Summary of risk management plan for Trazimera (trastuzumab)

Summary of risk management plan for PF-05280014 (trastuzumab)[1]

This is a summary of the RMP for PF-05280014. The RMP details important risks with PF-05280014, how these risks can be minimised, and how more information will be obtained about PF-05280014's risks and uncertainties (missing information).

PF-05280014's proposed SmPC and its package leaflet give essential information to healthcare professionals and patients on how PF-05280014 should be used.

This summary of the RMP for PF-05280014 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 to PF-05280014's RMP.

I. The Medicine and What It Is Used For

PF-05280014 has been developed as a biosimilar to Herceptin (trastuzumab). The comparable efficacy, safety, PK, pharmacodynamics, and immunogenicity of PF-05280014 with Herceptin had been demonstrated during the development programme. Therefore, the treatment benefits of PF-05280014 are comparable to those of Herceptin. It is intended for the treatment of MBC, EBC and MGC (see the proposed SmPC for the full indication). It contains trastuzumab as the active substance and it is given by IV infusion.

Further information about the evaluation of trastuzumab's (Herceptin) benefits can be found in trastuzumab EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000278/human_med_000818.jsp&mid=WC0b01ac058001d124.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of PF-05280014, together with measures to minimise such risks are outlined below.

[1] Changes are considered important if they relate to the following: new safety concerns or important changes/removal to a known safety concerns, major changes to the pharmacovigilance plan (e.g. addition of new studies or completion of ongoing studies), any 'additional risk minimisation measure' which is added or removed, routine risk minimisation activities recommending specific clinical measures to address the risk.

Measures to minimise 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 authorised 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 public (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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

Important information (treatment in male breast cancer patients) that may affect the safe use of trastuzumab is not yet available, and is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of PF-05280014 are risks that need special risk management activities to further investigate or minimise 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 PF-05280014. 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. Currently, there are no important potential risks for trastuzumab. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine). There is currently no missing information for trastuzumab.

Table 1. List of important risks and missing information

Important identified risks	• Cardiac dysfunction • Administration-related reactions • Oligohydramnios
Important potential risks	• None
Missing information	• None

II.B. Summary of Important Risks

Table 2. Important Identified Risk: Cardiac Dysfunction

Evidence for linking the risk to the medicine	PF-05280014 and Herceptin clinical trial data, Herceptin RMP and Herceptin product labels.
Risk factors and risk groups	**General considerations** Patients treated with trastuzumab are at increased risk for developing CHF (NYHA class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving trastuzumab therapy alone or in combination with P or D, particularly following anthracycline (doxorubicin or epirubicin) containing chemotherapy. These may be moderate to severe and have been associated with death. In addition, caution should be exercised in treating patients with increased cardiac risk, eg hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age. **MBC** Patients with MBC who have previously received anthracyclines are at increased risk of cardiac dysfunction with trastuzumab treatment. **EBC** In adjuvant and neoadjuvant EBC setting, the patients with history of MI, angina pectoris requiring medical treatment, history of or existing CHF (NYHA II–IV), LVEF of < 55%, other cardiomyopathy, cardiac arrhythmia requiring medical treatment, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medical treatment eligible), and haemodynamic effective pericardial effusion are at are increased risk of cardiac dysfunction, therefore treatment cannot be recommended in such patients. In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when trastuzumab was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of D and C and was more marked when trastuzumab was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months. Risk factors for a cardiac event identified in 4 large adjuvant studies included advanced age (> 50 years), low LVEF (<55%) at baseline, prior to or following the initiation of P treatment, decline in LVEF by 10-

Table 2. Important Identified Risk: Cardiac Dysfunction

	15 points, and prior or concurrent use of anti-hypertensive medicinal products. In patients receiving trastuzumab after completion of adjuvant chemotherapy the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of trastuzumab and a BMI >25 kg/m^2.
Risk minimisation measures	Routine risk minimisation measures: This risk is communicated through the label (Sections 4.2 and 4.4 of the proposed SmPC). Additional risk minimisation measures: None

Table 3. Important Identified Risk: Administration-Related Reactions

Evidence for linking the risk to the medicine	PF-05280014 and Herceptin clinical trial data, Herceptin RMP and Herceptin product labels.
Risk factors and risk groups	There are currently no reliable predictors of patients who may or may not be susceptible to ARRs to trastuzumab. However, patients, who are experiencing dyspnoea at rest due to complications of advanced malignancy or co-morbidities, may be at greater risk of severe reactions including fatal outcomes.
Risk minimisation measures	Routine risk minimisation measures: This risk is communicated through the label (Sections 4.2 and 4.4 of the proposed SmPC). Additional risk minimisation measures: None

Table 4. Important Identified Risk: Oligohydramnios

Evidence for linking the risk to the medicine	Trazimera and Herceptin clinical trial data, Herceptin RMP and Herceptin product labels.
Risk factors and risk groups	There are no reliable indicators of patients who may or may not be at risk.

Table 4. Important Identified Risk: Oligohydramnios

Risk minimisation measures	Routine risk minimisation measures: This risk is communicated through the label (Sections 4.6 and 4.8 of the proposed SmPC). Additional risk minimisation measures: None

II.C. Post-Authorisation Development Plan

Not applicable.