PERJETA®

Konzentrat zur Herstellung einer Infusionslösung, Zul.-Nr. 62’510

Public Risk Management Plan (RMP) Summary

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicinal products. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of “Perjeta” is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of “Perjeta” in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. “Roche Pharma (Schweiz) AG” is fully responsible for the accuracy and correctness of the content of the published summary RMP of Perjeta.

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 MINIMIZE OR FURTHER CHARACTERIZE 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 Congestive heart failure / Left ventricular dysfunction
Important potential risks	Oligohydramnios* Risk in fertility in humans Risk in patients aged 75 years or older 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

Important Identified Risk-Infusion-related reactions, Hypersensitivity reactions/anaphylaxis	
Evidence for linking the risk to the medicine	Randomized clinical trial data 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. Anti-Drug Antibodies (ADA) in Study WO20698 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. 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 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 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:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** In Section 4.4 of the EU SmPC, "Infusion reactions" and "Hypersensitivity reactions/anaphylaxis" part provides recommendations on risk management approach. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important Identified Risk - Congestive heart failure / Left ventricular dysfunction	
Evidence for linking the risk to the medicine	Clinical trial data 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-convertingenzyme 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 preexisting 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).
Risk minimization measures	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** 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. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** 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. 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 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).

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

Risk minimization measures	**Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** 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. 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 ≥ 75 years.
Risk minimization measures	**Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** 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:** None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** 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 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 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:** None **Medicine's legal status:** Legal Status: Perjeta is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

II.C Post-Authorization Development Plan

II.C.1 Studies That Are Conditions of the Marketing Authorization

There are no studies required for Perjeta.

II.C.2 Other Studies in Post-Authorization Development Plan

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