8.1 | 9.1;19.1 | 7.9;17.5 |

## Table 19 Cardiac Events, LVD/EFD and LVEF Declines with Confidence Intervals in the NEOSPHERE, TRYPHAENA, APHINITY, BERENICE, CLEOPATRA and PERUSE Studies (cont.)

### Metastatic Breast Cancer

| Safety Parameter | Patients Experiencing Event | | |
|---|---|---|---|
| | CLEOPATRA (overall treatment period) | | PERUSE |
| | Ptz+H+D n=408 | Pla+H+D n=396 | Ptz+H+Taxane N=1436 |
| **Cardiac Disorder AE[a]** | | | |
| Incidence (% pts) | 17.9 | 17.4 | 15.2 |
| 95% CI | 13.4;20.9 | 13.8;21.5 | 13.4, 17.1 |
| **LVD[b]** | | | |
| Incidence (% pts) | 7.8 | 8.6 | 13.6 |
| 95% CI | 4.4;9.5 | 6.0;11.8 | 11.9, 15.5 |
| **LVEF Decline[c]** | | | |
| Incidence (% pts) | 7.1 | 7.4 | 9.4 |
| 95% CI | 4.2;9.2 | 5.2;10.6 | 7.9, 11.0 |

AE = adverse event; EFD = ejection fraction decrease; FEC= 5 fluorouracil, epirubicin and cyclophosphamide; LVEF = left ventricular ejection fraction; LVD = left ventricular dysfunction; Pla+H+D=placebo+Herceptin+docetaxel; Ptz+H+D= Perjeta+Herceptin+docetaxel; TCH=docetaxel (Taxotere), carboplatin, Herceptin. ddAC= dose-dense doxorubicin and cyclophosphamide, T+PH=paclitaxel+Perjeta+Herceptin, FEC=5-fluorouracil, epirubicin, cyclophosphamide, D+PH=docetaxel+ Perjeta+Herceptin [a] Any AE in the Cardiac Disorder SOC.

[a] Incidence of any cardiac events where the SOC of the reported AE is 'Cardiac Disorders' - treatment period only. For BERENICE, data included the overall study period.

[b] Incidence of any LVD event where the reported AE preferred term is 'Left Ventricular Dysfunction' - treatment period only. For NEOSPHERE, the preferred term 'Cardiac Failure Congestive' was also included. For APHINITY the incidence is based only on the PTs 'cardiac failure and 'ejection fraction decreased' due to changes in MedDRA coding. For BERENICE the incidence is based on selected AE 'heart failure' and PT 'ejection fraction decreased'.

[c] Incidence of any significant LVEF declines where LVEF $< 50\%$ and $\geq 10\%$ decrease from baseline - including treatment-free follow-up period. The reporting period is different to that given for LVEF declines in the previous table.

[d] Based on PTs 'cardiac failure' and 'ejection fraction decreased'.

[e] Rate for the whole study period, not just the treatment period.

## Table 19 Cardiac Events, LVD/EFD and LVEF Declines with Confidence Intervals in the NEOSPHERE, TRYPHAENA, APHINITY, BERENICE, CLEOPATRA and PERUSE Studies (cont.)

Source: Table 64 in the Summary of Clinical Safety (neoadjuvant); APHINITY Primary CSR, t_ae_TRT1A_SE, t_ae_TRT1A_CFEFD_SE and t_saf_lvefc_TRT1A_SE and Tables 25, 26 and 30 of CLEOPATRA Final CSR. Data cut off dates: WO20697 NEOSPHERE (09 March 2012), BO22280/TRYPHAENA (04 July 2012), APHINITY (19 Dec 2016) and WO20698 CLEOPATRA (23 Nov 2018),
ROCHE\PERTUZUMAB\XSA84478_QSTR\BIOSTATISTICS\PRODUCTION\TABLES\ADHOC\T_AE_CARDIAC_CI_ADHOC.SAS] IQVIA 30APR2020. WO29217 BERENICE source: program: root/clinical_studies/RO4368451/CDPT3497/WO29217/data_analysis/Final_CSR/prod/program/ah_sa2003_t_ae_risks.sas, output: root/clinical_studies/RO4368451/CDPT3497/WO29217/data_analysis/Final_CSR/prod/output/ah_sa2003_t_ae_risks_SE.out 19Mar2021 12:52. Program: root/clinical_studies/RO4368451/CDPT3497/WO29217/data_analysis/Final_CSR/prod/program/ah_sa2003_t_saf_lvef_ov.sas. Output: root/clinical_studies/RO4368451/CDPT3497/WO29217/data_analysis/Final_CSR/prod/output/ah_sa2003_t_saf_lvef_ov_SIGDL_SE.out 18MAR2021 14:33.

**Severity and Nature of Risk:**

Cardiac dysfunction may manifest as an asymptomatic or mildly symptomatic decrease in LVEF (NCI CTCAE Grade 1 and Grade 2; NYHA Class I – II) or as a symptomatic decrease in LVEF/CHF (NCI CTCAE $\geq$ Grade 3; NYHA Class III or IV). In line with trastuzumab, a clinically relevant drop in LVEF has been defined as a decline $\geq$ 10%-points from baseline to an absolute value of $<$50% for Perjeta studies. However, the clinical importance of asymptomatic declines in LVEF is currently not known.

In the TRYPHAENA study, patients in Arm A received 5-fluorouracil, epirubicin, cyclophosphamide (FEC), Herceptin and Perjeta for three cycles, followed by docetaxel, Herceptin and Perjeta for three cycles (Ptz + H + FEC/Ptz + H + D); patients in Arm B received FEC for three cycles, followed by docetaxel, Herceptin and Perjeta for three cycles (FEC/Ptz + H + D); and patients in Arm C received Herceptin, carboplatin, docetaxel and Perjeta for six cycles (Ptz + TCH). During the post-treatment follow-up period, symptomatic left ventricular dysfunction (LVD) was observed in 1 patient in Arm B (no events were observed in Arms A and C). LVEF declines of at least 10%-points from baseline to below 50% were observed in 15 patients (5 in Arm A, 5 in Arm B, and 5 in Arm C), based on local and central data. At the end of the study, the LVEF measurements had improved to $\geq$ 50% in all but 4 patients: one symptomatic LVD patient who subsequently improved (this patient was asymptomatic at the last assessment with an LVEF of 47%) and 3 asymptomatic patients whose LVEF values were below 50% at the last assessment, based on either local or central readings.

In the APHINITY study, Grade $\geq$3 events of cardiac failure and ejection fraction decreased (EFD) were observed in 2.3% of patients in the Ptz + H + Chemo arm and in 2.0% of patients the Pla + H + Chemo arm. Note that a primary cardiac event (defined as either Heart Failure [NYHA Class III or IV] and a drop in LVEF of at least 10 EF points

from baseline AND to below 50%, or Cardiac Death) was reported in 0.7% of patients in the Ptz + H + Chemo arm and 0.3% of patients in the Pla + H + Chemo arm.

In the BERENICE study, the rates of cardiac toxicity during the overall study period were as expected in the two treatment arms:

- *Cohort A (ddAC → TPH):* NYHA Class III/IV heart failure incidence of 1.5% (n = 3 [95% CI: 0.31 – 4.34]) plus 2 patient with NYHA Class II heart failure.
- *Cohort B (FEC → DPH):* NYHA Class III/IV heart failure incidence of 1.0% (n=2 [95% CI: 0.12 – 3.60]) plus 1 patient with NYHA Class II heart failure.

The rates of declines in LVEF (of at least ≥10% points from baseline to a value of < 50%) as measured by echocardiography or MUGA were also as expected (13.6% [n = 27; 95% CI: 9.1 – 19.1] of patients in Cohort A and 12.1% [n = 24; 95% CI: 7.9 – 17.5] in Cohort B).The rates of asymptomatic LVEF decline (reported as an AE with the term 'ejection fraction decreased') were 13.6% (n = 27) of patients in Cohort A and 13.1% [n = 26] in Cohort B.

**Impact on quality of life:**

Cardiac failure may have a significant impact on the quality of life on individual patients and the presence of pre-existing risk factors or co-morbidities need to be taken into account when determining the benefit risk evaluation for individual patients.

Risk factors and risk groups:

Risk factors such as age of 60 years or older, prior chemotherapy, registration left ventricular ejection fraction (LVEF) less than 65%, hypertension and use of antihypertensive medications such as angiotensin-converting-enzyme inhibitor, angiotensin II receptor blockers and β-blockers were associated with an increased risk of cardiac events in patients with HER2-positive breast cancer (Russo et al, 2014; Anthony et al, 2015; Advani et al, 2015).

**Anthracycline exposure:** Risks for anthracycline-induced heart failure include cumulative dosage, age over 70 years, earlier or simultaneous radiation to the chest, concurrent treatment with other chemotherapeutic cardiotoxic agents, examples, taxanes, capecitabine or trastuzumab and pre-existing heart disease (Geiger et al, 2010; Fiuza 2009). The most important risk factor for late cardiac toxicity is reported as the cumulative anthracycline dose (Yeh et al, Keefe quoted in Senkus & Jassem 2011).

**Concurrent trastuzumab:** The cardiac changes associated with trastuzumab are mostly reversible, do not appear to be dose-related and do not involve histological changes in cardiac tissue. Identified risk factors include exposure to anthracyclines or paclitaxel, low LVEF at baseline, age > 60 years, obesity, previous heart disease and hypertension. Current monitoring of cardiac function uses changes in LVEF as a

reference for cardiotoxicity. Age, anthracycline exposure, and the presence of cardiovascular risk factors predicted cardiac AEs in trastuzumab recipients (Hudis, quoted in Guglin et al, 2009). No clear relation to a cumulative dose of trastuzumab has been described (Geiger et al, 2010). After treatment interruption, clinical and subclinical signs of heart failure are mostly reversible and reinitiating of trastuzumab after recovery is often well tolerated (Geiger et al, 2010).

**Adjuvant breast radiotherapy**: A relative increase of 30% in cardiac deaths was found in women treated with radiotherapy before the 1980s (Clark et al, quoted in Chargari et al, 2011). Among patients treated during 1973 – 82 and receiving radiotherapy, the cardiac mortality ratio (left vs. right tumor) was 1.58 (1.29-1.95) after 15 years or more and for patients diagnosed during 1993 – 2001, the cardiac mortality ratio was 0.96 (0.82-1.12) less than 10 years afterwards (Darby et al, quoted in Chargari et al, 2011). Internal mammary chain irradiation increases heart dose exposure particularly when outdated techniques are used or in patients with left-sided tumors, potentially translating into increased long-term heart disease (Chargari et al, 2011).

Preventability:

Careful monitoring and early detection of (asymptomatic) LVEF reduction from baseline is a reliable screening mechanism for the individual patient decisions to continue or stop treatment with anticancer agents in general (Geiger et al, 2010). All patients enrolled in Perjeta trials undergo routine cardiac monitoring by ECHO or MUGA scan.

Impact on the benefit-risk balance of the product:

The impact of congestive heart failure/left ventricular dysfunction on the benefit-risk balance of Perjeta is considered to be low. The incidence of CHF in patients receiving Perjeta, Herceptin and chemotherapy is low. Careful monitoring and following the dose management algorithm suggested in the product label further reduces the likelihood of a heart failure/left ventricular dysfunction event. The current pharmacovigilance plan and risk minimization measures in place are considered adequate to manage the risk.

Public health impact:

The potential public health impact of this safety concern is considered to be low because of the low frequency of CHF in patients with advanced malignancy receiving Perjeta, Herceptin and chemotherapy and because most cardiac events appear to be asymptomatic reversible declines in LVEF.

## 2. INFORMATION ON IMPORTANT POTENTIAL RISKS

### 2.1 OLIGOHYDRAMNIOS

MedDRA terms:

MedDRA PTs coded to SMQ Pregnancy and neonatal topics.

Potential mechanisms:

Pertuzumab-related embryo-fetal lethality, oligohydramnios, and microscopic evidence of delayed renal development occurred in an embryo-fetal study when pertuzumab was administered intravenously from GD 19 through GD50 to pregnant cynomolgus monkeys (the period of organogenesis in this species is GD20–50). In addition, consistent with fetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 30 mg/kg and 1 of 2 100 mg/kg), ventricular septal defects (1 of 6 30 mg/kg), thin ventricular wall 1 of 2 100 mg/kg) and minor skeletal defects (external - 3 of 6 30 mg/kg) were also noted. Systemic maternal and fetal exposure at clinically relevant pertuzumab concentrations, were confirmed.

The embryo-fetal effects observed with pertuzumab and trastuzumab are consistent with the role HER-family members play in the development and differentiation of ectodermal/epithelial tissues, including that of renal tissue (Bader et al, 2007).

Evidence source(s) and strength of evidence:

Non-clinical study in pregnant cynomolgus monkeys. Placental transfer of pertuzumab was confirmed in cynomolgus monkeys. Fetal to maternal pertuzumab serum concentration ratios were similar across a 10-fold range of doses at clinically relevant concentrations (20-fold greater than human clinical dose). Pertuzumab-related embryo-fetal lethality, oligohydramnios, and microscopic evidence of delayed renal development occurred in a study when pertuzumab was administered intravenously from GD19 through GD50 to pregnant cynomolgus monkeys, the period of organogenesis in this species (GD20 – 50). In addition, consistent with fetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 30 mg/kg and 1 of 2 100 mg/kg), ventricular septal defects (1 of 6 30 mg/kg), thin ventricular wall 1 of 2 100 mg/kg) and minor skeletal defects (external - 3 of 6 30 mg/kg) were also noted. Systemic maternal and fetal exposure at clinically relevant pertuzumab concentrations was confirmed.

No clinical studies have been performed in pregnant women.

Characterization of the risk:

**Background Incidence/Prevalence:**

There is no accepted standard definition for oligohydramnios. However, the incidence has been estimated as being between 0.4 and 1.7 % of pregnancies (Stoll et al, 1998; Alfirevic et al, 1997, Macharey et al, 2017). Stoll et al, (1998) reviewed 225,669 consecutive pregnancies births and concluded that 0.99/1000 pregnancies were complicated by oligohydramnios.

**Frequency with 95% CI:**

No events of oligohydramnios have been reported in patients receiving Perjeta in the MotHER pregnancy registry as of 31 January 2018 (cut-off date for the Final annual data summary [ADS] for this registry). Three patients exposed to Perjeta plus Herceptin enrolled in the registry; two patients had a live birth, and one patient was lost to follow-up).

Cumulatively, up to 7 June 2020 (data lock point for Perjeta PBRER Report 1101895, six initial cases of oligohydramnios were reported:

- AER PPD , normal baby girl delivered;
- AER PPD , pregnancy outcome: therapeutic abortion;
- AER PPD , pregnancy outcome: lost to follow-up;
- AER PPD , pregnancy outcome: therapeutic abortion;
- AER PPD , baby with congenital heart defect;
- AER PPD , no pregnancy.

One relevant follow-up case reported PT Amniotic fluid volume decreased (AER PPD ; pregnancy outcome not reported).

In addition, AEs were reported for 2 initial child cases: pulmonary hypoplasia (AER PPD premature delivery [thirty-fourth week of gestation) and atrial septic defect (AER PPD ; event outcome reported as resolved).

**Seriousness/Outcomes**

Oligohydramnios is associated with serious risks to fetal development. Perjeta-related embryo-fetal lethality, oligohydramnios, and microscopic evidence of delayed renal development were observed in cynomolgus monkeys. Further clinical complications of oligohydramnios could include renal and pulmonary hypoplasia (which could be lethal) and skeletal malformations due to intrauterine growth restriction.

No cases of oligohydramnios have been reported in patients receiving Perjeta in the MotHER pregnancy registry, which includes both clinical and post-marketing cases as of

31 January 2018 (cut-off date for the Final ADS for this registry). Three patients exposed to Perjeta plus Herceptin have enrolled in the registry. Of these, two patients had a live birth; no specific SAE has been reported for these patients. One patient was lost to follow-up.

A summary of the seven initial cases of oligohydramnios and AEs reported for 2 initial child cases reported cumulatively up to 7 June 2020 (data lock point for Perjeta PBRER Report 1101895) is presented above.

In conclusion, the available data are consistent with the known information in the Perjeta SmPC.

Events with a fatal outcome in clinical trials: No events of fatal oligohydramnios have been reported in patients receiving Perjeta.

**Severity and Nature of Risk:**

Oligohydramnios is classified as a potential risk based on non-clinical data and because cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving trastuzumab and because of findings in non-clinical studies. No events of oligohydramnios have been reported in patients receiving Perjeta.

**Impact on quality of life:**

Oligohydramnios is associated with serious risks to fetal development and therefore may have a significant impact on an individual patient. Women of childbearing potential are advised to use effective contraceptive measures during treatment and for 7 months after the last dose of Perjeta.

The need to avoid pregnancy during and for 7 months after Perjeta treatment may affect patients' quality of life. However, patients are likely to face the same restrictions even if Perjeta were not given, since most treatment for breast cancer (chemotherapy, Herceptin, hormone therapy and radiotherapy) are associated with significant risks to the developing fetus.

<u>Risk factors and risk groups:</u>

Premenopausal women of childbearing potential are at risk of this complication if they become pregnant during treatment. Since the median age at diagnosis of HER2-positive breast cancer is the mid-50s, at least half the patients likely to receive Perjeta treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the antiproliferative effects of

chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur.

Opioid abuse or dependence during pregnancy markedly increased the odds of oligohydramnios (Maeda et al, 2014). Pregnant women with sickle cell disease are at increased risk of oligohydramnios (Kuo and Caughey 2016). Primiparity is associated with an increased rate of oligohydramnios (Wielgos et al, 2015).

Preventability:

The risk of oligohydramnios is avoidable providing effective contraceptive measures are applied by women of childbearing potential during treatment and for 7 months after the last dose of Perjeta in combination with Herceptin.

Impact on the benefit-risk balance of the product:

Current pharmacovigilance plan and risk minimization measures in place are considered adequate to manage the risk.

Public health impact:

The public health impact associated with this safety concern is considered to be low. Pregnancies are usually contraindicated in patients with advanced malignancy due to the risks of cytotoxic drugs, hormone therapy and/or radiotherapy, as well as the limited life expectancy of the mother.

## 2.2 RISK IN FERTILITY IN HUMANS

MedDRA terms:

MedDRA HLT Fertility analyses, Sexual function and fertility disorders NEC.

Potential mechanisms:

There is no known mechanism for the risk in fertility in humans as a result of treatment with Perjeta. No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab on fertility. Only very limited data are available from repeat-dose toxicity studies with respect to the risk for adverse effects on the male reproductive system. No adverse effects were observed in sexually mature female cynomolgus monkeys exposed to pertuzumab. However, a non-clinical reproductivity study in cynomolgus monkeys showed embryo/fetal losses, oligohydramnios, delayed renal

development (renal hypoplasia) and intrauterine death with a dose-related increase in incidence and severity.

Evidence source(s) and strength of evidence:

No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab.

The Roche Global Safety Database has been reviewed for any cases of risk in fertility in humans or fertility disorders.

Characterization of the risk:

**Frequency with 95% CI:**

Cumulatively, no cases of the risk in fertility in humans or fertility disorders have been reported to the Roche global safety database (up to 3 May 2017).

**Seriousness/Outcomes**

Cumulatively, no cases of the risk in fertility in humans or fertility disorders have been reported to the Roche Global Safety Database (up to 3 May 2017).

SAEs of the risk in fertility in humans or fertility disorders in clinical trials: No SAEs of the risk in fertility in humans or or fertility disorders have been reported in patients receiving Perjeta in clinical trials.

**Severity and Nature of Risk:**

No cases of the risk in fertility in humans or fertility disorders have been reported in patients receiving Perjeta.

**Impact on quality of life:**

Attention to future fertility following diagnosis of breast cancer in younger patients who are pre-menopausal or of child-bearing age are extremely important. Both ESMO and ASCO guidelines recommend referral to a fertility specialist for women interested in preserving their fertility (Loren et al. 2013; Peccatori et al. 2013).

Standard options for fertility preservation such as embryo and oocyte cryopreservation or other treatments for fertility in patients who may develop fertility disorders may have an impact on the quality of life of the patient. However, younger women are more likely to present with a more advanced stage of disease and are also more likely to develop more aggressive subtypes of breast cancer (including HER2-positive breast cancer) and have lower survival rates compared to older women. Therefore, it is more likely that the benefit of treatment for the underlying disease outweighs the impact in younger women.

Risk factors and risk groups:

The median age at diagnosis of HER2-positive breast cancer is the mid-50s, therefore at least half the patients likely to receive Perjeta treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the anti-proliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur.

Preventability:

Currently there is no data of risk of fertility in humans following the use of Perjeta. Perjeta labelling indicates that women of child bearing potential and female partners of male patients of child bearing potential should use effective contraception while receiving Perjeta and for 6 months following the last dose of Perjeta. Chemotherapies are likely to reduce the chances of conception, implantation and embryogenesis and clinical guidelines recommend referral to a fertility specialist for women of childbearing potential with breast cancer interested in preserving their fertility (Loren et al. 2013; Peccatori et al. 2013).

Impact on the benefit-risk balance of the product:

Current routine risk minimization measures in place recommend avoidance of pregnancy during the use of Perjeta.

Public health impact:

The public health impact associated with this safety concern is considered to be low since to date there is no indication of the risk in fertility in humans following the use of Perjeta.

## 2.3 RISK IN PATIENTS AGED 75 YEARS OR OLDER

MedDRA terms:

Not applicable.

Potential mechanisms:

The elderly population is more susceptible to AEs, including those related to their co-morbidities.

Evidence source(s) and strength of evidence:

Adults were not excluded from participating in Perjeta trials on the grounds of age if they met the other eligibility criteria (i.e., no upper age limit was applied). No dedicated PK studies were performed in elderly patients. No Perjeta dose adjustment is required for adult patients of any age, including patients aged 65 years or older.

Characterization of the risk:

**Background Incidence/Prevalence:**

A considerable number of older patients have now been treated in Perjeta clinical trials. No upper age limit was applied and adult patients of any age could enter the trials if they met the other eligibility criteria. The relative lack of patients in the ≥75 year age category likely reflects the higher incidence of comorbidities (such as cardiac failure or renal impairment) in older patients and concerns about administration of chemotherapy to elderly patients. A total of 464 patients aged ≥65 years have been evaluated in key Perjeta clinical studies, including 47 patients aged ≥75 years (~10% of patients aged ≥65 years) (Table 20). An estimated cumulative total of 75,800 patients aged ≥65 years have received Perjeta in routine clinical practice (Table 12), and assuming a similar ratio to that seen in clinical trials, approximately 7,500 of these patients may have been aged ≥75 years.

**Table 20 Number of Patients Aged ≥65 years and ≥75 years Exposed to Perjeta by Study**

| Study number (Study name) | Aged ≥65 years | Aged ≥75 years |
|---|---|---|
| BO22280 (TRYPHAENA) | 26 | 4 |
| BO25126 (APHINITY) | 302 | 30 |
| WO20697 (NEOSPHERE) | 22 | 2 |
| WO20698 (CLEOPATRA) | 68 | 5 |
| WO29217 (BERENICE) | 46 | 6 |
| MO28047 (PERUSE) | 269 | Not available |
| **Total** | **733** | **47** |

| Study number (Study name) | Aged ≥65 years | Aged ≥75 years |
|---|---|---|

Source: BO22280 (TRYPHAENA, Primary CSR [Report 1046609; May 2012]); BO25126 (APHINITY, Primary CSR [Report 1075429, July 2017]); WO20697 (NEOSPHERE Primary CSR [Report 1032196; June 2011]); WO20698 (CLEOPATRA Primary CSR [Report 1046288; October 2011]); WO29217 (BERENICE Primary CSR [Report 1070920; December 2016])and Final CSR Study MO28047, (PERUSE) [Report 1101598;July 2020]

**Seriousness/Outcomes**

Analyses have been conducted comparing the safety of Perjeta in patients aged 65 – 75 years and adult patients aged below 65 years. To date, no significant differences in safety of Perjeta have been observed between elderly patients aged 65 – 75 years and patients aged below 65 years, with the exception of decreased appetite, anaemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesemia and diarrhea which had at least 5% higher in patients aged 65 years of age or higher, compared to patients aged less than 65 years of age. There are no distinct biological differences between patients aged 65 – 75 years and patients aged ≥ 75 years, and patients in these two age categories are likely to show considerable overlap in biological characteristics such as cardiac, renal and hepatic function, performance status and presence of comorbidities.

**Severity and nature of risk**

Accordingly, no differences in safety of Perjeta are expected for patients aged ≥ 75 years compared to patients aged 65 – 75 years. Also, as reported in the current Perjeta PBRER (reporting interval: 8 June 2019 to 7 June 2020), no meaningful increase in frequency, severity or specificity or a pattern of the reported events in patients aged 75 years and older was observed during the reporting interval. Subgroup analyses of efficacy based on age groups have also been conducted in all the key Perjeta studies, and no differences in efficacy have been observed.

**Impact on quality of life**

Not applicable.

Risk factors and risk groups:

Patients aged ≥ 75 years.

Preventability:

In elderly patients (≥ 65 years), diarrhea has been observed at a higher rate (increased risk of diarrhea in elderly patients is already included in Perjeta product label). Early intervention with loperamide, fluids and electrolyte replacement should be considered, particularly in elderly patients.

Impact on the benefit-risk balance of the product:

The impact of the risk of use of Perjeta in patients 75 years or older on the overall benefit-risk balance of the product is considered low. Age-related information is already included in the product label for Perjeta, notably the warning about increased risk of diarrhea in elderly patients. Current pharmacovigilance plan and risk minimization measures in place are considered adequate to manage the risk.

Public health impact:

The potential public health impact of Perjeta-related AEs in patients aged 75 years or older is considered low, due to the small number of these patients receiving Perjeta. The event of diarrhea which is seen at a higher rate in these patients is manageable with treatment.

## 2.4 LACK OF EFFICACY DUE TO IMMUNOGENICITY

MedDRA terms:

PTs Neutralising antibodies; neutralising antibodies positive; Drug specific antibody present.

Potential mechanisms:

The production of ADAs is considered to occur via well-understood humoral responses to foreign antigens, namely coordination between antigen presenting cells, T-helper cells and B-cells.

Nearly all biopharmaceuticals may induce antibodies by various mechanisms, however, the frequency of these antibodies and the clinical impact, if any, varies widely (Schellekens 2003). The mechanisms by which ADAs may impact efficacy include increased clearance of ADA/drug immune complexes thereby lowering drug exposure, as well as directly interfering with drug/target interactions (so-called neutralizing ADA).

Evidence source(s) and strength of evidence:

The immunogenicity of pertuzumab has been assessed in pertuzumab clinical trials by evaluating the incidence of ADAs to pertuzumab at baseline and following exposure to pertuzumab and a low incidence of ADA formation has been observed (2.4% in all studies to date).

Characterization of the risk:

**Background Incidence/Prevalence:**

The immunogenicity of pertuzumab has been assessed in many clinical trials by evaluating the incidence of ADAs to pertuzumab at baseline and following exposure to pertuzumab. ADA data available for Perjeta-treated patients in Phase I/II and Phase III studies are summarized in Table 21 and Table 22, respectively.

The incidence of ADA in the Phase I/II studies was lower (0.5%) than in the Phase III studies (2.9%) but the duration of therapy/observation was relatively short, reflecting the Phase I/II patient populations (which generally include patients with advanced refractory disease after failure of standard therapies) and the inclusion of patients with tumor types now known not to respond to Perjeta-based therapy.

## Table 21 Summary of ADA Data for Perjeta-Treated Patients in Phase I /II Studies

| Study Number | Study Phase | Number of Patients with Evaluable ADA Result [a] | Number of Patients with Positive ADA Response [b] |
|---|---|---|---|
| TOC2297g | I | 17 | 0 |
| JO17076 | I | 18 | 0 |
| WO20024 | I | 8 | 0 |
| BO16934 | II | 61 | 0 |
| TOC2682g | II | 31 | 0 |
| BO17004 | II | 59 | 0 |
| BO17931 | II | 46 | 1 |
| TOC2689g | II | 72 | 0 |
| TOC3258g | II | 26 | 0 |
| TOC2572g | II | 27 | 1 |
| TOC2664g | II | 1 | 0 |
| **Total** | | 366 | 2 |

[a] Number of patients with at least one post-dose (post− Perjeta treatment) ADA time point available for analysis.

[b] Number of patients who had a positive, confirmed ADA sample after Perjeta treatment.

## Table 22 Summary of ADA Data for Perjeta-Treated Patients in Phase III Studies

| Study Number (Study Name) | Indication | Incidence of ADA to date[a], Number of Patients (%) |
|---|---|---|
| WO20698 (CLEOPATRA) | First-line HER2-Positive Metastatic Breast Cancer | 21/390 (5.4%) |
| MO28113 (PENELOPE) | Recurrent platinum-resistant epithelial ovarian cancer with low HER3 mRNA expression | 4/63 (6.3%) |
| BO25114 (JACOB) | First-line HER2-positive metastatic gastric cancer | 2/347 (0.6%) |
| WO29217 (BERENICE) | Locally advanced, inflammatory, or early-stage HER2-positive breast cancer | 16/392 (4.1%) |
| **Total** | | 35/1191 (2.9%) |

| Study Number (Study Name) | Indication | Incidence of ADA to date[a], Number of Patients (%) |
|---|---|---|

[a] CSRs reporting the most recent ADA data available.

Source: WO20698 (CLEOPATRA Final CSR [Report 1092200; September 2019]); MO28113 (PENELOPE Final CSR [February 2017]); BO25114 (JACOB Primary CSR [Report 1078586; 1078586]); WO29217 (BERENICE Update CSR [Report 1077424]).

**Seriousness/Outcomes**

ADAs were extensively evaluated in the pivotal CLEOPATRA study in patients with metastatic breast cancer. Post-hoc exploratory analyses of the effects of ADAs on key efficacy parameters were also conducted (Primary CSR [Report 1046288; October 2011]). Exploratory analyses of independent review facility-assessed progression-free survival (IRF-assessed PFS) in Perjeta-treated patients with at least one post-baseline positive ADA assessment indicated shorter IRF-assessed PFS in comparison with IRF-assessed PFS in the overall intent-to-treat (ITT) population. The median PFS was 12.5 months (95% CI: 2; 14) for Perjeta-treated patients in the ADA positive subgroup, which was consistent with results of the ITT population in the control arm (12.4 months [95% CI: 10; 13]), whereas the median PFS for the Perjeta-treated/ADA negative subgroup was 18.7 months (95% CI: 16; 25). Overall response rate (ORR) was also lower in Perjeta-treated patients with ADA-positive samples than in the Perjeta-treated patients who were ADA-negative (ORR 45.5% [95% CI: 16.7; 76.6] vs. 80.2% [95% CI: 77.1; 85.7], respectively). However, these results should be viewed with caution since a low number of patients tested positive for ADA and the CIs were wide for PFS and ORR in the ADA positive subgroup. In addition, examination of individual IRF-assessed PFS data for each patient revealed that several of the patients with a positive ADA response receiving Perjeta treatment achieved prolonged disease control and there was no clear temporal association between development of a positive ADA response and IRF-assessed progressive disease.

In the BERENICE study, the incidence of ADAs at the time of primary analysis was considered too low (1/383 [0.3%]) to conduct efficacy analyses in the subgroup of patients determined to be positive for ADAs, however, the patient was determined to have achieved pCR. At the latest clinical cut-off date, 16/392 [4.1%] patients were positive for ADAs, however, there were no updates to efficacy endpoints in the study, and therefore, the impact of ADA to efficacy was not assessed at the time. In the other two studies (PENELOPE and JACOB), which were conducted in patients with ovarian cancer and gastric cancer respectively, there was insufficient evidence of Perjeta efficacy in the study overall (ITT population) to warrant subgroup analyses of efficacy based on ADA status. In addition, the number and/or frequency of ADAs were too low in these studies to warrant evaluation of efficacy in the subgroup of patients who developed ADA. However, 2 (of 2) patients in the JACOB study with ADAs achieved a partial response to therapy with PFS and overall survival in the expected range,

suggesting that the presence of ADAs had no detrimental effect on efficacy in these 2 patients.

A search of the post-marketing data did not identify any cases of lack of efficacy due to reported ADA or immunogenicity from clinical and post-marketing sources (Perjeta PBRER [reporting interval: 8 June 2019 to 7 June 2020]). However, this is to be expected given that patients are rarely tested for ADAs outside of clinical trials.

**Severity and nature of risk**

The presence of ADA at baseline or post-baseline has not been found to be associated with hypersensitivity/anaphylaxis. Although cases of Grade 3 hypersensitivity reactions have been reported in patients with ADAs, most patients with ADAs do not develop severe reactions and have continued Perjeta treatment as planned.

The immunogenicity of Perjeta has now been assessed in more than 1500 Perjeta-treated patients in clinical trials. Based on data available to date, the incidence of ADA formation is low (~2.4%). ADA formation is also not generally associated with hypersensitivity reactions or anaphylaxis. Although an adverse effect of ADA formation on Perjeta efficacy cannot be excluded, other causes of treatment failure (inherent or acquired resistance to HER2-targeted therapy) are likely to be much more common. Further investigation of ADA formation in Perjeta clinical trials is not likely to yield significant new information or to change this conclusion.

**Impact on quality of life**

The impact of lack of efficacy due to immunogenicity on quality of life is considered low.

Risk factors and risk groups:

Risk factors for the development of ADAs have been described in various regulatory guidance documents and industry white papers (EMEA 2007; Koren et al. 2008; FDA 2014), and includes genetic factors, patient immune status, and concomitant medications. However, there is currently no way to predict which patients will generate ADAs and of these which (if any) will lose drug benefits as a result.

Preventability:

Based on data available to date, the incidence of ADA formation is low (~2.4%). When ADAs are detected, they are often transient and titers also tend to be low, and are not generally associated with hypersensitivity reactions or anaphylaxis. Although an adverse effect of ADA formation of pertuzumab PK and/or efficacy cannot be excluded, other causes of treatment failure (inherent or acquired resistance to HER2-targeted therapy) are likely to be much more common. Further investigation of ADA formation in Perjeta clinical trials is not likely to yield significant new information or to change this conclusion. The low incidence of ADA formation in Perjeta-treated patients and the lack of apparent clinical consequences in most patients mean that ADA testing is unlikely to be introduced into routine clinical practice in the future. No additional pharmacovigilance or specific risk minimization measures are planned for patients receiving Perjeta.

Impact on the benefit-risk balance of the product:

The impact of the risk of lack of efficacy due to immunogenicity on the overall benefit-risk balance of the product is considered low given the risk factors cited above and because

of the low incidence of ADA formation observed to date. In particular, pertuzumab is a humanized monoclonal antibody with no endogenous counterpart is administered intravenously to cancer patients whose immune systems are generally suppressed, and does not have immunomodulatory activity further supporting its low immunogenic potential.

Public health impact:

The potential public health impact of lack of efficacy due to immunogenicity is considered low, due to the low incidence of ADA formation in Perjeta-treated patients.

## SVII.3.2. Presentation of the Missing Information

## 3. INFORMATION ON MISSING INFORMATION:

## 3.1 RISK IN PREGNANT OR LACTATING WOMEN

Evidence source:

Pregnant or lactating women were excluded from all Perjeta trials. A non-clinical reproductivity study in cynomolgus monkeys showed embryo/fetal losses, oligohydramnios, delayed renal development (renal hypoplasia) and intrauterine death with a dose-related increase in incidence and severity. These findings were consistent with evidence that antibodies can be transported across the placenta during the period of organogenesis in the cynomolgus monkey. Cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have also been reported in pregnant women receiving trastuzumab, which (like Perjeta) is an antibody that targets the HER2 receptor. Professional labeling documents indicate that Perjeta should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. Women of child bearing potential and female partners of male patients of child bearing potential should use effective contraception while receiving Perjeta and for 6 months following the last dose of Perjeta.

Because human IgG is secreted in human milk, and the potential for absorption and harm to the infant is unknown, a recommendation should be made to discontinue nursing during and after Perjeta treatment, taking into account the importance to the mother and the half-life of pertuzumab.

## PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

### Table 23 Summary of safety concerns

| Summary of safety concerns | |
|---|---|
| **Important identified risks** | Infusion-related reactions, Hypersensitivity reactions / anaphylaxis<br>Congestive heart failure / Left ventricular dysfunction |
| **Important potential risks** | Oligohydramnios*<br>Risk in fertility in humans<br>Risk in patients aged 75 years or older<br>Lack of efficacy due to immunogenicity |
| **Missing information** | Risk in pregnant or lactating women |

*Oligohydramnios has not been reported in patients treated with Perjeta but occurred in cynomolgus monkeys administered pertuzumab and in pregnant women treated with trastuzumab. Due to age, prior adjuvant treatment, concurrent chemotherapy, the advanced stage of disease and poor prognosis in the patient population, the MAH assesses the likelihood of pregnancies to be low.

## PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

### III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

**Specific adverse reaction follow-up questionnaires:**

- Guided Questionnaire – Pregnancy-Related Adverse Events

Oligohydramnios has been classified as an important potential risk for Perjeta. The guided questionnaire was implemented as part of the Global Enhanced Pharmacovigilance Pregnancy Program to request additional information on the mother's medical and obstetric history, the current pregnancy, fetal and infant condition, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life (Annex 4).

**Other forms of routine pharmacovigilance activities:**

Presentation of cumulative data in Periodic Safety Update Reports (PSURs) for the following risks:

- Infusion-related reactions, Hypersensitivity reactions/anaphylaxis
- Congestive heart failure/Left ventricular dysfunction
- Patients aged 75 years or older
- Lack of efficacy due to immunogenicity

Global Enhanced Pharmacovigilance Pregnancy Program for safety concern:

- Oligohydramnios

- Risk in fertility in humans
- Risk in pregnant or lactating women.

The Roche standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

- Cumulative data will be presented in Periodic Safety Update Reports (PSURs)/PBRERs

## III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not Applicable

## III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

## Table 24 On-going and Planned Additional Pharmacovigilance Activities

| Study Status | Summary of Objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization | | | | |
| NA | NA | NA | NA | NA |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances | | | | |
| NA | NA | NA | NA | NA |
| **Category 3** - Required additional pharmacovigilance activities | | | | |
| NA | NA | NA | NA | NA |

## PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

### Table 25 Planned and Ongoing post-authorization Imposed efficacy studies that are conditions of the marketing authorization or that are specific obligations

| Study Status | Summary of Objectives | Efficacy uncertainties addressed | Milestones | Due Date |
|---|---|---|---|---|
| **Efficacy studies which are conditions of the marketing authorization** | | | | |
| NA | NA | NA | NA | NA |
| **Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances** | | | | |
| BO25126 (APHINITY) | To provide long term efficacy data for Perjeta in the treatment of HER2-positive EBC | Long-term efficacy | Submission of final CSR | Within 12 months from the CCOD (~November 2024) |

CCOD=Clinical cutoff Date; CSR= Clinical study report, EBC=early breast cancer; NA=Not Applicable..

# PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

## V.1 ROUTINE RISK MINIMIZATION MEASURES

### Table 26 Description of Routine Risk Minimization Measures by Safety Concern

| Safety concern | Routine risk minimization activities |
|---|---|
| Infusion-related reactions, Hypersensitivity reactions/anaphylaxis | **Routine risk communication:**<br>Section 4.8 of the EU SmPC: Undesirable effects<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>In Section 4.4 of the EU SmPC, “Infusion reactions” and “Hypersensitivity reactions/anaphylaxis” part provides recommendations on risk management approach.<br>**Other risk minimization measures beyond the Product Information:**<br>None<br>**Medicine’s legal status:**<br>Legal Status: Perjeta is a prescription only medicine |
| Congestive heart failure / Left ventricular dysfunction | **Routine risk communication:**<br>Section 4.8 of the EU SmPC: Undesirable effects<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>In Section 4.2 of the EU SmPC, “Left ventricular dysfunction” part and Section 4.4 “Left ventricular dysfunction (including congestive heart failure)” provides recommendations on risk management approach.<br>**Other risk minimization measures beyond the Product Information:**<br>None<br>**Medicine’s legal status:**<br>Legal Status: Perjeta is a prescription only medicine |

| Safety concern | Routine risk minimization activities |
|---|---|
| Oligohydramnios | **Routine risk communication:**<br>Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>In Section 4.6 of the EU SmPC: “Fertility, pregnancy and lactation” part provides recommendations on risk management approach.<br>**Other risk minimization measures beyond the Product Information:**<br>None<br>**Medicine’s legal status:**<br>Legal Status: Perjeta is a prescription only medicine |
| Risk in fertility in humans | **Routine risk communication:**<br>Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>In Section 4.6 of the EU SmPC: “Fertility, pregnancy and lactation” part provides recommendations on risk management approach.<br>**Other risk minimization measures beyond the Product Information:**<br>None<br>**Medicine’s legal status:**<br>Legal Status: Perjeta is a prescription only medicine |
| Risk in patients aged ≥ 75 years | **Routine risk communication:**<br>Section 4.2 of the EU SmPC: “Elderly patients” part<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>In Section 4.4 “Diarrhoea” part provides recommendations on risk management approach.<br>**Other risk minimization measures beyond the Product Information:**<br>None |

| Safety concern | Routine risk minimization activities |
|---|---|
| | **Medicine's legal status:**<br>Legal Status: Perjeta is a prescription only medicine |
| Risk of lack of efficacy due to immunogenicity | **Routine risk communication:**<br>Section 5.1 of the EU SmPC: "Immunogenicity" part<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>None<br>**Other risk minimization measures beyond the Product Information:**<br>None<br>**Medicine's legal status:**<br>Legal Status: Perjeta is a prescription only medicine |
| Risk in pregnant or lactating women | **Routine risk communication:**<br>Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>In Section 4.6 of the EU SmPC: "Fertility, pregnancy and lactation" part provides recommendations on risk management approach.<br>**Other risk minimization measures beyond the Product Information:**<br>None<br>**Medicine's legal status:**<br>Legal Status: Perjeta is a prescription only medicine |

## V.2. ADDITIONAL RISK MINIMIZATION MEASURES

None

## V.3 SUMMARY OF RISK MINIMIZATION MEASURES

### Table 27 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| Infusion-related reactions, Hypersensitivity reactions/anaphylaxis | **Routine risk communication:**<br>Section 4.8 of the EU SmPC: Undesirable effects<br><br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>In Section 4.4 of the EU SmPC, “Infusion reactions” and “Hypersensitivity reactions/anaphylaxis” part provides recommendations on risk management approach.<br><br>**Other risk minimization measures beyond the Product Information:**<br><br>**Medicine’s legal status:**<br>Legal Status: Perjeta is a prescription only medicine<br><br>**Additional risk minimization measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>*Other forms of routine pharmacovigilance activities:*<br><br>Presentation of cumulative data in PSURs<br><br>**Additional pharmacovigilance activities:**<br>None |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| Congestive heart failure / Left ventricular dysfunction | **Routine risk communication:**<br>Section 4.8 of the EU SmPC: Undesirable effects<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>In Section 4.2 of the EU SmPC, "Left ventricular dysfunction" part and Section 4.4 "Left ventricular dysfunction (including congestive heart failure)" provides recommendations on risk management approach.<br>**Other risk minimization measures beyond the Product Information:**<br>**Medicine's legal status:**<br>Legal Status: Perjeta is a prescription only medicine<br>**Additional risk minimization measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>*Other forms of routine pharmacovigilance activities:*<br>Presentation of cumulative data in PSURs<br>**Additional pharmacovigilance activities:**<br>None |
| Oligohydramnios | **Routine risk communication:**<br>Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>In Section 4. 6 of the EU SmPC: "Fertility, pregnancy and lactation" part provides recommendations on risk management approach. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Global Enhanced Pharmacovigilance Pregnancy Program<br>**Additional pharmacovigilance activities:** None |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | **Other risk minimization measures beyond the Product Information:**<br>None<br>**Medicine's legal status:**<br>Legal Status: Perjeta is a prescription only medicine<br>**Additional risk minimization measures:**<br>None | |
| Risk in fertility in humans | **Routine risk communication:**<br>Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>In Section 4. 6 of the EU SmPC: "Fertility, pregnancy and lactation" part provides recommendations on risk management approach.<br>**Other risk minimization measures beyond the Product Information:**<br>None<br>**Medicine's legal status:**<br>Legal Status: Perjeta is a prescription only medicine<br>**Additional risk minimization measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Global Enhanced Pharmacovigilance Pregnancy Program<br>*Other forms of routine pharmacovigilance activities:*<br>Presentation of cumulative data in PSURs<br>**Additional pharmacovigilance activities:**<br>None |
| Risk in patients aged ≥ 75 years | **Routine risk communication:** | **Routine pharmacovigilance activities beyond adverse reactions reporting and** |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | Section 4.2 of the EU SmPC: "Elderly patients" part<br><br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br><br>In Section 4.4 "Diarrhoea" part provides recommendations on risk management approach.<br><br>**Other risk minimization measures beyond the Product Information:**<br><br>None<br><br>**Medicine's legal status:**<br><br>Legal Status: Perjeta is a prescription only medicine. | **signal detection:**<br><br>*Other forms of routine pharmacovigilance activities:*<br><br>Presentation of cumulative data in PSURs<br><br>**Additional pharmacovigilance activities:**<br>None |
| Risk of lack of efficacy due to immunogenicity | **Routine risk communication:**<br><br>Section 5.1 of the EU SmPC: Pharmacodynamic properties under Immunogenicity part<br><br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br><br>None<br><br>**Other risk minimization measures beyond the Product Information:**<br><br>None<br><br>**Medicine's legal status:**<br><br>Legal Status: Perjeta is a prescription only medicine | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>*Other forms of routine pharmacovigilance activities:*<br><br>Presentation of cumulative data in PSURs<br><br>**Additional pharmacovigilance activities:**<br>None |
| Risk in pregnant or lactating women | **Routine risk communication:**<br><br>Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | **Routine risk minimization activities recommending specific clinical measures to address the risk:**<br><br>In Section 4. 6 of the EU SmPC: "Fertility, pregnancy and lactation" part provides recommendations on risk management approach.<br><br>**Other risk minimization measures beyond the Product Information:**<br><br>None<br><br>**Medicine's legal status:**<br><br>Legal Status: Perjeta is a prescription only medicine<br><br>**Additional risk minimization measures:**<br><br>None | Global Enhanced Pharmacovigilance Pregnancy Program<br><br>*Other forms of routine pharmacovigilance activities:*<br><br>Presentation of cumulative data in PSURs<br><br>**Additional pharmacovigilance activities:**<br>None |

## REFERENCES


Advani PP, Ballman KV, Dockter TJ, Colon-Otero G, Perez EA. Long-term cardiac safety analysis of NCCTG N9831 (Alliance) adjuvant trastuzumab trial. Journal of clinical oncology. 2015 Sep 21;34(6):581-7. []

Alfirevic Z, Luckas M, Walkinshaw SA, McFarlane M, Curran R. A Randomized comparison between amniotic fluid index and maximum pool depth in the monitoring of post-term pregnancy. Br J Obstet Gynaecol 1997;104:207-211. [10250]

Anderson WF, Jatoi I, Tse J, Rosenberg PS. Male breast cancer: a population-based comparison with female breast cancer. Journal of Clinical Oncology. 2009 Dec 7;28(2):232-9. [11004]

Anthony FY, Yadav NU, Lung BY, Eaton AA, Thaler HT, Hudis CA, Dang CT, Steingart RM. Trastuzumab interruption and treatment-induced cardiotoxicity in early HER2-positive breast cancer. Breast Cancer Research and Treatment. 2015 Jan 1;149(2):489-95. [11005]

Bader AA, Schlembach D, Tamussino KF, Pristauz G, Petru E. Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. Lancet Oncology 2007 8(1) 79-81.[10066]

Barh D. Biomarkers, Critical Disease Pathways, Drug Targets, and alternative Medicine in Male Breast Cancer. Current Drug Targets, 2009, 10, 1-8.[10067]

Benson Jr, Jatoi I, Keisch M, Esteva FJ, Makris A, Jordan VC. Early breast cancer. Lancet 2009; 373:1463-79. [10074]

Blackwell KL et al, Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. JCO.2010;28:7:1124-1130. [10322]

Bleicher RJ, Ruth K, Sigurdson ER. Time to Surgery and Breast Cancer Survival in the United States. N Engl J Med. 2015 Dec 3;373(23):2203-14. [11057]

Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013 Mar 1;132(5):1133-45.

Burstein HJ, Harris LN, Gelman R et al, Preoperative Therapy with Trastuzumab and Paclitaxel Followed by Sequential Adjuvant Doxorubicin/ Cyclophosphamide for HER2 Overexpressing Stage II or III Breast Cancer: A Pilot Study. Journal Clinical Oncology 2003 21:46-53 [10083]

Cameron D, Piccart-Gebhart MJ, Gelber RD, et al, Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017; S0140-6736(16)32616-2. [10955]

Cancer Stat Facts: Female Breast Cancer. Surveillance, Epidemiology, and End Results Program, National Cancer Institute. Available from: https://seer.cancer.gov/statfacts/html/breast.html accessed on 17 July, 2017.

Capri G, Chang J, Chen SC, et al, An open-label expanded access study of lapatinib and capecitabine in patients with HER2-overexpressing locally advanced or metastatic breast cancer. Ann Oncol 2010; 21:474-80. [10090]

Carver JR. Management of trastuzumab-related cardiac dysfunction. Progress in cardiovascular diseases. 2010;53:130-9. [10094]

Chavez-MacGregor M, Clarke CA, Lichtensztajn DY. Delayed Initiation of Adjuvant Chemotherapy Among Patients With Breast Cancer. JAMA Oncol. 2016 Mar;2(3):322-9. [11059]

Chargari C, Kirov KM, Bollet MA at al. Cardiac toxicity in breast cancer patients: from a fractional point of view to a global assessment. Cancer Treat Rev. 2011 Jun;37(4):321-30.

Chia S, Norris B, Speers C, et al, Human epidermal growth factor receptor 2 overexpression as a prognostic factor in a large tissue microarray series of node-negative breast cancers. J Clin Oncol. 2008;26(35):5697-704. [10036]

Clarke C, Keega T, Yang J, et al. Age-specific incidence of breast cancer subtypes: understanding the Black-White crossover. Journal of the National Cancer Institute 2012;104:1094-1101.[10529]

Crabbe JC, Gregorio DI, Samociuk H, Swede H. Secular trends, race, and geographic disparity of early-stage breast cancer incidence: 25 years of surveillance in connecticut. American journal of public health. 2015 Jul;105(S3):e64-70. [11011]

Cronin KA, Harlan LC, Dodd KW, Abrams JS, Ballard-Barbash R. Population-based estimate of the prevalence of HER-2 positive breast cancer tumors for early stage patients in the US. Cancer investigation. 2010 Oct 1;28(9):963-8. [11055]

Crone SA et al, ErbB2 is essential in the prevention of dilated cardiomyopathy. Nature Medicine. 2002;8:5. [10285]

De Glas N, de Craen AJ, Bastiaannet E, Op't Land E, Kiderlen M, van de Water W, Siesling S, Portielje JE, Schuttevaer HM, de Bock GH, van de Velde CJ. Breast cancer screening in older women. Journal of Geriatric Oncology. 2014 Oct 1;5:S20-1. [11015]

EMEA. Committee for Medicinal Products for Human Use. Guideline on Immunogenicity Assessment of Biotechnology Derived Therapeutic Proteins. April 2007.

Esteva FJ, Valero V, Booser D et al, Phase II Study of Weekly Docetaxel and Trastuzumab for Patients With HER-2–Overexpressing Metastatic Breast Cancer. Journal Clinical Oncology 2002 20:1800-1808. [10121]

FDA. Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products. August 2014.

Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. Lancet 2006; 367:595-604.[10122]

Fiuza M. Cardiotoxicity associated with trastuzumab treatment of HER2+ breast cancer. Advances in Therapy 2009 26 (Suppl 1): S9-S17. [10246]

Geiger S. et al, Anticancer therapy induced cardiotoxicity: review of the literature, Anti-Cancer Drugs 2010, 21:578-590. [10247]

Guglin M, Hartlage G, Reynolds C et al, Trastuzumab-induced cardiomyopathy: Not as benign as it looks? A retrospective study. Journal of Cardiac Failure 2009; 15(8): 651-657. [10248]

Hennigs A, Riedel F, Gondos A et al, Prognosis of breast cancer molecular subtypes in routine clinical care: A large prospective cohort study. BMC Cancer. 2016 Sep 15;16(1):734. [11060]

Howlader N et al, SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site.

Howlader N, Noone AM, Krapcho M, et al SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016.

International Agency for Research on Cancer. Breast Cancer. 2018. https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf

Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States. Jama. 2015 Jan 13;313(2):165-73. [10896]

Iqbal J, Ginsburg O, Giannakeas V, Rochon PA, Semple JL, Narod SA. The impact of nodal micrometastasis on mortality among women with early-stage breast cancer. Breast Cancer Research and Treatment. 2017 Jan 1;161(1):103-15. [11020]

Johnston S, et al, Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for post-menopausal hormone-receptor positive metastatic breast cancer. J Clin Oncol 2009; 27(33): 5538-5546. [10527]

Köninki K, Tanner M, Auvinen A, Isola J. HER-2 positive breast cancer: decreasing proportion but stable incidence in Finnish population from 1982 to 2005. Breast Cancer Res 2009; 11:R37. [10150]

Koren E et al. Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products. J. Immunol. Methods, 2008; 333:1-9. [10694]

Kuo K, Caughey AB. Contemporary outcomes of sickle cell disease in pregnancy. American journal of Obstetrics and Gynecology. 2016 Oct 31;215(4):505-e1. [11025]

Kwan ML, Kushi LH, Weltzien E, Maring B, Kutner SE, Fulton RS, Lee MM, Ambrosone CB, Caan BJ. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. Breast Cancer Res. 2009;11(3):R31. [10632]

Lenz HJ. Management and Preparedness for Infusion and Hypersensitivity Reactions. The Oncologist 2007 12: 601-609. [10244]

Loren AW, Mangu PB, Beck LN et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013 Jul 1;31(19):2500-10. [11109]

Macharey G, Gissler M, Rahkonen L, et al, Breech presentation at term and associated obstetric risks factors-a nationwide population based cohort study. Arch Gynecol Obstet. 2017. [11047]

Maeda A, Bateman BT, Clancy CR, Creanga AA, Leffert LR. Opioid Abuse and Dependence during PregnancyTemporal Trends and Obstetrical Outcomes. The Journal of the American Society of Anesthesiologists. 2014 Dec 1;121(6):1158-65. [11030]

Mariotto AB, Etzioni R, Hurlbert M , et al, Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States. Cancer Epidemiol Biomarkers Prev. 2017 Jun;26(6):809-815. [11062]

Negro A et al, Essential roles of Her2/erbB2 in cardiac development and function. The Endocrine Society. 2004. [10308]

Neven P, Brouckaert O, Van Belle V, et al,, In early-stage breast cancer, the estrogen receptor interacts with correlation between human epidermal growth factor receptor 2 status and age at diagnosis, tumor grade, and lymph node involvement. J Clin Oncol. 2008 26(10):1768-9. [10635]

Nguyen PL, Taghian AG, Katz MS, Niemierko A, et al. Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol. 2008 May 10;26(14):2373-8. [11063]

O'Brien ME, Wigler N, Inbar M, et al, Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol 2004; 15:440-9. [10259]

Onami S, Ozaki M, Mortimer JE, Kumar Pal S. Male breast cancer: An update in diagnosis, treatment and molecular profiling. Review Article Maturitas 2010 65(4): 308-314 [10511]

Peccatori FA, Azim HA Jr, Orecchia R, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Oct;24 Suppl 6:vi160-70. [11111]

Perez EA, Romond EH, Suman VJ et al, Trastuzumab Plus Adjuvant Chemotherapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Planned Joint Analysis of Overall Survival From NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014;32(33):3744-52. [10831]

Piccart-Gebhart MJ, Holmes, AP & Baselga J et. al. First results from the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→ L), or their combination (T+L) in the adjuvant treatment of HER2-positive early breast cancer (EBC). J Clin Oncol 32:5s, 2014 (suppl; abstr LBA4). [10823]

Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 2009; 14:320-68. [10195]

Russo G, Cioffi G, Gori S, Tuccia F, Boccardi L, Khoury G, Lestuzzi C, Maurea N, Oliva S, Faggiano P, Tarantini L. Role of hypertension on new onset congestive heart failure in patients receiving trastuzumab therapy for breast cancer. Journal of cardiovascular medicine. 2014 Feb 1;15(2):141-6. [11037]

Rüschoff J, Lebeau A, Kreipe H, Sinn P, Gerharz CD, Koch W, Morris S, Ammann J, Untch M; Nicht-interventionelle Untersuchung (NIU) HER2 Study Group. Assessing HER2 testing quality in breast cancer: variables that influence HER2 positivity rate from a large, multicenter, observational study in Germany. Mod Pathol. 2017 Feb;30(2):217-226. [11045]

Sant M., Allemani C., Capocaccia R et al, Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. Int J Cancer, 2003; 106:416-22. [10583]

Schellekens H. Immunogenicity of therapeutic proteins. Nephrol Dial Transplant. 2003 Jul;18(7):1257-9.

Senkus E & Jassem J. Cardiovascular effects of systemic cancer treatment. Cancer Treatment Reviews 2011; 37: 300-311.[10326]

Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, Murphy M, Stewart SJ, Keefe D. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol. 2002 Mar 1;20(5):1215-21. [10204]

Slamon DJ, Leyland-Jones B, Shak S et al, Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. New England Journal of Medicine 2001 344 (11): 783-792. [10636]

Slamon D, Eiermann W, Robert NJ, et al, Ten year follow-up of the BCIRG-006 trial comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC®T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC®TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer patients. San Antonio Breast Cancer Symposium, 2015, abstract S5-04. [10963]

Smigal C, Jemal A, Ward E, et al, Trends in breast cancer by race and ethnicity: update 2006. CA Cancer J Clin 2006; 56:168-83. [10210]

Stoll C et al, Study of 224 Cases of Oligohydramnios and Congenital Malformations in a Series of 225,669 consecutive Births. Community Genet 1998;1:71–77. [10268]

Stortecky and Suter. Cancer drug-associated cardiovascular side-effects. Current Opinion in Oncology 2010, 22:312–317. [10265]

Swayer DB et al, Modulation of anthracycline-induced myofibrillar disarray in rat ventricular myocytes by neuregulin-1β and anti-erbB2. American Heart Association, Inc. 2002;105:1551-54. [10312]

Untch M, Loibl S, Bischoff J et al, Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a Randomized phase 3 trial. Lancet Oncol. 2012 Feb13; (2), 135-144. [10657]

Wielgos A, Szymusik I, Bartnik P, Kacperczyk J, Kosinska-Kaczynska K, Pietrzak B. Pregnancy beyond the age of 40–the influence of parity on perinatal outcome. Neuroendocrinology Letters. 2015 Jan 1;36(4). [11041]

Wolff AC, Hammond ME, Schwartz JN, et al, American Society of Clinical Oncology-College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007; 25(1): 118-145. [10573]

Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. Jama 2001; 285:885-92. [10235]

Zuppinger C, Suter TM. Cancer therapy-associated cardiotoxicity and signaling in the myocardium. Cardiovasc Pharmacol. 2010 56(2):141-6. [10242]

## PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

## SUMMARY OF RISK MANAGEMENT PLAN FOR PERJETA (PERTUZUMAB)

This is a summary of the risk management plan (RMP) for Perjeta. The RMP details important risks of Perjeta, how these risks can be minimized, and how more information will be obtained about Perjeta risks and uncertainties (missing information).

Perjeta's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Perjeta should be used.

This summary of the RMP for Perjeta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Perjeta RMP.

### I. THE MEDICINE AND WHAT IT IS USED FOR

Perjeta is authorized for Metastatic Breast Cancer as well as Neoadjuvant & Adjuvant Treatment of Early Breast Cancer (see SmPC for the full indication). It contains pertuzumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Perjeta benefits can be found in Perjeta's EPAR, including in its plain-language summary, available on the European Agency for the Evaluation of Medicinal Products (EMA) website, under the medicine's webpage.

### II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Perjeta, together with measures to minimize such risks and the proposed studies for learning more about Perjeta's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Perjeta is not yet available, it is listed under 'missing Information' below.

## II.A List of Important Risks and Missing Information

Important risks of Perjeta are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Perjeta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

| **List of important risks and missing information** | |
|---|---|
| **Important identified risks** | Infusion-related reactions, Hypersensitivity reactions / anaphylaxis<br>Congestive heart failure / Left ventricular dysfunction |
| **Important potential risks** | Oligohydramnios*<br>Risk in fertility in humans<br>Risk in patients aged 75 years or older<br>Lack of efficacy due to immunogenicity |
| **Missing information** | Risk in pregnant and lactating women |

*Oligohydramnios has not been reported in patients treated with pertuzumab but occurred in cynomolgus monkeys administered pertuzumab and in pregnant women treated with trastuzumab. Due to age, prior adjuvant treatment, concurrent chemotherapy, the advanced stage of disease and poor prognosis in the patient population, the MAH assesses the likelihood of pregnancies to be low.

## II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

| **Important Identified Risk-Infusion-related reactions, Hypersensitivity reactions/anaphylaxis** | |
|---|---|
| Evidence for linking the risk to the medicine | Randomized clinical trial data<br><br>Based on safety results from WO20698 (CLEOPATRA), WO20697 (NEOSPHERE), BO22280 (TRYPHAENA) and BO25126 (APHINITY) and MO28047 (PERUSE) |
| Risk factors and risk groups | There are currently no reliable predictors of patients who may or may not be susceptible to infusion-associated reactions, hypersensitivity or anaphylaxis to pertuzumab. Patients with a history of asthma, eczema or hay fever (atopy) had a slightly increased risk of developing an IRR (on the day of or the day after a pertuzumab infusion) than patients who did not have a history of atopy but the number of patients with a history of atopy was too small for any firm conclusions to be drawn. Moreover, patients with a history of atopy did not appear to be at increased risk of anaphylaxis or hypersensitivity reactions. Importantly, prior and concomitant trastuzumab exposure did not appear to reduce or exacerbate the infusion-associated events seen with pertuzumab.<br><br>*Anti-Drug Antibodies (ADA) in Study WO20698*<br><br>Serum samples were assayed for anti-drug antibodies (ADAs) to pertuzumab, also known as anti- therapeutic antibodies (ATAs) or human anti-human antibodies (HAHA). The incidence of ADA was calculated from the total number of patients who tested positive for ADA against pertuzumab after dosing, divided by the total number of patients who had post dose ADA samples available for the ADA analysis. A conservative approach was taken for calculating the incidence of ADA so that any patient confirmed to have an ADA positive sample after dosing was considered positive for ADA, regardless of baseline status.<br><br>Since trastuzumab and pertuzumab share the same framework structure, differing only in the complementarity determining region, it is possible that the positive ADA findings in patients treated with Pla+H+D were due to antibodies |

| Important Identified Risk-Infusion-related reactions, Hypersensitivity reactions/anaphylaxis | |
|---|---|
| | directed toward the common framework portion of pertuzumab and trastuzumab.<br><br>In Study WO20698, at the second clinical data cutoff (14 May 2012), 6.7% (25/372 patients) of placebo-treated patients and 3.3% (13/389 patients) of pertuzumab-treated patients tested positive for ADA. Of these 38 patients, none experienced anaphylactic/ hypersensitivity reaction was clearly related to the ADA. Patients with detectable ADA were able to continue study treatment, sometimes for prolonged periods. |
| Risk minimization measures | **Routine risk communication:**<br><br>Section 4.8 of the EU SmPC: Undesirable effects<br><br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br><br>In Section 4.4 of the EU SmPC, “Infusion reactions” and “Hypersensitivity reactions/anaphylaxis” part provides recommendations on risk management approach.<br><br>**Other risk minimization measures beyond the Product Information:**<br><br>**Medicine’s legal status:**<br><br>Legal Status: Perjeta is a prescription only medicine<br><br>**Additional risk minimization measures:**<br>None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br><br>None |

| Important Identified Risk - Congestive heart failure / Left ventricular dysfunction | |
|---|---|
| Evidence for linking the risk to the medicine | Clinical trial data<br><br>Based on safety results from WO20697 (NEOSPHERE), WO20698 (CLEOPATRA), BO22280 (TRYPHAENA), WO29217 (BERENICE),BO25126 (APHINITY)and MO28047 (PERUSE) |
| Risk factors and risk groups | Risk factors such as age of 60 years or older, prior chemotherapy, registration left ventricular ejection fraction (LVEF) less than 65%, hypertension and use of antihypertensive medications such as angiotensin-converting-enzyme inhibitor, angiotensin II receptor blockers and β-blockers were associated with an increased risk of cardiac events in patients with HER2-positive breast cancer (Russo et al 2014, Anthony et al 2015, Advani et al 2015).<br><br>**Anthracycline exposure:** Risks for anthracycline-induced heart failure include cumulative dosage, age over 70 years, earlier or simultaneous radiation to the chest, concurrent treatment with other chemotherapeutic cardiotoxic agents, examples, taxanes, capecitabine or trastuzumab and pre-existing heart disease (Geiger et al, 2010; Fiuza 2009). The most important risk factor for late cardiac toxicity is reported as the cumulative anthracycline dose (Yeh et al,, Keefe quoted in Senkus & Jassem 2011).<br><br>**Concurrent trastuzumab.** The cardiac changes associated with trastuzumab are mostly reversible, do not appear to be dose-related and do not involve histological changes in cardiac tissue. Identified risk factors include exposure to anthracyclines or paclitaxel, low LVEF at baseline, age > 60 years, obesity, previous heart disease and hypertension. Current monitoring of cardiac function uses changes in LVEF as a reference for cardiotoxicity. Age, anthracycline exposure, and the presence of cardiovascular risk factors predicted cardiac AEs in trastuzumab recipients (Hudis, quoted in Guglin et al 2009). No clear relation to a cumulative dose of trastuzumab has been described (Geiger et al, 2010). After treatment interruption, clinical and subclinical signs of heart failure are mostly reversible and reinitiating of trastuzumab after recovery is often well tolerated (Geiger et al, 2010). |

| Important Identified Risk - Congestive heart failure / Left ventricular dysfunction | |
|---|---|
| | **Adjuvant breast radiotherapy**: A relative increase of 30% in cardiac deaths was found in women treated with radiotherapy before the 1980s (Clark et al quoted in Chargari et al 2011). Among patients treated during 1973-82 and receiving radiotherapy, the cardiac mortality ratio (left vs. right tumor) was 1.58 (1.29-1.95) after 15 years or more and for patients diagnosed during 1993-2001, the cardiac mortality ratio was 0.96 (0.82-1.12) less than 10 years afterwards (Darby et al, quoted in Chargari et al 2011). Internal mammary chain irradiation increases heart dose exposure particularly when outdated techniques are used or in patients with left-sided tumors, potentially translating into increased long-term heart disease (Chargari et al 2011). |
| Risk minimization measures | **Routine risk communication:**<br><br>Section 4.8 of the EU SmPC: Undesirable effects<br><br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br><br>In Section 4.2 of the EU SmPC, “Left ventricular dysfunction” part and Section 4.4 “Left ventricular dysfunction (including congestive heart failure)” provides recommendations on risk management approach.<br><br>**Other risk minimization measures beyond the Product Information:**<br><br>**Medicine’s legal status:**<br><br>Legal Status: Perjeta is a prescription only medicine<br><br>**Additional risk minimization measures:**<br>None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br><br>None |

| Important potential risks - Oligohydramnios | |
|---|---|
| Evidence for linking the risk to the medicine | Non-clinical study in pregnant cynomolgus monkeys. Placental transfer of pertuzumab was confirmed in cynomolgus monkeys. Fetal to maternal pertuzumab serum concentration ratios were similar across a 10-fold range of doses at clinically relevant concentrations (20-fold greater than human clinical dose). Pertuzumab-related embryo-fetal lethality, oligohydramnios, and microscopic evidence of delayed renal development occurred in a study when pertuzumab was administered intravenously from Gestation Day 19 (GD19) through GD50 to pregnant cynomolgus monkeys, the period of organogenesis in this species (GD20＝50). In addition, consistent with fetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 30 mg/kg and 1 of 2 100 mg/kg), ventricular septal defects (1 of 6 30 mg/kg), thin ventricular wall 1 of 2 100 mg/kg) and minor skeletal defects (external - 3 of 6 30 mg/kg) were also noted. Systemic maternal and fetal exposure at clinically relevant pertuzumab concentrations was confirmed.<br><br>No clinical studies have been performed in pregnant women. |
| Risk factors and risk groups | Premenopausal women of childbearing potential are at risk of this complication if they become pregnant during treatment. Since the median age at diagnosis of HER2-positive breast cancer is the mid-50s, at least half the patients likely to receive pertuzumab treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the anti-proliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur. Opioid abuse or dependence during pregnancy markedly increased the odds of oligohydramnios (Maeda et al 2014). Pregnant women with sickle cell disease are at increased risk of oligohydramnios (Kuo and Caughey 2016). Primiparity is associated with an increased rate of oligohydramnios (Wielgos et al 2015). |

| Important potential risks - Oligohydramnios | |
|---|---|
| Risk minimization measures | **Routine risk communication:**<br>Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation<br>**Routine risk minimization activities recommending specific clinical measures to address the risk:**<br>In Section 4.6 of the EU SmPC: “Fertility, pregnancy and lactation part provides recommendations on risk management approach.<br>**Other risk minimization measures beyond the Product Information:**<br>**Medicine’s legal status:**<br>Legal Status: Perjeta is a prescription only medicine<br>**Additional risk minimization measures:**<br>None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None |

| Important potential risks – Risk in fertility in humans | |
|---|---|
| Evidence for linking the risk to the medicine | No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab.<br>The Roche Global Safety Database has been reviewed for any cases of risk in fertility in humans or fertility disorders. |
| Risk factors and risk groups | The median age at diagnosis of HER2-positive breast cancer is the mid-50s, therefore at least half the patients likely to receive Perjeta treatment are unlikely to become pregnant on the grounds of age alone. In addition, prior chemotherapy in the adjuvant setting and concurrent chemotherapy in the metastatic setting are likely to reduce the chances of conception, implantation and embryogenesis due to induction of a premature menopause and the anti-proliferative effects of chemotherapy. Finally, the advanced stage of disease and poor prognosis of patients with MBC make pregnancies less likely to occur. |

| Important potential risks – Risk in fertility in humans | |
|---|---|
| Risk minimization measures | **Other risk minimization measures beyond the Product Information:**<br>None<br>**Medicine's legal status:**<br>Legal Status: Perjeta is a prescription only medicine<br>**Additional risk minimization measures:**<br>None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None |

| Important potential risks – Risk in patients aged 75 years or older | |
|---|---|
| Evidence for linking the risk to the medicine | Adults were not excluded from participating in Perjeta trials on the grounds of age if they met the other eligibility criteria (i.e., no upper age limit was applied). No dedicated pharmacokinetcic studies were performed in elderly patients.<br>No Perjeta dose adjustment is required for adult patients of any age, including patients aged 65 years or older. |
| Risk factors and risk groups | Patients aged $\geq$ 75 years. |
| Risk minimization measures | **Other risk minimization measures beyond the Product Information:**<br>None<br>**Medicine's legal status:**<br>Legal Status: Perjeta is a prescription only medicine<br>**Additional risk minimization measures:**<br>None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None |

| Important potential risks – Lack of efficacy due to immunogenicity | |
|---|---|
| Evidence for linking the risk to the medicine | The immunogenicity of pertuzumab has been assessed in Perjeta clinical trials by evaluating the incidence of anti-drug antibodies (ADAs) to pertuzumab at baseline and following exposure to pertuzumab (or placebo), and a low incidence of ADA formation has been observed. |
| Risk factors and risk groups | Risk factors for the development of ADAs have been described in various regulatory guidance documents and industry white papers (EMEA 2007; Koren et al. 2008; FDA 2014). Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products, and include genetic factors, patient immune status, and concomitant medications. However, there is currently no way to predict which patients will generate ADAs and of these which will lose drug benefits as a result. |
| Risk minimization measures | **Other risk minimization measures beyond the Product Information:**<br>None<br>**Medicine's legal status:**<br>Legal Status: Perjeta is a prescription only medicine<br>**Additional risk minimization measures:**<br>None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None |

| Missing information – Risk in pregnant and lactating women | |
|---|---|
| Evidence for linking the risk to the medicine | Pregnant or lactating women were excluded from all Perjeta trials. A non-clinical reproductivity study in cynomolgus monkeys showed embryo/fetal losses, oligohydramnios, delayed renal development (renal hypoplasia) and intrauterine death with a dose-related increase in incidence and severity. These findings were consistent with evidence that antibodies can be transported across the placenta during the period of organogenesis in the cynomolgus monkey. Cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have also been reported in pregnant women receiving trastuzumab, which (like pertuzumab) is an |

| Missing information – Risk in pregnant and lactating women | |
|---|---|
| | antibody that targets the HER2 receptor. Professional labeling documents indicate that Perjeta should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. Women of child bearing potential and female partners of male patients of child bearing potential should use effective contraception while receiving Perjeta and for 6 months following the last dose of Perjeta.<br><br>Because human Immunglobulin G is secreted in human milk, and the potential for absorption and harm to the infant is unknown, a recommendation should be made to discontinue nursing during and after Perjeta treatment, taking into account the importance to the mother and the half-life of pertuzumab. |
| Risk minimization measures | **Other risk minimization measures beyond the Product Information:**<br>None<br>**Medicine's legal status:**<br>Legal Status: Perjeta is a prescription only medicine<br><br>**Additional risk minimization measures:**<br>None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None |

## II.C Post-authorization development plan

### II.C.1 Studies which are conditions of the marketing authorization

The following studies are conditions of the marketing authorization:

**Study short name: BO25126 (APHINITY)**

Purpose of the study: To provide long-term efficacy data for Perjeta in the treatment of HER2-positive EBC.

### II.C.2 Other studies in post-authorization development plan

There are no other studies in post-authorization development plan for Perjeta.

# ANNEX 4:

# SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

# ANNEX 4:

# SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

## Guided Questionnaire Pregnancy-Related Adverse Events

# Guided Questionnaire
# Pregnancy-Related Adverse Events

| | | | |
|---|---|---|---|
| AER: | | Local Case ID: | |
| Site No: | | Patient Date of Birth (dd-MMM-yyyy): | |
| Patient ID/Initials: | | Other Patient Identifiers | |
| Patient Gender: | ❑ M ❑ F | | |

Oligohydramnios, some associated with fatal pulmonary hypoplasia, and fetal renal impairment have been observed in some patients treated with Herceptin in the post-marketing setting. Oligohydramnios has been identified as an important identified risk for Herceptin, while for Perjeta and Kadcyla, oligohydramnios has been classified as an important potential risk.

*By filling out this questionnaire, you will help us to understand more fully the risk factors for this condition and associated abnormalities, to communicate potential adverse pregnancy complications and fetal/infant outcomes to Health Authorities, Healthcare Professionals and patients.*

| **Reporter Information** | |
|---|---|
| Name of reporter completing this form ***(if other than addressee, please provide contact information below)*:** | |
| Health Care Provider? ❑ Yes ❑ No - Please Specify: | |
| Phone number: | Fax number: |
| Email address: | |

☐ Drug: **Herceptin** Lot Number(s):_____
☐ Drug: **Perjeta** Lot Number(s):_____
☐ Drug: **Kadcyla** Lot Number(s):_____

## Maternal Information

| | **Selected Medical History** | | | Comment |
|---|---|---|---|---|
| ☐ | None | ☐ | Unknown | |
| ☐ | Hypertension | | | |
| ☐ | Diabetes; if yes, please, specify type | | | |
| ☐ | Seizure disorders | | | |
| ☐ | Thyroid disorder | | | |
| ☐ | Smoking / use of alcohol; specify | | | |
| ☐ | Family history of diabetes mellitus | | | |
| ☐ | Family history of congenital renal anomalies; if yes, please specify | | | |
| ☐ | Other; specify | | | |

| | **Selected Obstetric History (*previous pregnancies*)** | | | Please, provide specifics including contributing factors |
|---|---|---|---|---|
| ☐ | None | ☐ | Unknown | |
| ☐ | Gestational hypertension/preeclampsia/eclampsia | | | |
| ☐ | Gestational diabetes | | | |
| ☐ | Spontaneous or induced abortions; if yes and known, please specify cause | | | |
| ☐ | Oligohydramnios | | | |
| ☐ | History of other pregnancy complications; specify | | | |
| ☐ | Other; specify | | | |

# Guided Questionnaire
# Pregnancy-Related Adverse Events

| | Fetal Abnormalities in Previous Pregnancies | | Please, provide specifics including contributing factors |
|---|---|---|---|
| ☐ | None | ☐ Unknown | |
| ☐ | Delayed renal development | | |
| ☐ | Death in utero; if yes/known, specify reason | | |
| ☐ | Birth defects; if yes, specify | | |
| ☐ | Family history of birth defects; if yes, specify | | |
| ☐ | Other; specify | | |

## Current Pregnancy

| | | |
|---|---|---|
| Pre-pregnancy weight and height | Weight: | Height: |
| Blood pressure prior to conception | Date: | BP: |

**Prenatal Imaging and Aneuploidy Screening/testing** (e.g., ultrasound, amniocentesis, etc.)
Was a prenatal test performed? ☐ Yes ☐ No

| If yes, Prenatal Test Type | Date | Indication for test | Was a defect noted? | Specify |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

**Ultrasound Assessment Log**

| Date | Gestational Age | Amniotic Fluid (AF) Measurement | Provider's Assessment of AF | Estimated Fetal Weight | Reported Percentile Growth | Provider's Assessment of Growth |
|---|---|---|---|---|---|---|
| | _____ weeks | AF Index _____ cm<br>Maximum Vertical Pocket _____ cm<br>Other _____<br>☐ AF not measured | 1 Normal<br>2 Abnormal<br>3 Oligohydramnios<br>4 Anhydramnios<br>5 Polyhydramnios<br>6 Delayed renal development<br>7 Other: _____<br>8 Not assessed | _____ grams<br>☐ Not estimated | _____<br>☐ Not reported<br>☐ Growth not measured | ☐ Normal<br>☐ Abnormal<br>☐ IUGR* (< 10%ile)<br>☐ Severe IUGR (< 3%ile)<br>☐ Large for Gestational Age (> 90%ile)<br>☐ Growth not measured |
| | | | | | | |

* IUGR=Intrauterine growth retardation

# Guided Questionnaire
# Pregnancy-Related Adverse Events

| **Concomitant Medications**, including ACE inhibitors and prostaglandin synthase inhibitors and all known teratogens up to 6 months prior to conception or during pregnancy: | | | | |
|---|---|---|---|---|
| **Product Name** | **Indication** | **Total daily dose** | **Start date** | **Stop date/Ongoing** |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

| | **Maternal Medical Conditions During Current Pregnancy**<br>*Please check all that apply and provide detailed information on pregnancy-related complications on last page* | | | |
|---|---|---|---|---|
| ☐ | Gestational Hypertension/ Preeclampsia/Eclampsia<br>☐ chronic hypertension<br>☐ pregnancy-induced hypertension<br>☐ Preeclampsia-eclampsia<br>☐ Preeclampsia superimposed on chronic hypertension | Diagnostic tests: | Start date / Gestational age | Contributing factors |
| ☐ | Gestational Diabetes | Diagnostic tests: | Start date / Gestational age | Contributing factors |
| ☐ | Spontaneous or induced abortions; if yes/known, specify cause | Pathology results: | Start date / Gestational age | Contributing factors |
| ☐ | Chronic leakage of amniotic fluid | Start date / Gestational age | | Contributing factors |
| ☐ | Other; specify | Pathology results: | Start date / Gestational age | Contributing factors |
| | **Fetal Conditions During Current Pregnancy**<br>*Please check all that apply and provide detailed information on fetal complications on last page* | | | |
| ☐ | Renal abnormalities in fetus<br>☐ Normal fetal kidneys and fluid filled bladder<br>☐ Delayed renal development<br>☐ Renal agenesis<br>☐ Cystic dysplasia<br>☐ Ureteral obstruction | Diagnostic tests:<br>☐ Ultrasonography | Start date / Gestational age | Contributing factors |
| ☐ | Fetal abnormalities, including genetic disorders; if yes, specify | Diagnostic tests:<br>☐ Ultrasound<br>☐ Alpha-fetoprotein<br>☐ Amniocentesis<br>☐ Aneuploidy screening<br>☐ Other | Date / Gest. age | Specify |

# Guided Questionnaire
# Pregnancy-Related Adverse Events

| | | | | |
|---|---|---|---|---|
| ☐ | Post-maturity syndrome | Evidence: | Start date / Gestational age | Contributing factors |
| ☐ | Death in utero; if yes/known, specify reason | Pathology results: | Date / Gestational age | Contributing factors |
| ☐ | Other; specify | | | |

## Infant information

| | | | |
|---|---|---|---|
| Mode of birth | ☐ Spontaneous vaginal delivery<br>☐ Forceps / vacuum<br>☐ Cesarean section | Date | |
| Gestational age at birth | | Apgar score | |

*Please check all that apply and provide detailed information on complications in infants on last page*

| | Date of Assessment | | | Contributing factors |
|---|---|---|---|---|
| ☐ | Birth outcome | ☐ Live birth<br>☐ Neonatal death | Cause | |
| ☐ | Small for gestational age at birth (SGA) | ☐ Gestational age<br>☐ Weight/length | Date of assessment | |
| ☐ | Congenital anomalies | ☐ Major malformation<br>A defect that has either cosmetic or functional significance to the child | Specify | |
| | | ☐ Minor malformation<br>A defect that occurs infrequently but has neither cosmetic nor functional significance to the child | Specify | |
| | | ☐ Deformation<br>A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force) | Specify | |
| | | ☐ Disruption<br>A defect due to destruction of a structure, which has previously formed normally (may be of vascular, infectious, or mechanical origin) | Specify | |
| ☐ | Abnormal renal function | ☐ Proteinuria<br>☐ Electrolyte imbalance<br>☐ Other | Lab results | |
| ☐ | Other; specify | | | |

# Guided Questionnaire
# Pregnancy-Related Adverse Events

| FOR INTERNAL USE ONLY |
|---|
| Company Awareness Date: |
| MCN: |

**Completed by:**

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail: ..... Tel. No.: .....

**Contact name for further information on pregnancy and/or on the infant**:

Function ..... Tel. No.: .....

Contact Address: ..... Fax No.: .....

..... Email: .....

.....

# Guided Questionnaire
# Pregnancy-Related Adverse Events

## Detailed information on pregnancy-related complications

*Please enter text in dynamic box below:*

# ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (if applicable)

# ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

**Not Applicable**