Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Trastucip and Tuzucip

Active ingredients: Trastuzumab

Sponsor: Cipla Australia Pty Ltd

April 2023

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$	Area under concentration-time curve from time zero to the time of last measurable concentration
AUC_{all}	Area under the concentration time curve from time zero to the time of last sample
AUC_{ss}	Area under the concentration-time curve at steady state
CI	Confidence interval
C_{max}	Maximum concentration
$C_{max,ss}$	Maximum concentration at steady state
C_{min}	Minimum concentration
$C_{min,ss}$	Minimum concentration at steady state
EU	European Union
HER2	Human epidermal growth factor receptor 2
HLX02	Trastuzumab product proposed for registration
PI	Product Information
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
RECIST	Response Evaluation Criteria in Solid Tumours
$t_{1/2}$	Half-life
TGA	Therapeutic Goods Administration
V_z	Volume of distribution during terminal phase

Product submission

Submission details

Type of submission:	New biosimilar medicine
Product names:	Trastucip and Tuzucip
Active ingredient:	Trastuzumab
Decision:	Approved
Date of decision:	7 July 2022
Date of entry onto ARTG:	18 July 2022
ARTG numbers:	368972 and 368990
, *Black Triangle Scheme:*	No
Sponsor's name and address:	Cipla Australia Pty Ltd Level 1/132-136 Albert Road, South Melbourne, VIC, 3205
Dose form:	Powder for injection for intravenous infusion
Strength:	150 mg
Container:	Vial
Pack size:	One
Approved therapeutic use:	***Early breast cancer*** *Trastucip and Tuzucip is indicated for the treatment of HER2-positive early breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.* ***Locally advanced breast cancer*** *Trastucip and Tuzucip are indicated for the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant Trastucip and Tuzucip.* ***Metastatic breast cancer*** *Trastucip and Tuzucip are indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:* *a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease;*

	b) in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or *c) in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer* ***Advanced gastric cancer*** *Trastucip and Tuzucip are indicated in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.*
Route of administration:	Intravenous infusion
Dosage:	Trastucip solution is for intravenous use only. Trastucip must not be used for subcutaneous administration. Trastucip must be administered as an intravenous infusion. Do not administer as an intravenous push or bolus. In order to prevent medication errors, it is important to check the labels to ensure the correct formulation (intravenous or subcutaneous) is being administered. Check the vial labels to ensure the medicine being prepared and administered is trastuzumab and *not* trastuzumab emtansine. See the Product Information for further information. *HER2 testing* HER2 testing is mandatory prior to initiation of Tuzucip therapy (see 4.2 Dosage and method of administration, Detection of HER2 protein overexpression and gene amplification, of the Product Information for further information). *Early breast cancer* *Three-weekly schedule*: the recommended initial loading dose is 8 mg/kg body weight, followed by a maintenance dose of 6 mg/kg body weight administered at 3 weekly intervals. *Weekly schedule*: the recommended initial loading dose is 4 mg/kg body weight, followed by a maintenance dose of 2 mg/kg body weight administered at weekly intervals. *Locally advanced breast cancer* *Three-weekly schedule*: the recommended initial loading dose is 8 mg/kg body weight, followed by a maintenance dose of 6 mg/kg body weight administered at 3 weekly intervals. *Metastatic breast cancer*

Three-weekly schedule: the recommended initial loading dose is 8 mg/kg body weight, followed by a maintenance dose of 6 mg/kg body weight administered at 3 weekly intervals.

Weekly schedule: the recommended initial loading dose is 4 mg/kg body weight, followed by a maintenance dose of 2 mg/kg body weight administered at weekly intervals.

Advanced gastric cancer

Three-weekly schedule: the recommended initial loading dose is 8 mg/kg body weight, followed by a maintenance dose of 6 mg/kg body weight administered at 3-weekly intervals.

For all indications

Refer to Section 5.1 Pharmacodynamic Properties, Clinical Trials (including Table 5 for early breast cancer) in the Product Information for the sequence and dosing of chemotherapy medicines used in the supporting pivotal trials.

Refer also to the currently approved Product Information for the chemotherapy partners.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Cipla Australia Pty Ltd (the sponsor) to register Trastucip and Tuzucip (trastuzumab) 150 mg powder for injection for intravenous infusion;[1] for the following proposed indication:

Early breast cancer

[1] Trastucip and Tuzucup are two different brand names for the same medicinal product. Where only one product name is used, the information given in this AusPAR applies to both Trastucip and Tuzucip.

Trastucip and Tuzucip is indicated for the treatment of HER2-positive early breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.

Locally advanced breast cancer

Trastucip and Tuzucip is indicated for the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant Trastucip and Tuzucip.

Metastatic breast cancer

Trastucip and Tuzucip is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:

a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease;

b) in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or

c) in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer

Advanced gastric cancer

Trastucip and Tuzucip is indicated in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Trastuzumab is a humanised immunoglobulin G1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). It is produced by mammalian Chinese hamster ovary cells. It binds with high affinity to subdomain IV of HER2's extracellular domain.

Overexpression of HER2 is observed in 20% to 30% of primary breast cancers;[2] as well as in some cases of gastric cancer. The rates of HER2 overexpression in gastric cancer vary across studies depending on the method of testing used (for example by immunohistochemistry, fluorescence, or chromogenic in situ hybridisation (FISH/CISH));[3] but HER2-positvity has been reported at between 6.8% to 42.6%.[4,5] Human epidermal growth factor receptor 2 overexpression can occur in early breast cancer and metastatic breast cancer.[6] Breast cancer patients with HER2 overexpression tend to have a shorter disease free survival than patients who have tumours that do not express HER2.[7]

The HER2 receptor is a transmembrane tyrosine kinase receptor, a member of the ErbB (HER) family of receptor tyrosine kinases. The HER2 receptor consists of an extracellular ligand-binding domain, a transmembrane region, and an intracellular or cytoplasmic tyrosine kinase domain.[8] Upon HER2 activation, these receptors form homodimers or

[2] Iqbal N, and Iqbal N. Human Epidermal Growth Factor Receptor 2 (HER2) in Cancers: Overexpression and Therapeutic Implications. *Mol Biol Int*. 2014; 2014: 852748.
[3] Van Cutsem E, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. *Gastric Cancer*. 2015;18(3):476-484.
[4] Takehana T, et al. Status of c-erbB-2 in gastric adenocarcinoma: a comparative study of immunohistochemistry, fluorescence in situ hybridization and enzyme-linked immuno-sorbent assay. *Int J Cancer.* 2002;98:833–837.
[5] Brien TP, et al. Prognostic factors in gastric cancer. *Mod Pathol.* 1998;11:870–877.
[6] Li, X. et al. Discovery and development of pyrotinib: a novel irreversible EGFR/HER2 dual tyrosine kinase inhibitor with favorable safety profiles for the treatment of breast cancer. *Eur. J. Pharm. Sci.* 110, 51–61 (2017).
[7] Yarden, Y. Biology of HER2 and its importance in breast cancer. *Oncology* 61(Suppl. 2), 1–13 (2001).
[8] Kovacs E., et al. A Structural Perspective on the Regulation of the Epidermal Growth Factor Receptor. *Annu. Rev. Biochem.* 2015;84:739–764.

heterodimers with other epidermal growth factor receptor (EGFR) proteins, leading to activation of the EGFR intracellular domains, and subsequent activation of downstream signalling cascades, including pathways promoting cell growth and survival and cell cycle progression.[9]

In binding selectively to the extracellular domain of the HER2 receptor, trastuzumab targets and prevents HER2-mediated signalling of the downstream pathways implicated in disease. In addition, trastuzumab also binds to the Fc receptors on immune effector cells, thought to facilitate antibody-dependent cellular cytotoxicity and immune destruction of HER2-expressing cancer cells.[10]

Trastuzumab (as the product Herceptin);[11] was first approved in Australia and registered on the Australian Register of Therapeutic Goods in September 2000. At present, trastuzumab is indicated for use in HER2 positive breast cancer and HER2 positive gastric cancer.

The reference product (Herceptin) has been successfully used in Australia for many years to treat HER2 positive breast cancers and more recently advanced gastric cancer.

This submission seeks to register Trastucip and Tuzucip as biosimilar medicines;[12] for use in for same indications approved for Herceptin, using Herceptin as the reference product with which to show biosimilarity.

There are multiple biosimilar trastuzumab products approved in Australia. The reference product, Herceptin (as an intravenous formulation) is soon to be removed from the market. However, there will continue to be subsidised access to equivalent, biosimilar medicines by the Australian Government's Pharmaceutical Benefits Scheme (PBS).

Regulatory status

This product is considered a new biosimilar medicine for Australian regulatory purposes.

The reference product for this new biosimilar medicine submission is Herceptin (trastuzumab), first approved in September 2000.[11]

The innovator and reference product, Herceptin;**Error! Bookmark not defined.** powder for injection was first approved by the TGA for the treatment of the HER2 expressing advanced breast cancer.

At the time the TGA considered this submission, similar submissions had been approved in the European Union (EU) on 27 July 2020, in Switzerland on 6 July 2021 and in China on 12 August 2020.

In addition a similar submission was under consideration in Switzerland (submitted on 23 December 2019).

[9] Albanell J, et al. Mechanism of action of anti-HER2 monoclonal antibodies: scientific update on trastuzumab and 2C4. Adv Exp Med Biol. 2003;532:253-68.
[10] Boekhout AH, Beijnen JH, Schellens JH: Trastuzumab. *Oncologist*. 2011;16(6):800-10.
[11] Herceptin was first registered in Australia on 14 September 2000. ARTG number: 73229.
[12] A **biosimilar medicine** is a version of an already registered biological medicine (the reference medicine). Both the biosimilar and its reference medicine will have the following similar characteristics (demonstrated using comprehensive comparability studies) for physicochemical, biological and immunological effects, and efficacy and safety.
Most biosimilar medicines are likely to contain biotechnology-derived proteins as the active substance(s), but biosimilar medicines, also include as those consisting of vaccines and polysaccharides, such as low molecular weight heparins.
Further information on biosimilar medicines is available on the TGA website: Biosimilar medicines regulation | Therapeutic Goods Administration (TGA)

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
China	19 March 2019	Approved on 12 August 2020	***Metastatic Breast Cancer:*** *This product is indicated for HER2-positive metastatic breast cancer: As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease; In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer.* ***Early breast cancer:*** *This product is indicated for HER2-positive Early breast cancer:* *- Received surgery, adjuvant chemotherapy with anthracycline antibiotics, and radiotherapy (if applicable) after monotherapy.* *- Doxorubicin and cyclophosphamide chemotherapy followed by combined adjuvant therapy of this product and paclitaxel or docetaxel.* *- Adjuvant therapy combined with docetaxel and carboplatin.* *- Combined with chemotherapy and neoadjuvant therapy, followed by adjuvant therapy, for locally advanced breast cancer (including inflammatory) or breast cancer with a tumor diameter > 2 cm.* ***Metastatic Gastric Cancer:*** *This product combined with capecitabine or 5-fluorouracil and cisplatin is suitable for patients with HER2-positive metastatic gastric adenocarcinoma or gastroesophageal junction adenocarcinoma who have not previously received treatment for metastatic disease.* *Trastuzumab can only be used in patients with metastatic gastric cancer who are HER2-positive, and HER2-positive is defined as IHC3+ or IHC2+/FISH+ results obtained using a validated test method.*
European Union	29 May 2019	Approved on 27 July 2020	***Early breast cancer*** *(when the cancer has spread within the breast or to the*

Region	Submission date	Status	Approved indications
			lymph nodes, under the arm but not to other parts of the body) after surgery, chemotherapy, and radiotherapy if applicable. It can also be used earlier in treatment, in combination with chemotherapy. For cancers that are locally advanced or more than 2 cm wide, Zercepac is used before surgery in combination with chemotherapy and then again after surgery on its own; ***Metastatic breast cancer**. It is used on its own when other treatments have not worked or are not suitable. It is also used in combination with other cancer medicines: paclitaxel or docetaxel, or with another type of medicine called an aromatase inhibitor;* ***Metastatic gastric (stomach) cancer**, in combination with cisplatin and either capecitabine or fluorouracil.* *Zercepac can only be used when the cancer overexpresses HER2: this means that the cancer produces a protein called HER2 in large quantities on the cancer cells. HER2 is overexpressed in about a quarter of breast cancers and a fifth of gastric cancers.*
Switzerland	23 December 2019	Approved on 6 July 2021	***Breast cancer*** *Overexpression of HER2 must be demonstrated using immunohistochemical methods with 3+ or via molecular biology methods [determination of HER2 gene amplification using fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH)] in the patient's tumor tissue before starting Zercepac treatment.* ***Metastatic breast cancer*** *Zercepac is indicated for the treatment of patients with metastatic breast cancer when the tumors have an overexpression of HER2:* *a. as a mono-therapeutic agent for the treatment of patients who have already received one or more chemotherapy treatments for their metastatic disease,* *b. in combination with paclitaxel or docetaxel for the treatment of patients*

Region	Submission date	Status	Approved indications
			who have not yet received chemotherapy for their metastatic disease, *c.in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone receptor-positive metastatic breast cancer who have not yet received chemotherapy for their metastatic disease.* *No data are available on patients with breast cancer who received Zercepac as an adjuvant treatment in the early stages of their disease.* ***Early-stage breast cancer*** *Zercepac is indicated for the treatment of patients suffering from HER2-positive early-stage breast cancer* *- following surgery, (neo-adjuvant or adjuvant) chemotherapy and (if applicable) radiation therapy.* *- 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 neo-adjuvant chemotherapy followed by adjuvant Zercepac for locally advanced (including inflammatory) breast cancer or tumors measuring > 2 cm in diameter.* ***Metastatic gastric carcinoma or cancer of the esophagogastric junction*** *Zercepac in combination with capecitabine or intravenous 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not yet received chemotherapy for their metastatic disease. Zercepac should only be used in patients with metastatic gastric carcinoma whose tumors have an overexpression of HER2, as defined by IHC2+ and confirmed by a positive FISH+ or silver in situ hybridization (SISH) result, or IHC3+ determined by a validated test.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2021-00873-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	2 July 2021
First round evaluation completed	25 February 2022
Sponsor provides responses on questions raised in first round evaluation	9 March 2022
Second round evaluation completed	4 May 2022
Delegate's Overall benefit-risk assessment	3 May 2022
Registration decision (Outcome)	7 July 2022
Completion of administrative activities and registration on the ARTG	18 July 2022
Number of working days from submission dossier acceptance to registration decision*	216

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

The following guidance documents were considered applicable to this submission:

- European Medicines Agency (EMA): Guideline on similar biological medicinal products. (CHMP/437/04 Rev. 1).

  TGA-adopted, effective date: 25 May 2015.

- EMA: Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues (EMEA/CHMP/BMWP/31329/2005).

  TGA-adopted, effective date: 29 September 2006.

- EMA: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1).

TGA-adopted, effective date: 1 July 2015.

- EMA: Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins (CHMP/EWP/89249/2004).

  TGA-adopted, effective date: 6 January 2006.

- EMA: Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

  TGA-adopted, effective date: 16 June 2011.

- EMA: Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006).

  TGA-adopted, effective date: 22 June 2009

- EMA: Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).

  TGA-adopted, effective date: 17 August 2015

- EMA: Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006).

  TGA-adopted, effective date: 22 June 2009

- EMA: Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4).

  TGA-adopted, effective date: 1 April 2014

- EMA: Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/703715/2012 Rev. 2).

  TGA-adopted, effective date: 15 February 2016.

- TGA: Guideline on biosimilar medicines regulation by Australian Government Department of Health, Version 2.2.

  Last updated April 2018

- TGA: Guidance on Biopharmaceutic studies: Section 15.6 choice of the reference product for bioequivalence of generic medicines; The conditions for bioequivalence studies using an overseas reference product.

  Guideline on Biopharmaceutic studies by Australian government department of health. Version 1.2. Last updated: December 2019

In addition, the following non-TGA-adopted guidance was relevant to this submission:

United States (US) Food and Drug Administration: Guidance for Industry, Population Pharmacokinetics, draft. July 2019.

Quality

Trastuzumab is a recombinant humanised immunoglobulin G1-kappa monoclonal antibody against the human epidermal growth factor receptor 2 (HER2) protein and is expressed in Chinese hamster ovary cells. As such, trastuzumab is expected to target specifically HER2 protein by directly binding the extracellular domain of the receptor. Trastuzumab inhibits proliferation of HER2 overexpressing cells and induces loss of intrinsic resistance of cells that overexpress HER2 to the cytotoxic effects of tumour necrosis factor alpha (TNFα).

Trastucip/Tuzucip (also referred to as HLX02);[13] is a disulphide bond linked tetramer consisting of two identical 450 amino acid glycosylated heavy chains and two identical 214-amino acid kappa light chains. The whole antibody contains four pairs of interchain and 12 pairs of intrachain disulfide bonds, and one N-linked glycosylation site (N300) at each heavy chain.

Trastucip is available in a 150 mg vial dosage presentation as a sterile, lyophilised powder for reconstitution for infusion. Trastucip is presented as a lyophilised formulation of the same composition as the reference medicinal product Herceptin (EU-sourced Herceptin).

The product is available in a 20 mL type I borosilicate glass vial, a 20 mm bromobutyl rubber lyophilisation stopper and a 20 mm aluminium-plastic combination cap.

The sponsor proposed a shelf life of 24 months at -40 °C ± 5 °C and protected from light.

Stability data have been generated under real time and stressed conditions to characterise the stability profile of the active ingredient and to establish a shelf life. The real time data submitted support a shelf life of 24 months when stored at -40 °C ± 5 °C.

Conclusion

There are no objections, on quality grounds, to the registration of Trastucip and Tuzucip.

Nonclinical

There are no nonclinical objections to the registration of Trastucip provided comparability between Trastucip and EU-sourced and China-sourced Herceptin has been demonstrated by quality and clinical data.

The nonclinical dossier contained comparative studies on pharmacology (*in vivo* studies), pharmacokinetics and repeat dose toxicity, and tissue cross reactivity. The scope of the nonclinical program is adequate under the relevant EU guideline. These studies were conducted using EU-sourced and China-sourced Herceptin as the reference products. *In vitro* pharmacology studies are provided in the quality dossier and were reviewed by quality evaluation. No data were provided in the nonclinical dossier to verify the comparability of the EU/China-sourced and Australia-sourced Herceptin.

No meaningful differences between Trastucip and EU- and China-sourced Herceptin were observed in the comparative pharmacology, pharmacokinetic and toxicity studies, and in *in vitro* tissue cross reactivity tests.

The draft PI statements pertaining to nonclinical data are consistent with the PI of the innovator product.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- One pharmacokinetic study
  - Study HLX02-HV01; Part 1, a Phase I, open label, single dose escalation study to evaluate the safety and tolerability of different doses of HLX02 (Trastucip / trastuzumab biosimilar).

[13] HLX02 is the drug development code for the trastuzumab product proposed for registration

  - Study HLX02-HV01; Part 2, a Phase I, double blind, randomised, parallel study to compare the pharmacokinetic profile of HLX02 (Trastucip), China-sourced Herceptin and EU-sourced Herceptin.

- One efficacy/safety study
  - Study HLX02-BC01, a Phase III, double blind, randomised, parallel, active controlled study to compare the efficacy of HLX02 (Trastucip) versus EU-sourced Herceptin in combination with docetaxel using overall response rate at Week 24.
- One population pharmacokinetic (PopPK) analysis:
  - A selected covariant PopPK modelling of data collected from Part II of Phase I Study HLX02-HV01 and Phase III Study HLX02-BC01 to estimate patient demographic inter-individual pharmacokinetic variability (dated 17 April 2021).

Pharmacology

Pharmacokinetics

The comparative pharmacokinetic (PK) study was conducted in two parts. Part 1 was an open label, single dose escalation of Trastucip (the trastuzumab product proposed for registration) to evaluate safety, tolerability and immunogenicity. Twelve healthy Chinese men received single doses of Trastucip of 2, 4, 6 or 8 mg/kg with three subjects receiving each dose. This component of the study was performed to evaluate the safety and tolerability at different doses of Trastucip and to evaluate the immunogenicity of Trastucip and characterise the PK profile of Trastucip at different doses. This component of the study was required by the Chinese regulatory agency. It did not include a comparison with a reference product. No analyses were performed on plasma protein binding, hepatic metabolism, drug-drug interactions, special populations and other intrinsic and extrinsic PK factors. Part 1 showed increases in area under the concentration time curve from time zero to infinity ($AUC_{0\text{-}inf}$) greater than dose proportional. Mean values for the secondary endpoints of the observed exposure (area under concentration time curve from time zero to the time of last measurable concentration ($AUC_{0\text{-}t}$)), the area under the concentration time curve from time zero to the last sampling point (AUC_{all}) even if unquantifiable, maximum concentration (C_{max}), and half life ($t_{1/2}$) all increased in a dose dependent manner, while time after administration of a drug when the maximum plasma concentration is reached and volume of distribution during terminal phase (V_z) were similar across the four treatment groups. Clearance decreased with dose.

Part 2 of this study compared the PK profiles and assessed the safety, tolerability, and immunogenicity similarity of Trastucip , China-sourced (US-manufactured) Herceptin, and EU-sourced (Germany-manufactured) Herceptin. In this randomised, double blind, three armed, parallel group, controlled study a total of 111 healthy Chinese male subjects were enrolled, with 37 subjects in each treatment group. Subjects enrolled in Part 1 of the study were not to participate in Part 2. Subjects were randomised at 1:1:1 ratio to receive a single 6 mg/kg intravenous infusion of either Trastucip, or China-sourced Herceptin or EU-sourced Herceptin for 90 minutes. Blood samples were collected to Day 57 post dose.

Three way PK bioequivalence between any of the three potential product versus product comparisons (Trastucip versus EU-sourced Herceptin; Trastucip versus China-sourced Herceptin; and China-sourced Herceptin/EU-sourced Herceptin) was assessed on the basis of the 90% confidence interval (CI) of the estimated least squares mean ratios of their primary PK parameter $AUC_{0\text{-}inf}$, in relation to the conventional bioequivalence criteria of 0.8 to 1.25.

Pharmacokinetic similarity was demonstrated between Trastucip and China-sourced Herceptin and EU-sourced Herceptin. The 90% CI of the geometric mean ratio for each

product pairwise comparison for the primary pre-specified PK endpoint of $AUC_{0\text{-}inf}$ fell within the pre-specified margin of 80% to 125% as shown in Table 3 and Table 4 below.

Table 3: Study HLX02-HV01 Statistical comparison of pharmacokinetic parameters between HLX02 and EU-sourced Herceptin (based on uncorrected serum concentration data)

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio of A/B	90% CI of Ratio
$AUC_{0\text{-}inf}$ (µg·h/mL)	HLX02	37	37	20400.2	0.855	(0.803, 0.911)
	EU-sourced Herceptin	37	37	23846.9		
$AUC_{0\text{-}t}$ (µg·h/mL)	HLX02	37	37	20254.8	0.856	(0.804, 0.911)
	EU-sourced Herceptin	37	37	23656.8		
AUC_{all} (µg·h/mL)	HLX02	37	37	20254.8	0.856	(0.804, 0.911)
	EU-sourced Herceptin	37	37	23656.8		
C_{max} (µg/mL)	HLX02	37	37	130.160	0.978	(0.916, 1.043)
	EU-sourced Herceptin	37	37	133.116		

Abbreviations: $AUC_{0\text{-}inf}$ = area under the concentration time curve from time zero to infinity, $AUC_{0\text{-}t}$ = area under concentration time curve from time zero to the time of last measurable concentration, AUC_{all} = area under concentration time curve from time zero to the time of last measurable concentration area under the concentration time curve from time zero to the time of the last measurement regardless of whether it is quantifiable point, C_{max} = maximum concentration, geo-LSMean = geometric least-squares mean ratio, CI = confidence interval, PK = pharmacokinetic(s)

Table 4: Study HLX02-HV01 Statistical comparison of pharmacokinetic parameters between HLX02 and China-sourced Herceptin (based on uncorrected serum concentration data)

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio of A/B	90% CI of Ratio
$AUC_{0\text{-}inf}$ (µg·h/mL)	HLX02	37	37	20400.2	0.882	(0.827, 0.940)
	CN-sourced Herceptin	35	35	23140.6		
$AUC_{0\text{-}t}$ (µg·h/mL)	HLX02	37	37	20254.8	0.882	(0.827, 0.939)
	CN-sourced Herceptin	35	35	22976.3		
AUC_{all} (µg·h/mL)	HLX02	37	37	20254.8	0.882	(0.827, 0.939)
	CN-sourced Herceptin	35	35	22976.3		
C_{max} (µg/mL)	HLX02	37	37	130.160	0.922	(0.864, 0.985)
	CN-sourced Herceptin	35	35	141.115		

Abbreviations: $AUC_{0\text{-}inf}$ = area under the concentration time curve from time zero to infinity, $AUC_{0\text{-}t}$ = area under concentration time curve from time zero to the time of last measurable concentration, AUC_{all} = area under concentration time curve from time zero to the time of last measurable concentration area under the concentration time curve from time zero to the time of the last measurement regardless of whether it is quantifiable point, C_{max} = maximum concentration, geo-LSMean = geometric least-squares mean ratio, CI = confidence interval, PK = pharmacokinetic(s)

Population pharmacokinetic data

A population pharmacokinetic (popPK) analysis was performed at the request of the European Medicines Agency. The popPK model was developed based on a dataset of 754 subjects with 5,882 samples enrolled in two clinical studies. This analysis allowed an estimate of typical values and inter-individual variability of PK parameters in healthy volunteers and patients with HER2 positive, recurrent or previously untreated metastatic breast cancer. It also allowed an assessment of the effects of demographic (for example, age, body weight, race (Asian versus Non-Asian subjects)), pathophysiologic (for example, HER2 receptor (shed antigen)), and immunogenicity related covariates (for example, anti-drug and neutralising anti-drug antibodies) on the PK of both Trastucip and Herceptin.

The model predicted higher Trastucip exposures in anti-drug antibody or neutralising anti-drug antibody negative subjects compared with anti-drug antibody or neutralising anti-drug antibody positive subjects. However, it is not meaningful due to limited sample size. Steady state exposures in Asians were lower than those of in non-Asians (12.2%, 9.67% and 14.3% lower for area under the concentration time curve at steady state (AUC_{ss}), maximum concentration at steady state ($C_{max,ss}$), and minimum concentration at steady state ($C_{min,ss}$) of Trastucip ; 8.14%, 8% and 5.1% lower for AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$ of Herceptin). This is partially attributed to the lower body weight in Asian subjects as compared to non-Asian subjects (60 kg versus 75 kg for Trastucip, 60 kg versus 72 kg for Herceptin).

No significant difference is identified in steady state exposures between Trastucip and EU-sourced Herceptin/ China-sourced Herceptin. Steady state exposures in healthy volunteers were lower than those in patients for both HLX02 (11.3% for AUC_{ss}, 1.98% for $C_{max,ss}$, and 25.7% for $C_{min,ss}$) and EU-sourced Herceptin (7.31% for AUC_{ss}, 0.572% for $C_{max,ss}$, and 18.4% for $C_{min,ss}$).

Efficacy

Study HLX02-BC01, a Phase III clinical comparative study was performed. Clinical input was provided by the Committee for Medicinal Products for Human Use (European Medicines Agency, European Union). As of January 2020, this study was ongoing to monitor overall survival at 24 and 36 months. The data presented was to 10 July 2019 (data cut-off date).

Study HLX02-BC01 is a double blind, randomised, two arm parallel controlled, multicentre, international study to compare the efficacy of Trastucip versus EU-sourced Herceptin in combination with docetaxel;[14] using overall response rate at Week 24, to demonstrate clinical bioequivalence. A total of 649 patients from 89 sites (81 with enrolment) in China, Ukraine, Philippines and Poland were randomised to receive the study treatment (Trastucip (the trastuzumab biosimilar) or EU-sourced Herceptin (trastuzumab), in combination with docetaxel) either at time of first evidence for metastatic disease, or at time of relapse after prior diagnosis of early breast cancer, provided (neo-adjuvant treatment was completed for at least 12 months prior to study enrolment except hormone therapy, which must be stopped at least 2 weeks before randomisation). Patients were required to have HER2 overexpressing metastatic breast cancer and have not received chemotherapy or biologic therapy for their metastatic disease.

Trastucip or EU-sourced Herceptin was administered intravenously at a loading dose of 8 mg/kg over 90 minutes on Day 1, Cycle 1 followed by at a dose of 6 mg/kg once every three weeks in 3-weekly cycles for up to a maximum of 12 months. Docetaxel (75 mg/m^2) was co-administered intravenously (after Trastucip or EU-sourced Herceptin) once every three weeks for at least eight cycles and thereafter at the investigator's discretion for up to a maximum of 12 months.

Tumour response for the primary efficacy analysis was evaluated by an independent, blinded central imaging review according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1);[15] for determination of tumour response up to Week 24,

[14] Docetaxel was first registered in Australia on 6 December 2010. ARTG number: 163801.
[15] The Response Evaluation Criteria In Solid Tumours (RECIST) is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in February 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective

after completion of up to eight cycles of treatment. For patients with multiple measurable lesions, a maximum of two lesions per organ and five lesions in total that were representative of all involved organs were designated as target lesions and recorded and measured at screening period. A central imaging review occurred at screening period to confirm eligibility and at Weeks 6, 12, 18, and 24 to compare the pattern of response.

The primary evaluation parameter of the efficacy in this study was overall response rate at Week 24, calculated as the proportion of patients with a best response of complete response or partial response from first assessment up to Week 24 according to RECIST 1.1.[15]**Error! Bookmark not defined.** Secondary efficacy endpoints were objective response rate at Weeks 6, 12, 18, and 24, duration of response, disease control rate, clinical benefit rate, progression free survival up to 12 months, and overall survival at 12, 24, and 36 months.

An equivalence margin for overall response rate at Week 24 was derived from two published studies comparing overall response rate following treatment with Herceptin and paclitaxel;[16] or equivalent, versus paclitaxel or equivalent alone. An equivalence limit marginally tighter than the lower bound of that confidence interval was used as the criterion of equivalence: (-0.1350, 0.1350). This equivalence margin also meets the European Medicines Agency scientific advice suggestion (12% to 14%).

Equivalence, defined as overall response rate at Week 24 was demonstrated as shown below in Table 5.

Table 5: Study HLX02-BC01 Summary of overall response rate up to Week 24 by central imaging review in intention to treat set

Characteristics	Trastucip N = 324	Herceptin N = 325
Best overall response		
Complete response (CR), n (%)	17 (5.2)	12 (3.7)
Partial response (PR), n (%)	214 (66)	220 (67.7)
Non-complete response/non-progressive disease (non CR/non PD), n (%)	5 (1.5)	3 (0.9)
Stable disease (SD), n (%)	48 (14.8)	65 (20)
Progressive Disease (PD), n (%)	24 (7.4)	16 (4.9)
Inevaluable (NE)	16 (4.9)	9 (2.8)
Objective response rate		
n (%)	231 (71.3)	232 (71.4)
Risk ratio and 90% CI	0.999 (0.920, 1.0084)	
Asymptotic 95% CI of the rate	66.4, 76.2	66.5, 76.3
Difference and 95% CI	-0.1 (-7, 6.9)	
Stratified difference and 95% CI	0.1 (-6.9, 7)	
CMH test P-value	0.983	

response in solid tumours use RECIST. These criteria were developed and published in February 2000, and subsequently updated in 2009.

[16] Paclitaxel was first registered in Australia on 12 January 1995. ARTG number: 50577.

Abbreviations: CI = confidence interval, CMH = Cochran-Mantel-Haenszel, CR = complete response, ITT = intention to treat, NE = inevaluable, non CR/non PD = non-complete response/non-progressive disease, ORR= objective response rate, PD = progressive disease, PR = partial response, SD = stable disease.

Sensitivity analyses were generally consistent with the primary analysis of overall response rare at Week 24. The secondary efficacy endpoint results also showed comparable results for the two trastuzumab products. Of note in the intention to treat set, by cut-off date, number of patients with progression events in Trastucip and Herceptin treatment groups was 159 (49.1%) versus 174 (53.5%); number of patients censored in Trastucip and Herceptin treatment groups was 165 (50.9%) versus 151 (46.5%). The median progression free survival in HLX02 and Herceptin treatment groups was 11.73 months versus 10.55 months, no statistical difference was found between two treatment groups (p = 0.086).

Safety

A total of 772 subjects received at least one dose of study drug in the two studies (Trastucip (n = 373), China-sourced Herceptin [n = 37], and EU-sourced Herceptin (n = 362)). Of the 772 subjects, 649 received at least one infusion of the study drug (Trastucip (n = 324) and EU-sourced Herceptin (n = 325)) in the Phase III study. Safety results were not pooled.

Adverse events of special interest for trastuzumab (of any source) include: infusion related reactions; cardiac dysfunction; hypersensitivity reactions including anaphylaxis; pulmonary reactions; tumour lysis syndrome; and haematotoxicity. There were no clinically meaningful differences in these events in the two patient groups in the Phase III study.

Immunogenicity was assessed in both studies. In Study HLX02-BC01, a total of 23 (3.6%) patients (six (1.9%) in Trastucip and 17 (5.3%) in Herceptin group) tested positive for anti-drug antibody at screening. These patients were not considered for immunogenic response analysis. Anti-drug antibody positivity without prior exposure has been previously reported. In this study only four patients had prior exposure to trastuzumab.

During the study, a total of four (0.6%) patients (two patients in each treatment group), tested overall positive results for anti-drug antibody. The mean trastuzumab serum concentrations at the individual time point were generally similar between Trastucip and Herceptin treatment groups regardless of the anti-drug antibody status. Consistent safety results were observed between the four anti-drug antibody positive patients. None of the four patients were reported with any serious adverse event and one patient in Herceptin group experienced an infusion related reaction. In Study HLX02-HV01 two subjects were positive for anti-drug antibody at screening and no subjects developed anti-drug antibody after exposure.

In Study HLX02-BC01 0.6% patients, two in each treatment arm, had at least one positive result for neutralising anti-drug antibody. No meaningful differences between mean trastuzumab levels in the overall neutralising anti-drug antibody negative and neutralising anti-drug antibody positive groups were seen for either Trastucip or EU-sourced Herceptin.

Risk management plan

The sponsor is required to comply with product vigilance and risk minimisation requirements.

Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Risk-benefit analysis

Delegate's considerations

The clinical component of this submission has demonstrated satisfactory pharmacokinetic and clinical similarity. The biochemistry and nonclinical aspects were satisfactory.

Proposed action

The Delegate considers that the sponsor's trastuzumab product under the tradenames Trastucip and Tuzucip is approvable.

Advisory Committee considerations

The Delegate did not refer this submission to the Advisory Committee on Medicines for advice.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Trastucip and Tuzucip (trastuzumab) 150 mg powder for injection for intravenous infusion, indicated for:

Early breast cancer

Trastucip and Tuzucip are indicated for the treatment of HER2-positive early breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.

Locally advanced breast cancer

Trastucip and Tuzucip are indicated for the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant Trastucip and Tuzucip.

Metastatic breast cancer

Trastucip and Tuzucip are indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:

a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease;

b) in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or

c) in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer

Advanced gastric cancer

Trastucip and Tuzucip are indicated in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Specific conditions of registration applying to these goods

No specific conditions of registration unique to this submission.

Attachment 1. Product Information

The PI for Trastucip and Tuzucip approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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