Risk Management Plan for Zercepac® (trastuzumab)

RMP version to be assessed as part of this application:

RMP Version number: 1.4

Data lock point for this RMP: 04-Mar-2024

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Rationale for submitting an updated RMP: This RMP has been revised to update the targeted follow-up questionnaire based on Herceptin EPAR, RMP version 23.0, published by EMA on 22-Feb-2024.

Summary of significant changes in this RMP: Significant changes have been done in following sections of RMP: Part-I, Part V (V.3), and Part VII (Annex 4, Annex 7 and Annex 8).

Other RMP versions under evaluation: Not Applicable

Details of the currently approved RMP:

Version number: 1.3

Approved with procedure: EMEA/H/C/005209/II/0008

Date of approval (opinion date): 17-May-2023

QPPV name: Agata Gesiewicz

QPPV signature: 

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Part I: Product(s) Overview

Table Part I.1 Product Overview

Active substance(s) **(INN or common name)**	Trastuzumab
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, monoclonal antibodies; L01FD01
Marketing Authorisation Applicant	Accord Healthcare S.L.U.
Medicinal products to which this RMP refers	03 Zercepac 150 mg powder for concentrate for solution for infusion (HLX02) Zercepac 60 mg powder for concentrate for solution for infusion (HLX02) Zercepac 420 mg powder for concentrate for solution for infusion (HLX02)
Invented name(s) in the European Economic Area (EEA)	Zercepac®
Marketing authorisation procedure	Centralised Procedure EMA # EMEA/H/C/005209/0000
Brief description of the product	Chemical class Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2).
	Summary of mode of action Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). *In vitro*, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.
	Important information about its composition. <u>Zercepac 60 mg powder for concentrate for solution for infusion</u> One vial contains 60 mg of trastuzumab <u>Zercepac 150 mg powder for concentrate for solution for infusion</u> One vial contains 150 mg of trastuzumab <u>Zercepac 420 mg powder for concentrate for solution for infusion</u>

	One vial contains 420 mg of trastuzumab Zercepac® is a biosimilar to Herceptin.
Hyperlink to the Product Information	Zercepec (HLX02) PI SN0004_May 2020
Indication(s) in the EEA	Current: *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 gastro-oesophageal 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.
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current: HER2 testing is mandatory prior to initiation of therapy. Zercepac treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy and should be administered by a healthcare professional only. Zercepac intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only. In order to prevent medication errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Zercepac (trastuzumab) and not another trastuzumab-containing product (e.g. trastuzumab emtansine or trastuzumab deruxtecan). **Posology** *Metastatic breast cancer* *Three-weekly schedule:* The recommended initial loading dose is 8 mg/kg body weight; the recommended maintenance dose at 3-weekly intervals is 6 mg/kg body weight, beginning 3 weeks after the loading dose. *Weekly schedule:* The recommended initial loading dose is 4 mg/kg body weight; weekly maintenance dose is 2 mg/kg body weight, beginning one week after the loading dose. *Administration in combination with paclitaxel or docetaxel* In the pivotal trials (H0648g, M77001), paclitaxel or docetaxel was administered the day following the first dose of trastuzumab and immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated. *Administration in combination with an aromatase inhibitor* In the pivotal trial (BO16216) trastuzumab and anastrozole were administered from day 1. There were no restrictions on the relative timing of trastuzumab and anastrozole at administration.

	Early breast cancer *Three-weekly and weekly schedule* As a three-weekly regimen the recommended initial loading dose of Zercepac is 8 mg/kg body weight. The recommended maintenance dose of Zercepac at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide. *Metastatic gastric cancer* *Three-weekly schedule* The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. *Breast cancer and gastric cancer* *Duration of treatment* Patients with MBC or MGC should be treated with Zercepac until progression of disease. Patients with EBC should be treated with Zercepac for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond one year is not recommended *Dose reduction* No reductions in the dose of Zercepac were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. Refer to the SmPC for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays. If left ventricular ejection fraction (LVEF) percentage drops ≥ 10 points from baseline AND to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of Zercepac should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up. *Missed doses* If the patient has missed a dose of Zercepac by one week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively. If the patient has missed a dose of Zercepac by more than one week,

	a re-loading dose of Zercepac should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) as soon as possible. Subsequent Zercepac maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules respectively. Method of administration Zercepac is for intravenous use only. The loading dose should be administered as a 90-minute intravenous infusion. Do not administer as an intravenous push or bolus. Zercepac intravenous infusion should be administered by a healthcare provider prepared to manage anaphylaxis and an emergency kit should be available. Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Interruption or slowing the rate of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current: 60 mg, 150 mg and 420 mg Powder for concentrate for solution for infusion.
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication

Zercepac® (trastuzumab biosimilar HLX02) is indicated for the treatment of 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.

In patients with HER2 positive metastatic breast cancer:

- 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.

In patients with HER2 positive early breast cancer (EBC):

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy

- 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 trastuzumab therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter

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 gastro-oesophageal 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.

<u>The main existing treatment options:</u>

Treatment options for patients with early and metastatic HER2 positive breast cancer include Herceptin and Herceptin biosimilars. Trastuzumab is a humanized monoclonal antibody that specifically binds to the extracellular parts of the HER2 to competitively inhibit the receptor function, resulting in the inhibition of tumour cell growth. Trastuzumab was initially developed by Genentech and Roche and was approved by the United States' Food and Drug Administration (FDA) in 1998 for patients with HER2 overexpressing

metastatic breast cancer, both as single-agent therapy and in combination with chemotherapy. The efficacy and safety of trastuzumab have been demonstrated during the development of Herceptin over the past 2 decades.

Since the discovery of a targeted treatment for HER2 positive cancer, alternative treatment options, such as taxanes, may be used in combination with anthracycline-based chemotherapy in patients with breast cancer, but these regimens have potentially more toxicity than other options. NICE suggest the use of adjuvant trastuzumab in patient with HER-2 positive invasive breast cancer, but highlights the potential for cardiac problems.

In Western countries, most gastric cancer patients are diagnosed when the tumour is at an unresectable stage. For these patients, systemic chemotherapy is the main treatment option because it prolongs survival without compromising the quality of life. Many single agents and combinations are active in the treatment of metastatic disease. Palliative chemotherapy including fluoropyrimidine, platin compounds, docetaxel and epirubicin prolongs survival, and improves a high quality of life to a greater extent than best supportive care. Although a large number of chemotherapy regimens have been tested in randomised studies, there is no internationally accepted standard of care, and uncertainty remains regarding the choice of the chemotherapy regimen. Objective response rates may range from 10% to 30% for single-agent therapy and 30% to 60% for combination regimens.

There is mounting evidence of the role of HER2 overexpression in patients with metastatic gastric cancer (MGC), and it has been solidly correlated to poor prognosis and a more aggressive disease with shorter survival. Agents targeting the epidermal growth factor receptor 1 and human epidermal growth factor receptor 2 (HER2) have been widely tested. Trastuzumab was the first target drug developed, and pivotal phase III trials showed improved survival when trastuzumab was integrated into cisplatin/fluoropyrimidine-based chemotherapy in patients with metastatic gastric cancer and thus is a recommended treatment option for patients with HER2-positive oesophago-gastric junctional adenocarcinoma.

Concomitant Medications:

As detailed above in the indication section, dependent upon the indication patients may also be taking capecitabine or 5-fluorouracil (gastric cancer), paclitaxel or docetaxel or an aromatase inhibitor (MBC), or docetaxel and carboplatin (EBC).

Clinically significant interactions between trastuzumab and the concomitant medicinal products used in clinical trials have not been observed. There have been concerns about the concomitant administration of trastuzumab and other chemotherapy and the impact on cardiotoxicity. A recent paper assessing the long-term safety and real-world effectiveness of trastuzumab in breast cancer [Mazzotta 2019[1]] indicates that patients from the real-world setting in whom trastuzumab was administered with a concomitant chemotherapy generally experienced longer overall survival than those treated with trastuzumab as a monotherapy. However, the concern of its concomitant use with chemotherapy, as well as after an anthracycline treatment, increases the cardiac adverse event rates. The paper reviews three separate studies

- a randomized prospective study investigated the concomitant use of trastuzumab and anthracyclines in the neoadjuvant setting (exceptional outcomes in terms of pCR with the addition of trastuzumab to the anthracyclines) no CHF events were reported and the incidence of asymptomatic decline of LVEF was comparable to the non-trastuzumab-treated counterpart. In this study exposure to trastuzumab in this trial was 24 weeks.

[1] Marco Mazzotta et al Long-Term Safety and Real-World Effectiveness of Trastuzumab in Breast Cancer. J. Clin. Med. 2019, 8, 254

- A subsequent in this same setting confirmed this outcome also in patients having received standard duration of trastuzumab.
- A recent Italian phase II trial also explored the use of trastuzumab concomitantly to taxane and anthracycline treatment in the neoadjuvant setting, showing no increase in the rates of clinically overt heart failure and higher percentage of pCR than usually reported in trials assessing consecutive administration of these agents

All three studies reported a reversible and rapidly recovering LVEF values in most of the cases.

Important co-morbidities:

The risk of breast cancer increases with age, and thus the likelihood that a patient will have co-morbidities increases with the patient's age at the time of treatment. There is an increased risk of cardiotoxicity complications with age.

In the OHERA trial (3733 patients with eBC treated with trastuzumab) has been published, age greater than 65 years, pre-existing cardiac pathologic conditions, hypertension, or LVEF ≤55% at baseline were associated with higher rates of trastuzumab-related cardiotoxicity.

Part II: Module SII - Non-clinical part of the safety specification

As a Biosimilar, the non-clinical development of Zercepac has primarily focussed on the in *vitro* comparison of Zercepac to Herceptin for biosimilarity. However, in order to comply with regulatory requirements of several geographic regions, an array of *in vivo* non-clinical studies have been conducted to investigate and demonstrate the similarity between Zercepac and Herceptin, in addition to a number of *in vitro* analytical/functional comparability studies.

Based on the outcome of the similarity exercise and the supporting information provided by the nonclinical *in-vivo* studies, the similarity between Zercepac and Herceptin has been established. As such, the non-clinical data generated for Herceptin can be referenced for Zercepac, and there are no additional non-clinical safety findings which could constitute an important potential risk to the target population.

In conclusion, there are no additional safety concerns, as a result of non-clinical studies, that require inclusion in the RMP for Zercepac.

Part II: Module SIII - Clinical trial exposure

The clinical development program for the Zercepac® (HLX02 trastuzumab biosimilar) consisted of one Phase 1 pharmacokinetic (PK) study (HV01) conducted in healthy volunteers, and one Phase 3 study (BC01).

As Zercepac® is a biosimilar, safety data collected from studies conducted with trastuzumab licenced in the EU as Herceptin provide the main data used to support a safety assessment of Zercepac® (HLX02). Thus the data in the SmPC for Herceptin provides the basis of the known safety data base for trastuzumab.

The exposure of subjects to Zercepac® through the Phase 1 clinical study and Phase 3 clinical study in Breast Cancer is defined in Table SIII.1 and the demographic information in Table SIII.2 to Table Table SIII.3 below.

At the cut-off date of the originally submitted RMP for sequence SN0000, of 649 SAS population (324 patients received HLX02 and 325 received Herceptin), the median number of cycles (11.0) completed

by patients was same in the HLX02 treatment group and the Herceptin treatment group. In general, the median total exposure duration was similar between the 2 treatment groups: 240.5 (range: 21-381) days in the HLX02 treatment group and 232.0 (range: 21-387) days in the Herceptin treatment group.

By the new cut-off date (second interim analysis, 10 July 2019), in the 649 SAS population (324 patients received HLX02 and 325 received Herceptin), the median number of cycles completed by patients was similar in the HLX02 treatment group (15) and the Herceptin treatment group (14). The total drug exposure duration of HLX02 group and Herceptin group was 264.6 (114.76) days and 253.4 (114.29) days, respectively (See Table SIII.1).

Overall and relative dose intensity were similar in both the treatment groups. The median cumulative dose of the study medication was 5488.5 mg (for HLX02) and 4945.0 mg (for Herceptin) treatment groups, respectively. Dose reduction was reported in 1 patient in Herceptin treatment group. Dose delay was reported in 55 patients in HLX02 treatment group and 46 patients in Herceptin treatment group. Dose interruption was reported in a total of 21 and 16 patients from the HLX02 and Herceptin treatment groups, respectively.

The higher exposure in the HLX02 group compared to the Herceptin group may be explained because the overall response time of HLX02 group was longer than that of Herceptin group. In this regard, the median PFS of HLX02 group and Herceptin group was 11.73 (11.10, 12.02) months and 10.55 (9.49, 11.73) months, respectively. The associated the longer treatment duration resulted in the relatively long total exposure duration. See Table SIII.1

Table SIII.1: Exposure to Study Treatment -Overall (Safety Analysis Set) in study HLX02-BC01 –data lock 21 July 2019

Characteristic	HLX02 N=324	Herceptin N=325	Total N=649
Number of cycle completed			
n (missing)	324(0)	325(0)	649(0)
Mean (SD)	12.4(5.43)	11.8(5.38)	12.1(5.41)
Median	15.0	14.0	14.0
Q1, Q3	8.0, 17.0	7.0, 17.0	8.0, 17.0
Min, Max	1, 17	1, 17	1, 17
Number of cycle has completed N, n (%)			
Cycle 1	9 (2.8)	3 (0.9)	12 (1.8)
Cycle 2	20 (6.2)	21 (6.5)	41 (6.3)
Cycle 3	3 (0.9)	4 (1.2)	7 (1.1)
Cycle 4	13 (4.0)	20 (6.2)	33 (5.1)
Cycle 5	5 (1.5)	5 (1.5)	10 (1.5)
Cycle 6	17 (5.2)	24 (7.4)	41 (6.3)
Cycle 7	3 (0.9)	6 (1.8)	9 (1.4)
Cycle 8	19 (5.9)	21 (6.5)	40 (6.2)
Cycle 9	8 (2.5)	7 (2.2)	15 (2.3)
Cycle 10	8 (2.5)	8 (2.5)	16 (2.5)
Cycle 11	23 (7.1)	33 (10.2)	56 (8.6)
Cycle 12	5 (1.5)	7 (2.2)	12 (1.8)
Cycle 13	9 (2.8)	3 (0.9)	12 (1.8)
Cycle 14	18 (5.6)	18 (5.5)	36 (5.5)
Cycle 15	5 (1.5)	5 (1.5)	10 (1.5)
Cycle 16	4 (1.2)	2 (0.6)	6 (0.9)
Cycle 17	155 (47.8)	138 (42.5)	293 (45.1)
Total exposure duration (days)			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	264.6 (114.76)	253.4 (114.29)	259.0 (114.57)
Median	312.0	292.0	297.0
Q1, Q3	171.5, 358.0	165.0, 358.0	169.0, 358.0
Min, Max	21, 408	21, 417	21, 417
Injection times			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	12.4 (5.43)	11.8 (5.38)	12.1 (5.41)
Median	15.0	14.0	14.0
Q1, Q3	8.0, 17.0	7.0, 17.0	8.0, 17.0
Min, Max	1, 17	1, 17	1, 17
Total exposure intensity (mg/day)			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	19.12 (3.811)	18.78 (3.768)	18.95 (3.791)
Median	18.39	18.11	18.23
Q1, Q3	16.42, 21.13	16.27, 20.47	16.35, 20.77
Min, Max	12.2, 33.9	11.1, 37.1	11.1, 37.1
Relative dose intensity			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	99.95 (0.661)	100.01 (1.099)	99.98 (0.907)
Median	100.00	100.00	100.00
Q1, Q3	100.00, 100.00	100.00, 100.00	100.00, 100.00
Min, Max	93.3, 103.0	88.9, 110.8	88.9, 110.8
Dose reduced of IP, n (%)	0	1 (0.3)	1 (0.2)

Characteristic	HLX02 N=324	Herceptin N=325	Total N=649
Dose delayed of IP, n (%)	55 (17.0)	46 (14.2)	101 (15.6)
Dose interrupted of IP, n (%)	21 (6.5)	16 (4.9)	37 (5.7)

Source: Table 12-1, Listing 16.2.5.1.1.1, Table 14.1.10.1 and Table 14.1.10.4 of HLX02-BC01 CSR

- Percentages were based on the number of patients in the safety set. Subgroup percentages were based on the number of patients in the subgroup safety set.
- Investigational Product: HLX2 or Herceptin.
- Total exposure duration (days) = last study drug date – first study drug date + 21.
- Actual exposure duration (days) = Injection times.
- Actual dose intensity = Actual total dose/ Total exposure duration (days)
- Planned dose intensity = Planned total dose/ Total exposure duration (days)
- Relative Dose Intensity (RDI) = (Actual dose intensity)/ (Planned dose intensity)×100

The subjects in the HLX02-HV01 study consisted of 12 healthy Chinese males, ranging in age from 19 to 35 years, weight from 58.0 to 73.5 kg, and ranging in height from 166.0 to 175.0 cm in Part 1 and Part 2, consisted of 111 healthy Chinese males, ranging in age from 18 to 45 years, ranging in weight from 51.0 to 80.0 kg, and ranging in height from 159.5 to 185.0 cm. Demographics at baseline for Safety Set for Part 2 of the study (SS2) in presented in Table SIII.2 Patients enrolled in Part 2 presented similar demographic characteristics in all arms.

For Study HLX02-BC01, the overall population for the HLX02 and Herceptin groups, were similar in most demographic and baseline characteristics. This was also confirmed in sub-group comparisons (Asian vs. non-Asian, and Chinese vs. non-Chinese). Demographics at baseline for the Overall ITT/Safety population are presented in Table SIII.3. As shown below the mean (SD) age of all patients in the ITT set was 53.2 (9.90) years (ranging from 26 to 80 years): 53.6 (9.73) years for the HLX02 treatment group versus 52.8 (10.08) years for the Herceptin treatment group. The majority of the patients were of non-childbearing potential (433 [66.7%]).

Overall, 473 (72.9%) patients were Chinese and 150 (23.1%) patients were White. A total of 26 (4.0%) patients were Asians excluding Chinese. The distribution of patients in the HLX02 and Herceptin treatment groups were similar. Two (0.3%) patients were of unknown origin, 1 each in the HLX02 and Herceptin treatment group.

All patients had an ECOG performance status (ECOG PS) of either 0 or 1. Overall, 276 (42.5%) patients had an ECOG PS of 0; 137 (42.3%) patients in HLX02 treatment group and 139 (42.8%) patients in Herceptin treatment group. Overall, 373 (57.5%) patients had an ECOG PS of 1; 187 (57.7%) patients in the HLX02 treatment group and 186 (57.2%) patients in the Herceptin treatment group.

The mean (SD) weight was 64.14 (12.542) kg; 64.60 (12.628) kg in HLX02 treatment group and 63.69 (12.458) kg in Herceptin treatment group. The mean (SD) body mass index (BMI) was 25.28 (4.416) kg/m^2; 25.36 (4.275) kg/m^2 for HLX02 treatment group and 25.21 (4.556) kg/m^2 for the Herceptin treatment group.

Table SIII.2: Demographics at Baseline (Safety Set 2) in study HLX02-HV01

Demographic variable	HLX02 (N=37) n (%)	CN-sourced Herceptin (N=37) n (%)	EU-sourced Herceptin (N=37) n (%)	Total (N=111) n (%)
Age (years)				
n	37	37	37	111
Mean (SD)	28.0 (6.1)	25.8 (6.0)	28.0 (6.3)	27.3 (6.2)
Median	27.0	24.0	27.0	27.0
Min, Max	18, 43	18, 45	18, 43	18, 45
Sex, n (%)				
n	37	37	37	111
Male	37 (100.0)	37 (100.0)	37 (100.0)	111 (100.0)
Female	0	0	0	0
Ethnicity, n (%)				
n	37	37	37	111
Chinese	37 (100.0)	37 (100.0)	37 (100.0)	111 (100.0)
Other	0	0	0	0
Height (cm)				
n	37	37	37	111
Mean (SD)	170.08 (5.47)	171.51 (4.86)	171.04 (5.71)	170.88 (5.34)
Median	169.00	173.00	171.00	171.00
Min, Max	160.0, 184.0	161.0, 181.0	159.5, 185.0	159.5, 185.0
Weight (kg)				
n	37	37	37	111
Mean (SD)	63.21 (7.35)	66.50 (8.39)	65.16 (8.35)	64.96 (8.09)
Median	63.00	66.00	64.00	64.00
Min, Max	52.0, 76.0	53.0, 80.0	51.0, 80.0	51.0, 80.0
BMI (kg/m^2)				
n	37	37	37	111
Mean (SD)	21.85 (2.33)	22.57 (2.45)	22.25 (2.44)	22.23 (2.40)
Median	21.60	22.20	22.00	22.00
Min, Max	19.1, 26.6	19.0, 27.0	19.0, 27.5	19.0, 27.5

Source: Table 14.1.3.2.1 of HLX02-HV01 CSR

Table SIII.3: Demographics at Baseline (ITT Set) in study HLX02-BC01*-updated

Characteristics	HLX02 N=324	Herceptin N=325	Total N=649
Age (years)			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	53.6 (9.73)	52.8 (10.08)	53.2 (9.90)
Median	54.0	53.0	54.0
Q1, Q3	47.0, 60.0	45.0, 60.0	46.0, 60.0
Min, Max	30, 80	26, 76	26, 80
Sex, n (%)			
Female	324 (100.0)	325 (100.0)	649 (100.0)
Male	0	0	0
Race, n (%)			
Asian excluding Chinese	11 (3.4)	15 (4.6)	26 (4.0)
American Indian or Alaska Native	0	0	0
Chinese	237 (73.1)	236 (72.6)	473 (72.9)
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islanders	0	0	0
White	76 (23.5)	74 (22.8)	150 (23.1)
Other	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	2 (0.6)	1 (0.3)	3 (0.5)
Not Hispanic or Latino	316 (97.5)	319 (98.2)	635 (97.8)
Not Reported	5 (1.5)	4 (1.2)	9 (1.4)
Unknown	1 (0.3)	1 (0.3)	2 (0.3)
Child-bearing potential (a), n (%)			
Yes	105 (32.4)	111 (34.2)	216 (33.3)
No	219 (67.6)	214 (65.8)	433 (66.7)
Last Menstrual Period (a), n (%)			
More than 12 Months	217 (67.0)	210 (64.6)	427 (65.8)
Equal or less than 12 Months	107 (33.0)	114 (35.1)	221 (34.1)
Missing	0	3 (0.9)	3 (0.5)
ECOG performance status, n (%)			
0	138 (42.6)	139 (42.8)	277 (42.7)
1	186 (57.4)	186 (57.2)	372 (57.3)
Left Ventricular Ejection Fraction			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	64.7 (5.06)	64.0 (4.93)	64.4 (5.01)
Median	65.0	64.0	64.0
Q1, Q3	61.0, 68.0	60.0, 67.0	60.0, 67.0
Min, Max	52, 82	50, 80	50, 82
ECG result, n (%)			
Normal	200 (61.7)	203 (62.5)	403 (62.1)
Abnormal Finding	123 (38.0)	122 (37.5)	245 (37.8)
Missing	1 (0.3)	0	1 (0.2)
Height (cm)			
n (missing)	322 (2)	325 (0)	647 (2)
Mean (SD)	159.4 (6.12)	158.9 (5.99)	159.1 (6.05)
Median	159.5	158.0	159.0
Q1, Q3	155.0, 163.0	155.0, 163.0	155.0, 163.0
Min, Max	145, 181	143, 175	143, 181
Weight (kg)			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	64.60 (12.628)	63.69 (12.458)	64.14 (12.542)
Median	62.00	62.00	62.00
Q1, Q3	55.25, 70.00	55.50, 70.00	55.50, 70.00
Min, Max	41.5, 118.0	37.2, 120.0	37.2, 120.0
BMI (kg/m^2)			

Characteristics	HLX02 N=324	Herceptin N=325	Total N=649
n (missing)	322 (2)	325 (0)	647 (2)
Mean (SD)	25.36 (4.275)	25.21 (4.556)	25.28 (4.416)
Median	24.65	24.52	24.54
Q1, Q3	22.46, 27.53	22.27, 27.43	22.35, 27.53
Min, Max	17.3, 42.1	16.2, 44.6	16.2, 44.6
Body Surface Area (m^2)			
n (missing)	322 (2)	325 (0)	647 (2)
Mean (SD)	1.69 (0.179)	1.67 (0.173)	1.68 (0.176)
Median	1.66	1.65	1.65
Q1, Q3	1.56, 1.78	1.56, 1.77	1.56, 1.77
Min, Max	1.3, 2.4	1.2, 2.3	1.2, 2.4
Country, n (%)			
China	241 (74.4)	247 (76.0)	488 (75.2)
Philippines	7 (2.2)	4 (1.2)	11 (1.7)
Ukraine	76 (23.5)	74 (22.8)	150 (23.1)

Source: Table 10-6 of HLX02-BC01 CSR
-*ITT data set and safety data set are similar in patient numbers.
- Percentages were based on the number of patients in intention-to-treat set. Subgroup percentages were based on the number of patients in the subgroup intention-to-treat set.
- Age was derived as the difference in years between the date of birth and the date of informed consent.
- ECOG: Eastern Cooperative Oncology Group; ECG: Electrocardiogram.
- Body Mass Index (BMI) (kg/m^2) = weight (kg) / (height/100 [cm])^2.
- (a) Denominator of 'Child-bearing potential' and 'Last Menstrual Period' only based on female patients.

In study HLX02-HV01, all subjects were male and Asian (Chinese). In study HLX02-BC01, all patients were female and majority was Asian (76.9% Asian with 72.9% of Chinese; 23.1% White).

Overview of Safety data from Clinical Study HLX02-BC01.

Of the 649 patients enrolled in the Phase 3 study HLX02-BC01, 641 (98.8%) patients reported at least one AE and TEAE (HLX02: 320 of 324 [98.8%] patients; Herceptin: 321 of 325 [98.8%]). A similar number of AEs (HLX02=6975 vs Herceptin=7144) and TEAEs (HLX02=6828 and Herceptin=7002) were reported in the 2 treatment groups.

The most commonly reported SOCs were investigations (HLX02: 299 [92.3%] patients; Herceptin: 303 [93.2%] patients); skin and subcutaneous tissue disorders (HLX02: 208 [64.2%] patients; Herceptin: 204 [62.8%] patients); and blood and lymphatic system disorders (HLX02: 182 [56.2%] patients; Herceptin: 205 [63.1%] patients). The most commonly reported TEAEs by PT were WBC decreased (HLX02: 267 [82.4%] patients; Herceptin: 276 [84.9%]), neutrophil count decreased (HLX02: 266 [82.1%] patients; Herceptin: 268 [82.5%]), alopecia (HLX02: 180 [55.6%] patients; Herceptin: 174 [53.5%] patients) and anaemia (HLX02: 167 [51.5%]) patients; Herceptin: 187 [57.5%] patients). In general, the incidence of TEAEs in HLX02 or Herceptin treated patients and frequency of occurrence was similar among both the treatment groups in overall population (section 2.7.4.2.1.1, in Module 2.7.4)

This TEAE profile is consistent with the safety profile described in the product information of the reference medicinal product (Herceptin SmPC).

As of the data cut-off date, in both the treatment groups similar number of patients were reported with TEAEs of severity grade as Grade 1, Grade 2, Grade 3, Grade 4, and 5. A total of 469/649 (72.3%) of the overall patients reported at least one TEAE of any Grade related to the study medication. The incidence of TEAEs of any Grade related to the study medication was similar between the 2 treatment groups with similar number of patients reporting these events (HLX02: 236 [72.8%] patients; Herceptin: 233 [71.7%] patients). Grade 2 and Grade 4 TEAEs related to the study medication had the highest incidence rate (range from 20.7% to 22.8%) with both the treatment groups reporting similar numbers. Incidence of Grade 5 TEAEs related to study medication was very low, with 2 patients each in both the

treatment groups. HLX02 treatment group had slightly higher incidence of Grade 1 and lower incidence of Grade 3 TEAEs related to the study medication than the Herceptin treatment group. See section 2.7.4.2.1.1, in Module 2.7.4.

Overall, 59/649 (9.1%) patients experienced a TEAE leading to study drug interruption or withdrawal during the active treatment period. There was a similar incidence of patients who had TEAEs leading to study drug interruption or withdrawal in the HLX02 and Herceptin treatment groups.

A total of 518 (79.8%) patients reported 5934 TEAEs of special interest (HLX02: 260 [80.2%] patients; Herceptin: 258 [79.4%] patients). A similar number of patients were reported with TEAEs of special interest related to HLX02 or Herceptin in the 2 treatment groups. The most commonly reported SOCs were investigations (HLX02: 234 [72.2%] patients; Herceptin: 232 [71.4%] patients); and blood and lymphatic system disorders (HLX02: 141 [43.5%] patients; Herceptin: 155 [47.7%] patients). Most commonly reported AESIs were WBC decreased (HLX02: 225 [69.4%] patients; Herceptin: 224 [68.9%] patients), neutrophil count decreased (HLX02: 214 [66.0%] patients; Herceptin: 209 [64.3%] patients); and anaemia (HLX02: 122 [37.7%] patients; Herceptin: 133 [40.9%] patients). In general, the incidence of TEAESIs in HLX02 or Herceptin treated patients and frequency of occurrence was similar among both the treatment groups in overall population. With regards to allergic-like reactions or hypersensitivity, in study HLX02-BC01, those were reported in 1.9% of patients dosed with HLX02 and 2.5% of patients dosed with EU-sourced Herceptin, and cardiac disorders suggesting cardiac toxicity were reported in 4.9% of patients dosed with HLX02 vs. 5.2% of patients dosed with EU-sourced Herceptin.

The overall safety profile as reflected by the most frequently reported TEAEs, severity of the TEAEs and number reported as related, is consistent with the known safety profile of Herceptin. There were no clinically meaningful differences observed between the HLX02 and Herceptin groups in MBC patients. Overall, the frequency and severity of AEs, SAEs and AESIs were similar between HLX02 and EU-sourced Herceptin up to Week 24 and in line with safety characteristics reported in the EU-sourced Herceptin SmPC. The development of anti-trastuzumab antibodies (immunogenicity profiles) was also similar for HLX02 and Herceptin.

The safety data above derived from Study HLX02-BC01 with a median total follow-up duration was 456.0 days (457.0 days in the HLX02 treatment group and 455.0 days in the Herceptin treatment group identified no new signals. Thus, based on the available clinical data for HLX02, the safety profile defined in the Herceptin SmPC is applicable to Zercepac.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Patients with an allergy or hypersensitivity to trastuzumab (or murine proteins)

Reason for exclusion: Similar to all medicinal products patients should not be administered Zercepac® if they are known to be hypersensitive to any of the ingredients i.e. trastuzumab or to murine proteins or to any of the excipients because of the risk of hypersensitivity or anaphylactic type reactions. For this reason prior hypersensitivity was an exclusion criterion.

Is it considered to be included as missing information? No

Rationale: This risk (infusion/administration related reactions and hypersensitivity) is important identified risk, and is listed in the Herceptin SmPC and in the proposed Zercepac® SmPC.

Subjects with chronic heart failure (CHF) based on any New York Heart Association (NYHA) criteria, or left ventricular hypertrophy.

Reason for exclusion: In the phase 3 clinical trial of Herceptin and docetaxel versus docetaxel alone, more patients in the combination group had left ventricular ejection fraction (LVEF) decreases ≥15%, compared with the docetaxel alone group (17% versus 8%), and 1 patient (1%) in the combination group experienced symptomatic congestive heart failure (CHF). The most significant AE observed in patients who receive trastuzumab is cardiac dysfunction, reflected by asymptomatic decreases in LVEF and, less frequently, by clinically symptomatic CHF. Risk factors for cardiac failure include co-administration with anthracycline-based chemotherapy, increasing age, a declining LVEF during treatment to below the lower limit of normal, and the use of anti-hypertensive medications. The exclusion criteria used in the clinical trial were intended to define a population for which the benefit of adding trastuzumab would largely exceed the risk of cardiac AEs.

Patients with CHF or cardiac dysfunction are contraindicated in the Herceptin SmPC.

Is it considered to be included as missing information? No

Rationale: This risk (cardiac dysfunction) is an important identified risk that is covered in the SmPC, both in the warnings and precautions, and contraindications section.

Subjects who were pregnant or breastfeeding.

Reason for exclusion: Similar to the majority of medicinal products, the clinical trials for Zercepac® excluded female subjects who were pregnant or breast feeding. The inclusion criteria for the Phase III clinical trial required that female patients eligible for the study must either be of non-child bearing potential, or have a negative serum pregnancy test at screening and use highly effective contraception.

Is it considered to be included as missing information? No. It is known that there is the potential for oligohydramnios in pregnant women treated with trastuzumab. Cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Herceptin, as such the Herceptin SmPC and the proposed Zercepac® SmPC contain advice in Section 4.6 about the risk of oligohydramnios and foetal harm and advises that women of childbearing potential should use effective contraception during treatment and for 7 months after treatment with trastuzumab. It also states that trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is specific to that for biosimilars and is therefore unlikely to detect certain types of adverse reactions such as rare or uncommon 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 SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with renal or hepatic impairment • Patients with cardiovascular impairment • Immunocompromised patients or those at risk of infection	Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. According to the Herceptin EPAR, pharmacokinetic data from a single-agent study were analysed by a number of baseline characteristics. There was no apparent relationship between age, or renal function (baseline serum creatinine) and PK parameters but heavier patients tended to have higher trough concentrations. According to the Herceptin SmPC population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition. Patients with cardiovascular impairment
Population with relevant different ethnic origin	The incidence of AESIs was higher in Asian population than the non-Asian population in Study. A total of 442/499 Asian and 38/150 non-Asian patients were reported with 4977 and 284 AESIs, respectively. The most commonly reported AESIs in Asians were WBC decreased, neutrophil count decreased, and anaemia. The most commonly reported AESIs in non-Asians were neutrophil count decreased, WBC decreased.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	Trastuzumab has not been studied in paediatrics in the clinical development program.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable.

Zercepac® is a treatment for cancer and therefore is not open to potential recreational use.

Potential for transmission of infectious agents

Zercepac® has no potential for transmission of infectious agents by residuals of biological material used in the manufacturing process as well as contaminations introduced by the manufacturing process.

Potential for immunogenicity

Zercepac® has no potential for immunogenicity.

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.
As Zercepac® is a biosimilar the safety concerns mirror that of the Reference Medicinal Product. No new risks were identified as a result of the clinical trials conducted with Zercepac.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

> Not Applicable. As Zercepac® is a biosimilar the safety concerns mirror that of the Reference Medicinal Product. No new risks were identified as a result of the clinical trials conducted with Zercepac.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

> Not Applicable. As Zercepac® is a biosimilar the safety concerns mirror that of the Reference Medicinal Product. No new risks were identified as a result of the clinical trials conducted with Zercepac.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

> Infections: Section 4.8 of the SmPC lists the following undesirable effects-Infection, Nasopharyngitis, Neutropenic sepsis, Cystitis, Influenza, Sinusitis, Skin infection, Rhinitis, Upper respiratory tract infection, Urinary tract infection and Pharyngitis. Whilst these were previously considered as a safety concern (original Herceptin EPAR) they are no longer included in the Risk Management Plan for the reference medicinal product

Known risks that do not impact the risk-benefit profile:

> Haematotoxicity: Febrile neutropenia, leukopenia, anaemia, thrombocytopenia and neutropenia occurred very commonly. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy. However, these risks are common to most cancer treatment options, and can-be managed if monitoring is conducted as recommended in the proposed SmPC.

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

Cardiac dysfunction:

Risk-benefit impact: 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.

Hypersensitivity:

Risk-benefit impact: 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 product. 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.

Use during pregnancy (Oligohydramnios):

Risk-benefit impact: 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.

Trastuzumab is not recommended during pregnancy and in women of childbearing potential not using contraception. 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.

Medication error (subcutaneous administration):

Risk-benefit impact: Zercepac is presented as a lyophilised formulation for intravenous infusion. The reference medicinal Herceptin is available in two presentations for both intravenous and subcutaneous administration. It is therefore possible that a mistake could be made and Zercepac could be administered subcutaneously which could lead to patient harm through over dosing, under dosing or treatment toxicity. However, the risk is greater with the reference medicinal product Herceptin, than for trastuzumab biosimilars which have been approved with a single route of administration. Herceptin has now been used for several years as standard practice with successful risk strategies.

This event has been classified as important potential risk for Zercepac® based on its seriousness, but the risk benefit defined in the SmPC is not impacted.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

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

Cardiac dysfunction:

Potential mechanisms: HER2-directed drugs are known to be associated with left ventricular dysfunction. Patients treated with trastuzumab are known to be at increased risk for developing chronic heart failure (CHF; New York Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction (Herceptin® SmPC, Mohan 2018). The mechanism for trastuzumab-induced cardiotoxicity, remain incompletely understood. Trastuzumab-induced cardiac dysfunctions have been considered less severe than that caused by anthracyclines and largely reversible because primary cardiomyocytes have not shown the ultrastructure changes that are associated with anthracycline-induced cardiotoxicity, and primary myocyte injury does not occur in patients that were treated with trastuzumab. However there may be other mechanism of toxicity and thus there continues to be a need to define the long-term cardiovascular risks associated with trastuzumab therapy and thus continued cardiac follow-up for patients. Other risk factors include prior chemotherapy with taxanes or anthracyclines, being more than 50 years of age, hypertension requiring treatment, and low heart function.

Evidence source(s) and strength of evidence: Cardiac dysfunction or failure has been commonly reported in clinical trials and the scientific literature, and is also reflected in the SmPC of the reference medicinal 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. The Herceptin EPAR and Herceptin product information reflect this information.

Characterisation of the risk: As per the Herceptin SmPC formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. In all patients cardiac function should be monitored during treatment (e.g. every 12 weeks). Monitoring may help to identify patients who develop cardiac dysfunction. If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of trastuzumab therapy has been seen. For patients who experience cardiac dysfunction (LVEF drops) the safety of continuation or resumption of trastuzumab therapy should be carefully considered (as per the SmPC) and discontinuation considered unless the benefits are considered to outweigh the risks.

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).

Preventability: As recommended in the proposed SmPC all candidates for treatment with Zercepac, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging. Monitoring may help to identify patients who could develop cardiac dysfunction. The same cardiac assessments should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment up to 24 months from the last administration of Zercepac. A careful risk-benefit assessment should be made before deciding to treat with Zercepac, thereby reducing the potential risk.

Impact on the risk-benefit balance of the product: The impact on the risk-benefit has been considered for the reference medicinal product (Herceptin) and considered to be acceptable

Public health impact: The public health impact is considered to be the same as that for the reference medicinal product Herceptin.

Hypersensitivity:

Potential mechanisms: These reactions are acquired, predictable, and rapid. Allergy is one of four forms of hypersensitivity and is formally called type I (or immediate) hypersensitivity. Allergic reactions are distinctive because of excessive activation of certain white blood cells called mast cells and basophils by a type of antibody called Immunoglobulin E (IgE). This reaction results in an inflammatory response which can range from uncomfortable to dangerous.

Anaphylaxis is due to the release of inflammatory mediators and cytokines from mast cells and basophils, typically due to an immunologic reaction but sometimes non-immunologic mechanism.

In the immunologic mechanism, IgE binds to the antigen, the foreign material that provokes the allergic reaction. Antigen-bound IgE then activates FcεRI receptors on mast cells and basophils. This leads to the release of inflammatory mediators such as histamine. These mediators subsequently increase the contraction of bronchial smooth muscle, trigger vasodilation, increase the leakage of fluid from blood vessels and cause heart muscle depression.

Evidence source(s) and strength of evidence: HLX02 and Herceptin clinical trial data, Herceptin RMP and Herceptin product labels.

Characterisation of the risk: Hypersensitivity refers to undesirable reactions produced by the normal immune system, including allergies and autoimmunity. Allergic reactions may be mild or they may be damaging, uncomfortable, or occasionally fatal. Hypersensitivity reactions require a pre-sensitised state of the host. Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death; anaphylactoid reactions have been observed in isolated cases.

It is estimated that approximately 40 % of patients who are treated with trastuzumab will experience some form of hypersensitivity reaction. However, the majority of hypersensitivity reactions are mild to moderate in intensity and tend to occur earlier in treatment. Severe anaphylactic reactions requiring immediate additional intervention occur usually during either the first or second infusion of trastuzumab and have been associated with a fatal outcome.

Risk factors and risk groups: 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 rate of hypersensitivity reactions of all grades varied between studies depending on the indication, the data collection methodology, and whether trastuzumab was given concurrently with chemotherapy or as monotherapy.

Preventability: This effect is preventable by patient and HCP awareness about the possible risk of allergic reaction in the summary of product characteristics.

Patients known to be hypersensitive to trastuzumab or mouse proteins or to any of the excipients in HLX02 are contraindicated from using the product.

Pre-medication may be used to reduce risk of occurrence of these IRR events. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms.

Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab.

Impact on the risk-benefit balance of the product: The impact on the risk-benefit has been considered for the reference medicinal product (Herceptin) and considered to be acceptable.

Public health impact: The public health impact is considered to be the same as that for the reference medicinal product.

Oligohydramnios:

Potential mechanisms: 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. Trastuzumab administration from the second trimester onwards is known to increase the risk of oligohydramnios. The main hypothesis for this is that as HER2 is expressed in the foetal kidneys, trastuzumab administration affects foetal urine production and amniotic fluid reabsorption. In addition, the expression of vascular endothelial growth factor, which regulates the production and reabsorption of amniotic fluid by altering the permeability of the foetal membranes, is also believed to be inhibited by trastuzumab. The oligohydramnios that occurs due to these mechanisms increases the risk of premature delivery and, as a result, neonates often present with respiratory and renal failure. However, oligohydramnios caused by trastuzumab improves when the drug is discontinued, thereby indicating reversibility.

Evidence source(s) and strength of evidence: Herceptin RMP (post marketing setting reports) and Herceptin product labels. Literature references containing case study reports.

Characterisation of the risk: In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving trastuzumab. Women who become pregnant should be advised of the possibility of harm to the foetus.

Trastuzumab has been shown to cross the placenta in monkeys. In addition lactating Cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg i.v. Herceptin demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age. It is not known whether trastuzumab is secreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breast-feed during Herceptin therapy and for 7 months after the last dose.

As per a literature report 2013 in a meta-analysis of 17 studies there were 18 reports of trastuzumab use during pregnancy. Occurrence of oligohydramnios/anhydramnios (O/A) was the most common (61.1 %) adverse event. 73.3 % of pregnancies exposed to trastuzumab during the second/third trimester were complicated with O/A and the respective rate of pregnancies exposed to trastuzumab exclusively during the first trimester was 0 % (P = 0.043). The mean gestational age at delivery was 33.8 weeks, and the mean weight of babies at delivery was 2.26 kg. In 52.6 % of cases, a healthy neonate was born. At the long-term evaluation, all children without problems at birth were healthy with a median follow-up of 9 months, while four out of nine children facing troubles at birth were dead within an interval ranging between birth and 5.25 months. All children exposed to trastuzumab in utero exclusively in the first trimester were completely healthy at birth.

Risk factors and risk groups: Pregnant women receiving trastuzumab.

Preventability: Trastuzumab is not recommended during pregnancy and in women of childbearing potential not using contraception.

Impact on the risk-benefit balance of the product: The impact on the risk-benefit has been considered for the reference medicinal product (Herceptin) and considered to be acceptable.

Public health impact: The public health impact is considered to be the same as that for the reference medicinal product.

SVII.3.2. Presentation of the missing information

None

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Cardiac dysfunction • Hypersensitivity • Oligohydramnios
Important potential risks	Medication error (subcutaneous administration)
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

In addition, in line with reference product, MAH has also developed targeted follow-up questionnaires for

- Pregnancy related adverse events (Oligohydramnios)

Follow up any reports of pregnancy (and outcome) and to analyse any adverse events of foetal harm for causal factors which is summarized in Annex 4.

Purpose: For collection and reporting of safety information while use of Zercepac® (trastuzumab).

- Medication error

For Zercepac®: IV administration of SC formulation or SC administration of IV formulation

It is important to check the vial labels to ensure that the drug being prepared and administered is Zercepac® (trastuzumab) intravenous formulation and not another trastuzumab-containing product (e.g. trastuzumab emtansine or trastuzumab deruxtecan). Please see RMP Annex 4 for details.

III.2 Additional pharmacovigilance activities

There are no risk minimisation measures which require the use of non-routine pharmacovigilance activities to measure the effectiveness; therefore, this section is not applicable.

III.3 Summary Table of additional Pharmacovigilance activities

None proposed.

Part IV: Plans for post-authorisation efficacy studies

No additional post authorisation efficacy studies applicable to Herceptin or other trastuzumab biosimilars were identified by the Applicant, nor in the publicly available information on the reference product Herceptin. Therefore, no additional post authorisation efficacy studies are proposed.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Identified Risk- Cardiac dysfunction	Routine risk communication: SmPC section 4.2, 4.4, 4.8, 5.1 PL section 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for treatment suspension or discontinuation based on LVEF measure included in section 4.2. Details warnings of risk factors and monitoring for cardiac dysfunction are included in SmPC sections 4.2 and 4.4* Other routine risk minimisation measures beyond the Product Information: Legal status: POM (POM = Prescription only medicine)
Identified Risk- Hypersensitivity	Routine risk communication: SmPC section 4.2, 4.3, 4.4, 4.8 PL section 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for pre-medication to avoid risk of serious Infusion related reactions are included in SmPC section 4.4 including advice on management of infusion reactions.* *A warning about late onset of IRR (six hours post infusion) are included in the PL Section 4* Other routine risk minimisation measures beyond the Product Information: Legal status: POM

Safety concern	Routine risk minimisation activities
Identified Risk- Oligohydramnios	Routine risk communication: SmPC section 4.6, 4.8 PL section 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: *In Section 4.6 women of childbearing potential should be advised to use effective contraception during treatment with Zercepac® and for 7 months after treatment has concluded. In addition women who become pregnant or are pregnant while receiving Zercepac® or within 7 months should be advised of the possibility of harm to the foetus and close monitoring* Other routine risk minimisation measures beyond the Product Information: Legal status: POM
Identified Risk- Medication error (subcutaneous administration)	Routine risk communication: SmPC section 4.2 PL section 3 and tear off section. Routine risk minimisation activities recommending specific clinical measures to address the risk: *In Section 4.2: Zercepac intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only. In order to prevent medication errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Zercepac (trastuzumab) and not another trastuzumab-containing product (e.g. trastuzumab emtansine or trastuzumab deruxtecan).* *In the PL Section 3 and Profession section: Zercepac intravenous formulation is given as an intravenous infusion ("drip") directly into your veins. The first dose of your treatment is given over 90 minutes and you will be observed by a health professional while it is being given in case you have any side effects. …In order to prevent medication errors it is important to check the vial labels to ensure that the medicine being prepared and given is Zercepac (trastuzumab)* Other routine risk minimisation measures beyond the Product Information: Legal status: POM

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cardiac dysfunction	Routine risk minimisation measures: • SmPC section 4.2, 4.4, 4.8, 5.1 • PL section 2, 4 • Warning in section 4.4 of the SmPC concerning the risk of cardiac dysfunction and the need for caution in patients with increased cardiac risk. Recommendations concerning cardiac assessment and monitoring before, during and after treatment with trastuzumab. Criteria for discontinuing or interrupting treatment with trastuzumab based on LVEF. The need to institute CHF treatment. • Cardiac undesirable effects listed in section 4.8 of the SmPC including Ejection fraction decreased, Cardiac failure congestive, Cardiogenic shock, Acute pulmonary oedema, Pulmonary oedema and Orthopnoea. Legal Status: Prescription only medicine	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Hypersensitivity	Routine risk minimisation measures: • *SmPC section 4.2, 4.3, 4.4, 4.8* • *PL section 2, 4* • Section 4.2 of the SmPC describes the correct method of administration for the first and subsequent infusions and the recommended observation times following these infusions. The need to be prepared for managing anaphylaxis and possible actions including interrupting or slowing the infusion rate if hypersensitivity reactions occur are also described. • Section 4.4 warns about the risk of hypersensitivity reactions and informs that patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. This section also provides information concerning pre-medication and treatment for these reactions and warns about the possibility of delayed reactions.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• Section 4.8 of the SmPC lists the following undesirable effects: Infusion related reaction, Erythema, Rash, Swelling face, Wheezing, Dyspnoea, Cough and Lip swelling, Hypersensitivity, Maculopapular rash, Pruritus, Asthma and Hypotension, Urticaria, Anaphylactic reaction, Anaphylactic shock, Angioedema, Respiratory distress, Respiratory failure, Bronchospasm and Laryngeal oedema. Legal Status: Prescription only medicine	
Oligohydramnios	Routine risk minimisation measures: • *SmPC section 4.6, 4.8* • *PL section 2, 4* • Section 4.6 of the proposed SmPC warns about the risk of oligohydramnios and foetal harm and advises that women of childbearing potential should use effective contraception during treatment and for 7 months after treatment with trastuzumab. The SmPC also states that trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. • If a pregnant woman is treated with trastuzumab, or if a patient becomes pregnant while receiving trastuzumab or within 7 months following the last dose of trastuzumab, close monitoring by a multidisciplinary team is desirable. • Section 4.8 of the proposed SmPC lists the following undesirable effects: Oligohydramnios, pulmonary hypoplasia and renal hypoplasia. Legal Status: Prescription only medicine	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaires for follow up of any reports of pregnancy (and outcome) and to analyse any adverse events of foetal harm for causal factors
Medication error (subcutaneous administration).	Routine risk minimisation measures: • SmPC section 4.2 • PL section 3 and tear off section • Warning in section 4.2 ‘Posology and method of administration’ of the SmPC concerning the administration of Zercepac, such that Zercepac intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only. In addition product will only be administered by healthcare professionals. Text is also included to prevent medication errors, re checking the vial labels to ensure that the medicinal product being prepared and administered correctly. Legal Status: Prescription only medicine	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire has been proposed for this safety concern

Part VI: Summary of the risk management plan

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. 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 https://www.ema.europa.eu/en/medicines/human/EPAR/zercepac.

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, 4.8 and 5.1. PL section 2, 4 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: 4.6 and 4.8. PL section 2, 4 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 PL section 3 and tear off section 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.' In addition, targeted follow-up questionnaires for the report of medication errors for IV administration of SC formulation or SC administration of IV formulation <u>Additional risk minimisation measures:</u> 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).

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

MAH has developed targeted follow-up questionnaires for following safety concerns:

- Pregnancy and birth outcomes
- Medication error.

Targeted Follow-up Questionnaires for Pregnancy and birth outcomes

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

Oligohydramnios, some associated with fatal pulmonary hypoplasia, and fetal renal impairment have been observed in some patients treated with Zercepac in the post-marketing setting. Oligohydramnios has been identified as an important identified risk for Zercepac, 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: **Zercepac** 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, specify type			
☐	Seizure disorders			
☐	Thyroid disorder			

☐	Smoking/ use of alcohol; specify	
☐	Family history of diabetes mellitus	
☐	Family history of congenital renal anomalies; if yes, 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/known, specify cause			
☐	Oligohydrominos			
☐	History of other pregnancy complications; specify			
☐	Other; specify			

	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) Measurements**	**Provider's assessment of AF**	**Estimated Fetal weight**	**Reported percentile Growth**	**Provider's assessment of growth**
	_____ Weeks	AF Index _____CM Maximum Vertical Pocket _____ CM Other _____ ☐ AF not measured	1 Normal 2 Abnormal 3 Oligohydramnios 4 Anhydramnios 5 Polyhydramnios 6 Delayed renal Development 7 Other: _____ 8 Not assessed	_____ Grams ☐ Not estimated	_____ ☐ Not reported ☐ Growth not measured	☐ Normal ☐ Abnormal ☐ IUGR * (< 10 % ile) ☐ Sever IUGR (< 3 % ile) ☐ Large for Gestational Age (> 90 %ile) ☐ Growth not measured

- ***IUGR=Intrauterine growth retardation**

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 Please check all that apply and provide detailed information on pregnancy-related complications on last page			
☐	Gestational Hypertension/ Preeclampsia/Eclampsia ☐ chronic hypertension ☐ pregnancy-induced hypertension ☐ Preeclampsia-eclampsia ☐ 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 Please check all that apply and provide detailed information on fetal complications on last page			
☐	Renal abnormalities in fetus ☐ Normal fetal kidneys and fluid filled bladder ☐ Delayed renal development ☐ Renal agenesis ☐ Cystic dysplasia ☐ Ureteral obstruction	Diagnostic tests: ☐ Ultrasonography	Start date/ Gestational age	Contributing factors
☐	Fetal abnormalities, including genetic disorders; if yes, specify	Diagnostic tests: ☐ Ultrasound ☐ Alpha-fetoprotein ☐ Amniocentesis ☐ Aneuploidy screening ☐ Other	Date/ Gest. age	Specify
☐	Post-maturity syndrome	Evidence:	Start date/ Gestational age	Contributing factors
☐	Death in utero; if yes/known, specify reason	Pathology results:	Date/ Gest. age	Contributing factors
☐	Other; specify			

Infant Information

Mode of birth	☐ Spontaneous vaginal delivery ☐ Forceps / vacuum ☐ 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 ☐ Neonatal death	Cause	
☐	Small for gestational age at birth (SGA)	☐ Gestational age ☐ Weight/length	Date of assessment	
☐	Congenital anomalies	☐ Major malformation A defect that has either cosmetic or functional significance to the child	Specify	
		☐ Minor malformation	Specify	

		A defect that occurs infrequently but has neither cosmetic nor functional significance to the child		
		☐ Deformation A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force)	Specify	
		☐ Disruption 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 ☐ Electrolyte imbalance ☐ Other	Lab results	
☐	Other; specify			

FOR INTERNAL USE ONLY
Company Awareness Date:
MCN:

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E- Mail: _____

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

	.....		
Function	.....	Tel. No.:	.....
Contact	.....	Fax No:	.....
address:			
	.....	Email:	.....

Detailed information on pregnancy-related complications

Please enter text in dynamic box below:

Zercepac® follow-up Questionnaire
Medication Errors

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

Patient Details:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

With the introduction of the Zercepac® and other trastuzumab-containing products, medication errors may occur. It is important to check the drug being prepared and administered is Zercepac® (trastuzumab) intravenous formulation and not another trastuzumab-containing product (e.g. trastuzumab emtansine or trastuzumab deruxtecan). By filling in this questionnaire, you will help us to gain an understanding of the types of errors that occur, which enable preventative measures to be put into place.

Details of medication error	
Date of medication error (dd-mmm-yyyy):	Zercepac® Start Date (dd-mmm-yyyy):
Zercepac® indication:	Dosage administered:
Product Administered: ☐ Zercepac® ☐ Trastuzumab emtamsine ☐ Trastuzumab deruxtecan Route of Administration: ☐ Intravenous (IV) ☐ Subcutaneous (SC)	

Description of the error (e.g. incorrect route, incorrect dose or overdose, accidental exposure, wrong technique in drug usage process, drug administration error etc.)

Zercepac® (Trastuzumab) Treatment Details	
Please provide details of the prescribed or intended treatment details of Zercepac®	
Zercepac® indication:	
Start Date (dd-mmm-yyyy):	End Date (if applicable): dd-mmm-yyyy):
Treatment Dosage	
Formulation prescribed: ☐ Zercepac®	

Adverse Events (as a result of the medication error)		
Adverse Event	**Onset Date (dd-mmm-yyyy)**	**Event Outcome (date if applicable: dd-mmm-yyyy)**
1.		
2.		
3.		
4.		

Relevant Medical History and Clinical Conditions

Concurrent / Previous Anti-neoplastic Drug Information

Drug name Generic/Trade	Start Date (dd-mmm-yyyy):	End Date (dd-mmm-yyyy):	On going
			O Yes
			O Yes
			O Yes

Other Concomitant Medications			
Drug name Generic/Trade	Start Date (dd-mmm-yyyy):	End Date (dd-mmm-yyyy):	On going
			O Yes
			O Yes
			O Yes

Relevant Laboratory Tests/Diagnostic Data						
Test	Baseline (pre-event onset)		At Event Onset		Following Event Resolution	
	Date (dd-mmm-yyyy)	Results	Date (dd-mmm-yyyy)	Results	Date (dd-mmm-yyyy)	Results

Reporter Details:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

None Proposed.