Phesgo® (Pertuzumab/Trastuzumab) Injektionslösung (zur subkutanen Anwendung), 1200 mg/600 mg/15 ml; 600 mg/600 mg/10 ml Zul.-Nr. 67828

Public Risk Management Plan (RMP) Summary

Document Version 1.0
Document Date: 07.06.2021
Based on: EU-RMP Vers. 2.0

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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 medicine. 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 "Phesgo" 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 "Phesgo" 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 Phesgo.

PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR PHESGO

This is a summary of the risk-management plan (RMP) for Phesgo™ (pertuzumab and trastuzumab fixed dose combination for subcutaneous injection). The RMP details important risks of Phesgo, how these risks can be minimized, and how more information will be obtained about Phesgo's risks and uncertainties (missing information).

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

This summary of the RMP for Phesgo 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 Phesgo's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Phesgo is authorized for metastatic and early breast cancers (see SmPC for the full indication). It contains pertuzumab and trastuzumab as the active substance, and it is given by subcutaneous injection.

Further information about the evaluation of Phesgo's benefits can be found in Phesgo's EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's Web page.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Phesgo, together with measures to minimize such risks and the proposed studies for learning more about Phesgo'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 as 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.

Important information that may affect the safe use of Phesgo is not yet available, and it is listed under “missing Information” below.

II.A List of Important Risks and Missing Information

Important risks of Phesgo 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 Phesgo. 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 about 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	Congestive heart failure / Left ventricular dysfunction Administration-related reactions
Important potential risks	Oligohydramnios Lack of efficacy due to immunogenicity Medication errors (altered safety and efficacy)
Missing information	None

II.B Summary of Important Risks

Important Identified Risk: Congestive heart failure / Left ventricular dysfunction	
Evidence for linking the risk to the medicine	Randomized clinical trial data, based on safety results from FeDeriCa.
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 (Advani et al. 2016; Russo et al. 2014; Yu et al. 2015).
Risk-minimization measures	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects Package Leaflet: Section 4 Possible side 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. Package Leaflet: Section 2 ‘Heart Problems’ provides recommendations for patients **Other risk minimization measures beyond the Product Information:** None **Medicine’s legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

Important Identified Risk: Administration-related reactions	
Evidence for linking the risk to the medicine	Randomized clinical trial data, based on safety results from FeDeriCa.
Risk factors and risk groups	There are currently no reliable predictors of patients who may or may not be susceptible to administration related reactions to Phesgo.
Risk-minimization measures	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects Package Leaflet: Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk**: Guidance on observation period after administration has been adequately captured in Section 4.2 of E.U. SmPC. Section 2 of the package leaflet, 'Injection reactions' provides guidance for patients on observation period after administration. **Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

Important Potential Risk: Oligohydramnios	
Evidence for linking the risk to the medicine	Oligohydramnios has not been reported in patients treated with Phesgo but occurred in cynomolgus monkeys administered pertuzumab and in pregnant women treated with trastuzumab. 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 Phesgo 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).
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. Package Leaflet: Section 2 ‘Pregnancy, breast-feeding and contraception’ provides recommendations for patients

	Other risk minimization measures beyond the Product Information: None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

Important Potential Risk: Lack of efficacy due to immunogenicity	
Evidence for linking the risk to the medicine	The risk of lack of efficacy due to immunogenicity is determined to be low and is confirmed by the low incidence and negligible impact of anti-drug antibodies (ADAs, previously known as anti-therapeutic antibodies or ATAs, which are the result of an unwanted response caused by the body's immune response to a treatment and can render the treatment ineffective or cause adverse events) to date in pertuzumab (IV) clinical studies, as well as experience of immunogenicity of trastuzumab (SC) and rHuPH20 in previous clinical studies. Immunogenicity data available at the time of the primary analysis of Study WO40324 (FeDeriCa) also further confirms the low risk.
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; FDA 2014; Koren et al. 2008), 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.
Risk-minimization measures	**Routine risk communication:** Section 4.8 of the EU SmPC: "Immunogenecity" part **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Updated immunogenicity report for Study WO40324

Important Potential Risk: Medication errors (altered safety and efficacy)	
Risk-minimization measures	**Routine risk communication:** Section 4.2 of the EU SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk:** At the beginning of Section 4.2 of the SmPC, there is a statement re-enforcing the need to check the vial labels to ensure that the drug being prepared and administered is Phesgo. Additionally, the fact that Phesgo should be administered via subcutaneous injection only is stated. Outer and inner packaging differentiation: between each strength of Phesgo as well as between HER2 approved products - peel off label - subcutaneous is stated in bold and red on the vial and packaging, in addition to the SmPC. - difference in vial size **Other risk minimization measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimization measures:** None
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 that are conditions of the marketing authorization or specific obligation of Phesgo.

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

There are no studies required for Phesgo.

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