RMP Summary

RMP Version 0.1.0 – 20-May-2020

Zercepac®,

Pulver für ein Konzentrat zur Herstellung einer Infusionslösung

ZL-Nr.: 67829

Trastuzumab

Accord Healthcare AG
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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 Zercepac 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 Zercepac in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Accord Healthcare AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Zercepac.

Summary of risk management plan for Zercepac® – (Trastuzumab biosimilar - HLX02)

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

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

This summary of the RMP for Zercepac® 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 Zercepac®'s RMP.

I. The medicine and what it is used for

Zercepac® is authorised for the treatment of HER-2 positive metastatic breast cancer, early breast cancer and gastric cancer in adult patients:

Breast cancer

Metastatic breast cancer

Zercepac® is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer

(MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments.
- Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.
- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

Early breast cancer

Zercepac® is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC):

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.

- in combination with neoadjuvant chemotherapy followed by adjuvant Zercepac® therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter.

Zercepac® should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay.

Metastatic gastric cancer

Zercepac® in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease. Zercepac® should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used.

Zercepac® contains trastuzumab (HLX02) as the active substance and it is given as powder for concentrate for solution for infusion. One vial contains 150 mg of trastuzumab. The reconstituted Zercepac® solution contains 21 mg/mL of trastuzumab.

Further information about the evaluation of Zercepac®'s benefits can be found in Zercepac®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage < link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

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 minimises its risks.

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

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

II.A List of important risks and missing information

Important risks of Zercepac® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Trastuzumab biosimilar (HLX02). 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	• Cardiac dysfunction • Hypersensitivity • Oligohydramnios
Important potential risks	• Medication error (subcutaneous administration)
Missing information	• None

II.B Summary of important risks

Cardiac dysfunction	
Evidence for linking the risk to the medicine	Cardiac dysfunction or failure has been commonly reported in clinical trials and the scientific literature, which is also reflected in the SmPC of the reference product. Clinical courses ranging from mild to fatal have been reported in association with the reference product, whereby higher-grade cardiac dysfunction or failure of any cause is a potentially life-threatening condition. This event has been classified as important identified risk for Zercepac® based on its seriousness, severity and frequency of occurrence as per the proposed SmPC.
Risk factors and risk groups	The risk factors described for the development of trastuzumab-induced cardiotoxicity include age >50 years, borderline LVEF before trastuzumab treatment, history of cardiovascular disease, cardiovascular risk factors such as diabetes, dyslipidaemia or elevated body mass index (>30), sequence in which chemotherapy is administered and prior treatment with anthracyclines (cumulative doses >300 mg/m^2).
Risk minimisation measures	Routine risk minimization measures: SmPC Sections: 4.2, 4.4 and 4.8. Additional risk minimisation measures: None.

Hypersensitivity	
Evidence for linking the risk to the medicine	Hypersensitivity reactions such as shortness of breath, low or high blood pressure, wheezing or skin rash during or shortly after administration (mostly within 2-3 hours but sometimes later) have been very commonly reported in clinical trials and the scientific literature, which is also reflected in the SmPC of the reference medicinal product Herceptin. These reactions are usually self-limited or respond to standard medicines. However, in rare cases, life-threatening allergic reactions may occur. This event has been classified as important identified risk for Zercepac® based on its seriousness, severity and frequency of occurrence, as per the proposed SmPC.
Risk factors and risk groups	No risk groups or risk factors are known. However, patients with dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal outcome in the event that an infusion reaction occurs. In general risk factors for allergic reactions include heredity, gender, race and age, with heredity being by far the most significant. In addition, environmental factors can play a role including alterations in exposure to infectious diseases during early childhood, environmental pollution, allergen levels, and dietary changes. The risk of hypersensitivity and anaphylaxis will be increased in those known to be hypersensitive to trastuzumab, murine proteins or to any of the excipients.
Risk minimisation measures	Routine risk minimization measures: SmPC Sections: 4.2, 4.3, 4.4 and 4.8. *PL section 2, 4* Additional risk minimisation measures: None.
Oligohydramnios	
Evidence for linking the risk to the medicine	Oligohydramnios and anhydramnios are severe complications, usually associated with abnormal foetal outcomes, such as intrauterine growth retardation, post-maturity syndrome, lung hypoplasia, soft tissue deformities, and foetal distress in labour, and may be fatal. Oligohydramnios has been classified as important identified risk for Zercepac® based on its seriousness.
Risk factors and risk groups	No risk factors for trastuzumab-associated oligohydramnios have been established with certainty. In the above-mentioned literature review, oligohydramnios occurred only in women who were exposed to trastuzumab (also) during the second and/or third trimester (11 cases/15 pregnancies) but did not complicate any of the 3 pregnancies exposed only during the first trimester
Risk minimisation measures	Routine risk minimization measures: SmPC Sections: 4.2 and 4.6. In addition, targeted follow-up questionnaires for follow up of any reports of pregnancy (and outcome) to analyse any adverse events of foetal harm for causal factors. Additional risk minimisation measures: None.
Medication error (subcutaneous administration)	
Evidence for linking the risk to the medicine	The reference medicinal product Herceptin is available both as a formulation for intravenous and for subcutaneous administration. Zercepac is only available for iv administration

Risk factors and risk groups	No specific risk factors or groups
Risk minimisation measures	Routine risk minimization measures: SmPC Sections: 4.2 SmPC includes a warning that treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy. The text emphasises the importance of checking the product label to avoid a medication (administration) error and reiterates information in section 3 that Zercepac is an intravenous formulation is therefore not intended for subcutaneous administration and should be administered via an intravenous infusion only. 'It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous fixed dose) is being administered to the patient, as prescribed.' Additional risk minimisation measures: None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Zercepac® (HLX02 trastuzumab biosimilar).

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Zercepac® (HLX02 trastuzumab biosimilar).