



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Pertuzumab/trastuzumab

Proprietary Product Name: Phesgo SC

Sponsor: Roche Products Pty Ltd

September 2021

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
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Contents

List of abbreviations	4
I. Introduction to product submission	6
Submission details _____	6
Product background _____	7
Regulatory status _____	10
Product Information _____	11
II. Registration timeline	11
III. Submission overview and risk/benefit assessment	12
Quality _____	12
Nonclinical _____	13
Clinical _____	14
Risk management plan _____	18
Risk-benefit analysis _____	18
Outcome _____	19
Attachment 1. Product Information	20

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
ADCC	Antibody dependent cell mediated cytotoxicity
AE	Adverse event
AIHW	Australian Institute of Health and Welfare
Akt	Protein kinase B
ALT	Alanine transaminase
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
AUC _{21d}	Area under the concentration-time curve at 21 days
AUC _{IV}	Area under the concentration-time curve for the intravenous route
AUC _{SC}	Area under the concentration-time curve for the subcutaneous route
CI	Confidence interval
C _{max}	Maximum concentration
CPD	Certified Product Details
C _{trough,ss}	Trough concentration at steady state
EBC	Early breast cancer
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency (European Union)
ER	Estrogen receptor
EU	European Union
Fc	Fragment crystallisable
FDA	Food and Drug Administration (United States of America)

Abbreviation	Meaning
FDC	Fixed dose combination
GMR	Geometric mean ratio
HER2	Human epidermal growth factor receptor 2
HER3	Human epidermal growth factor receptor 3
ICD	International Classification of Diseases
IgG1	Immunoglobulin G1
IRR	Injection/infusion-related reaction
IV	Intravenous
MBC	Metastatic breast cancer
mTor	Mammalian target of rapamycin
PBMC	Peripheral blood mononuclear cell
PI	Product Information
PI3K	Phosphatidylinositol-3-kinase
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PR	Progesterone receptor
PSUR	Periodic safety update report
rHuPH20	Recombinant human hyaluronidase PH20 enzyme
SAE	Serious adverse event
SC	Subcutaneous
SEER	Surveillance, epidemiology and end results
TGA	Therapeutic Goods Administration
T _{max}	Time to maximum concentration
tpCR	Total pathological complete response
USA	United States of America

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New combination of active ingredients
<i>Product name:</i>	Phesgo SC
<i>Active ingredients:</i>	Pertuzumab/trastuzumab
<i>Decision:</i>	Approved
<i>Date of decision:</i>	5 May 2021
<i>Date of entry onto ARTG:</i>	6 July 2021
<i>ARTG numbers:</i>	332180 and 332181
<i>, Black Triangle Scheme:¹</i>	No
<i>Sponsor's name and address:</i>	Roche Products Pty Ltd Level 8, 30–34 Hickson Road Sydney NSW 2000
<i>Dose form:</i>	Solution for injection
<i>Strengths:</i>	1200 mg/15 mL pertuzumab and 600 mg/15 mL trastuzumab 600 mg/10 mL pertuzumab and 600 mg/10 mL trastuzumab
<i>Container:</i>	Vial
<i>Pack size:</i>	One
<i>Approved therapeutic use:</i>	Early breast cancer (EBC) <i>Phesgo is indicated in combination with chemotherapy for the:</i> <ul style="list-style-type: none"> <i>neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either > 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer</i> <i>adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence</i> <i>Select patients for therapy based on a validated test.</i>

¹ The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Metastatic breast cancer (MBC)

Phesgo is indicated in combination with docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Select patients for therapy based on a validated test.

Route of administration: Subcutaneous

Dosage: Phesgo SC therapy should only be initiated under the supervision of a physician experienced in the use of anti-cancer agents.

Phesgo SC should always be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation facilities are immediately available (see Section 4.4 Special warnings and precautions for use in the Product Information).

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 application by Roche Products Pty Ltd (the sponsor) to register Phesgo SC (pertuzumab/trastuzumab) 1200 mg/15 mL pertuzumab and 600 mg/15 mL trastuzumab; 600 mg/10 mL pertuzumab and 600 mg/10 mL trastuzumab, solution for injection for the following proposed indication:

Early breast cancer (EBC)

Phesgo is indicated in combination with chemotherapy for the:

- *neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either >2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer*
- *adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence*

Metastatic breast cancer (MBC)

Phesgo is indicated in combination with docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Over 1.2 million women world-wide receive a diagnosis of breast cancer every year. This is a disease affecting 10% to 12% of women.² Around 94% to 95% of breast cancer patients in the United States of America (USA) and Europe are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread.³ Since human epidermal growth factor receptor 2 (HER2)-positive disease accounts for approximately 20% of cases of breast cancer,⁴ it is estimated that approximately 264,000 new cases of HER2-positive breast cancer occur each year globally. Mortality from breast cancer is typically due to metastatic disease.

Based on a review of 107 published studies, Ross et al. (2009);⁴ reported that the mean relative risk for poor outcome (overall survival) of untreated HER2-positive breast cancer was 2.74 (range from 1.39 to 6.93). Despite advances in the treatment of breast cancer, approximately 30% of women initially diagnosed with earlier stages of breast cancer eventually develop recurrent advanced or metastatic disease.⁵ According to an analysis of the surveillance, epidemiology and end results (SEER) data (n = 1800), Stage IV breast cancer is associated with a 27-fold increase in mortality compared to Stage I disease.⁶

The Australian Institute of Health and Welfare (AIHW) collects Australian data on breast cancer incorporating the International Classification of Diseases (ICD);⁷ tenth edition cancer code C50 (malignant neoplasm of the breast), although it does not distinguish between stages or record biomarker status (such as HER2). AIHW projections predicted age standardised incidence rates of 132.6 cases per 100,000 females and 1.1 cases per 100,000 males for 2020.⁸ Age standardised mortality was projected to be 18.1 deaths per 100,000 females (second to lung cancer) and 0.2 cases per 100,000 males for 2020. Between 2012 and 2016, the five year survival rate for breast cancer was 91.1% (95% confidence interval (CI): 90.8, 91.3).

The sponsor stated that the combination of Perjeta;⁹ with Herceptin;¹⁰ and chemotherapy has become standard of care for treating HER2-positive early breast cancer and metastatic breast cancer. Perjeta given intravenously (IV) in combination with Herceptin given subcutaneously (SC) and chemotherapy is approved in Australia for the neoadjuvant and adjuvant treatment of early breast cancer and for the treatment of metastatic breast cancer.

² Benson, J.R. et al. Early Breast Cancer, *Lancet*, 2009; 373: 1463-1479.

³ Howlader, N. et al. SEER Cancer Statistics Review, 1975-2010, National Cancer Institute, 2013. Available from SEER.cancer.gov website.

⁴ Ross, J.S. et al. The HER-2 Receptor and Breast Cancer: Ten Years of Targeted Anti-HER-2 Therapy and Personalized Medicine, *Oncologist*, 2009; 14: 320-368.

⁵ O'Shaughnessy, J. Extending Survival with Chemotherapy in Metastatic Breast Cancer, *Oncologist*, 2005; 10 Suppl 3: 20-29.

⁶ Yancik, R. et al. Effect of Age and Comorbidity in Postmenopausal Breast Cancer Patients Aged 55 Years and Older. *JAMA*, 2001; 285: 885-892

⁷ The **International Classification of Diseases (ICD)** is a diagnostic classification standard compiled and maintained by the World Health Organization (WHO) and is used to classify diseases and other health problems on many types of health and vital (essential to life) records, as well as death certificates. As well as enabling the storage and retrieval of diagnostic information for clinical, epidemiological (which deals with the study of the causes, distribution, and control of disease in populations) and quality purposes, ICD records also form the basis for compiling national mortality and morbidity statistics by WHO Member States.

⁸ Australian Institute of Health and Welfare (AIHW) Cancer Data in Australia. 2020, Cat. No. CAN 122. Canberra: AIHW, viewed 11 June 2020. Available from aihw.gov.au website.

⁹ Perjeta was first registered on the ARTG on 6 May 2013 (ARTG number: 196218).

¹⁰ Herceptin was first registered on the ARTG on 3 December 2010 (ARTG number: 171014).

Trastuzumab is a recombinant immunoglobulin G1 (IgG1) kappa monoclonal antibody that selectively targets the extracellular domain of the HER2 protein.¹¹ The innovator product is Herceptin;¹¹ and was originally developed as product for IV administration, however a SC Herceptin formulation and five trastuzumab biosimilar products (Herzuma,¹² Kanjinti,¹³ Ogivri,¹⁴ Ontruzant;¹⁵ and Trazimera;¹⁶) have been registered in recent years.¹⁷ Antibody dependent cell mediated cytotoxicity (ADCC) is the most strongly supported mechanism of action for trastuzumab against HER2-positive cancers.¹⁸ In ADCC, the fragment crystallisable (Fc) portion of trastuzumab is recognised by immune effector cells, principally natural killer cells, which attack the cancer cell to which trastuzumab is bound. Herceptin, as a monotherapy, is registered for the treatment of early breast cancer and metastatic breast cancer. None of the registered Herceptin indications in Australia make mention of pertuzumab.¹¹

Pertuzumab is a fully humanised, recombinant IgG1 kappa monoclonal antibody that specifically interacts with subdomain II of the HER2 extracellular domain, sterically blocking a binding pocket necessary for receptor dimerisation.¹⁹ The innovator product is Perjeta (for IV administration);¹⁹ and no biosimilars or other formulations are currently registered in Australia. The limited available data mostly indicate that pertuzumab's mechanism of action primarily relies on blocking heterodimerisation between HER2 and HER3 receptors, which in turn blocks the activation of HER2 and HER3 mediated signal transduction pathways leading to cancer cell proliferation and survival.¹⁸

As constitutive activation of HER2/HER3 heterodimer mediated activation of phosphatidylinositol-3-kinase (PI3K), protein kinase B (Akt), and mammalian target of rapamycin (mTor) protein kinases is an important oncogenic signalling pathway driving the development of breast cancer, and has been identified as a major mechanism of trastuzumab resistance, there is scientific rationale for combination therapy with both pertuzumab and trastuzumab in breast cancer.¹⁸ Randomised clinical trials have indicated that pertuzumab adds clinical benefit when given in combination with trastuzumab to patients with locally advanced, inflammatory and early breast cancer suitable for neoadjuvant treatment, to patients with operable early breast cancer at high risk of recurrence, and to patients with locally recurrent breast cancer and metastatic breast cancer. The aforementioned randomised studies have all been reviewed previously by the Therapeutic Goods Administration (TGA), and are reflected in the approved Australian Product Information for Perjeta as they supported its approval for these uses, all in combination with trastuzumab.¹⁹ Pertuzumab is not registered in Australia for any monotherapy indications.

This application proposes a new fixed dose combination (FDC) product of trastuzumab and pertuzumab that are both already approved in Australia for the treatment of early breast cancer and metastatic breast cancer. The sponsor stated that Phesgo SC has been developed to offer patients a less invasive and faster administration of pertuzumab and trastuzumab as a single product compared to individual IV infusions. The sponsor noted

¹¹ Australian Product Information for Herceptin. Available at:

<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-02054-3>

¹² Herzuma was first registered on the ARTG on 17 July 2018 (ARTG number: 289146).

¹³ Kanjinti was first registered on the ARTG on 16 May 2019 (ARTG number: 296881, 296882 and 296883).

¹⁴ Ogivri was first registered on the ARTG on 11 December 2018 (ARTG number: 288222 and 288223).

¹⁵ Ontruzant was first registered on the ARTG on 9 January 2019 (ARTG number: 298457).

¹⁶ Trazimera was first registered on the ARTG on 19 August 2019 (ARTG number: 304049 and 304050).

¹⁷ List of products registered on the Australian Register of Therapeutic Goods (ARTG) that contain

trastuzumab. Search conducted 11 January 2020. Available at: [https://tga-](https://tga-search.clients.funnelback.com/s/search.html?query=trastuzumab&collection=tga-artg)

[search.clients.funnelback.com/s/search.html?query=trastuzumab&collection=tga-artg](https://tga-search.clients.funnelback.com/s/search.html?query=trastuzumab&collection=tga-artg)

¹⁸ Nami, B. et al. Mechanisms Underlying the Action and Synergism of Trastuzumab and Pertuzumab in Targeting HER2-Positive Breast Cancer. *Cancers (Basel)*, 2018; 10(10): 342.

¹⁹ Australian Product Information for Perjeta. Available at:

<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01655-1>

that the pertuzumab and trastuzumab formulations in Phesgo SC are identical to the IV formulations. Phesgo SC is administered SC, as a fixed non-weight based dose, which is similar to the approved Perjeta IV and Herceptin SC formulations. Administration and post-dose observation times for Phesgo SC are shorter than those for the IV formulations.

The sponsor noted the long treatment period associated with targeted HER2 therapy, which may extend from one to several years for some patients depending on the indication. The required procedure to establish IV access is considered invasive. Patients who are treated repeatedly, especially those with malignant diseases, often require installation of a port under the skin which can be associated with increased risk of infection, thrombosis, discomfort and high cost.

The sponsor noted that available data from other SC administered monoclonal antibodies (Herceptin and Mabthera);²⁰ have consistently demonstrated that SC administration results in comparable and consistent anti-tumour activity to the IV administration, and that patient and health care providers prefer SC to IV administration.

Regulatory status

This product is considered a new combination of active ingredients for Australian regulatory purposes.

Pertuzumab (as Perjeta) was first approved on 6 May 2013 in a FDC, and has the following indications:

Early Breast Cancer

Perjeta is indicated in combination with trastuzumab and chemotherapy for:

- *the neoadjuvant treatment of patients with HER2-positive inflammatory or locally advanced, or early stage (either > 2 cm in diameter or node positive) breast cancer as part of a complete treatment regimen for early breast cancer*
- *the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.*

Metastatic Breast Cancer

Perjeta is indicated in combination with trastuzumab and docetaxel for patients with metastatic HER2-positive breast cancer who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease.

Trastuzumab (as Herceptin) was first approved on 3 December 2010 as a monotherapy or in a FDC, and has for the following indications:

Early Breast Cancer

Herceptin is indicated for the treatment of patients with HER2-positive localised breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.

Locally Advanced Breast Cancer

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

²⁰ Mabthera was first registered on the ARTG on 28 May 2014 (ARTG number: 207334).

Metastatic Breast Cancer

Herceptin 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

Herceptin 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.

At the time the TGA considered this application, similar applications were under consideration in the USA (submitted on 19 December 2019) and the European Union (EU) (submitted on 10 January 2020).

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 website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-01326-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	30 April 2020
First round evaluation completed	30 September 2020
Sponsor provides responses on questions raised in first round evaluation	2 November 2020
Second round evaluation completed	30 November 2020
Delegate's Overall benefit-risk assessment	5 March 2021
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable

Description	Date
Registration decision (Outcome)	5 May 2021
Completion of administrative activities and registration on the ARTG	6 July 2021
Number of working days from submission dossier acceptance to registration decision*	197

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

Following container closure system components were chosen:

- a 20 mL Type I borosilicate glass vial, colourless (USP/Ph. Eur./JP)²¹ for the loading dose; and
- a 15 mL Type I borosilicate glass vial, colourless (USP/Ph. Eur./JP) for the maintenance dose;
- a 20 mm fluororesin-laminated rubber stopper, liquid-type (USP/Ph. Eur./JP) for both loading dose and maintenance dose; and
- a 20 mm, aluminium seal with plastic flip-off cap (cool green flip-off colour for loading dose and orange flip-off colour for maintenance dose).

The compatibility of the drug product with the primary packaging system with respect to extractables and leachables was assessed. The results of the extractables and leachables studies performed on the commercial primary packaging configuration for FDC drug product demonstrated that the selected vial or stopper configuration is suitable for use for the drug product. No significant amount of leaching components from the product contacting packaging components was observed in FDC drug product.

These are standard primary packaging components. The graphic representation of the vials has been provided. The colour difference in flip-off caps between the loading dose and maintenance dose vials are adequate.

The TGA quality evaluation came to the following conclusion:

- Sufficient evidence has been provided to demonstrate that the risks related to adventitious agents in the manufacturing of Phesgo SC have been managed to an acceptable level.
- All outstanding issues were satisfactorily resolved. There were no objections on quality grounds to the approval of Phesgo SC.

²¹ USP = United States Pharmacopeia; Ph. Eur. = European Pharmacopoeia; JP = Japanese Pharmacopoeia.

Nonclinical

The nonclinical evaluation concluded with the following:

- The nonclinical module was limited to literature pharmacology studies, only two of which included pertuzumab and trastuzumab in combination, and a pharmacokinetic drug interaction study in mini pigs.
- No dedicated pharmacology studies with the proposed fixed pertuzumab/trastuzumab SC combination were conducted. However, trastuzumab and pertuzumab synergistically inhibited the survival of HER2-overexpressing BT474 breast cancer cells *in vitro*. Trastuzumab increased pertuzumab mediated disruption of HER2 dimerisation with the epidermal growth factor receptor and HER3. Trastuzumab and pertuzumab had an additive but not synergistic effect on antibody dependent cellular cytotoxicity in peripheral blood mononuclear cells (PBMCs) *in vitro*.
- A synergistic effect of pertuzumab and trastuzumab was observed on tumour growth inhibition in human lung and breast tumour models in mice *in vivo*, with complete tumour regression observed in some animals. Doses in these studies were associated with clinically relevant pertuzumab and trastuzumab concentrations.
- In a single pharmacokinetic interaction study, administration of pertuzumab IV or SC in the presence or absence of trastuzumab (with recombinant human hyaluronidase PH20 enzyme (rHuPH20) to mini pigs at doses of around 12 mg/kg per agent was well tolerated, with no remarkable effect on the SC absorption or systemic exposure of either agent alone. Bioavailability of co-administered pertuzumab by the SC route was similar to that reported for trastuzumab SC.
- No acute or repeat dose toxicity studies with the proposed fixed pertuzumab/trastuzumab combination have been conducted. However, repeat dose toxicity studies conducted with either agent alone have not demonstrated any remarkable adverse effects and did not indicate potential toxicological interactions in patients.
- No reproductive toxicity studies with the proposed fixed pertuzumab/trastuzumab combination have been conducted. However, pertuzumab has been shown to be embryo and fetotoxic, and teratogenic at clinically relevant doses in monkeys. Phesgo SC is not indicated for use in pregnancy, consistent with pregnancy category D;²² for both pertuzumab and trastuzumab.
- No dedicated nonclinical local SC tolerance study with Phesgo SC has been conducted, which is considered a deficiency of this application for a new SC administration route and dose for pertuzumab. However, no local effects were reported in mini pigs given a 12 mg/kg SC dose of pertuzumab with or without 12 mg/kg SC trastuzumab. Weekly SC doses of 250 mg/kg pertuzumab to cynomolgus monkeys for four weeks were also not associated with any clinical signs of local irritation. However, investigations in these studies were limited, thus assessment of potential local irritation with Phesgo SC will rely on clinical data.

To conclude, there are no objections on nonclinical grounds to the registration of Phesgo SC.

²² **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.

Clinical

The clinical data package consisted of neoadjuvant pharmacokinetics (PK), efficacy and safety data from one ongoing pivotal Phase III study, Study WO40324 (the FEDERICA trial) in patients with HER2-positive EBC. The registration approach is to use this PK study to bridge to efficacy and safety of the product for the proposed usages, which are primarily supported by the previously reviewed clinical data that supported TGA registration of those usages for Perjeta.

The clinical dossier consisted of the following information:

- The FEDERICA trial: this was a PK non-inferiority trial, with primary endpoint Cycle 7 serum pertuzumab steady state trough concentration ($C_{\text{trough,ss}}$) and key secondary PK endpoint Cycle 7 serum trastuzumab $C_{\text{trough,ss}}$ for Phesgo SC with chemotherapy compared to IV Perjeta plus IV Herceptin with chemotherapy in patients with HER2-positive early breast cancer.
- A Phase Ib single dose study (Study BO30185) in healthy male volunteers and female patients with early breast cancer designed to identify the appropriate dose of pertuzumab SC to use in Phesgo SC.
- A population pharmacokinetic (popPK) and exposure response analysis of SC pertuzumab in the FEDERICA trial.
- An integrated summary of immunogenicity for Phesgo SC.
- Previously submitted and evaluated Phase III studies (the CLEOPATRA, NEOSPHERE, BERENICE, APHINITY, and HANNAH trials), and popPK analysis of trastuzumab SC and IV formulations in EBC using data from Study BO22227 (the HANNAH trial).
- Reports of *in vitro* bioanalytical and analytical methods for human studies.

Pharmacology

Dose selection

The commercial manufacturing process and specification for the approved trastuzumab SC drug product are the same for the Phesgo SC trastuzumab ingredient. The dose of trastuzumab in Phesgo SC is unchanged from the approved trastuzumab SC dose, which is the same whether used in monotherapy (see the PI for Herceptin SC);¹¹ or combination with pertuzumab (see the PI for Perjeta).¹⁹

The physicochemical, biological, and immunological characteristics of pertuzumab SC drug substance are the same as those of the pertuzumab IV drug substance. The SC dose of pertuzumab for inclusion in Phesgo SC was selected based on Study BO30185.

The safety and efficacy of hyaluronidase products have been widely established, with SC formulations of trastuzumab and rituximab both approved and reported to be well tolerated.^{23,24,25,26}

²³ EMA, European Public Assessment Report (EPAR), Herceptin (trastuzumab), EMA/CHMP/751770/2012/corr1, 27 June 2013. Available from the EMA website.

²⁴ EMA, European Public Assessment Report (EPAR) for Mabthera (rituximab), EMA/CHMP/71722/2014, 23 January 2014. Available from the EMA website.

²⁵ Gligorov, J. et al. Safety and Tolerability of Subcutaneous Trastuzumab for the Adjuvant Treatment of Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer: Safeher Phase III Study's Primary Analysis of 2573 Patients, *Eur J Cancer*, 2017; 82: 237-246.

²⁶ Davies, A. et al. Subcutaneous Rituximab for the Treatment of B-Cell Hematologic Malignancies: a Review of the Scientific Rationale and Clinical Development, *Adv Ther*, 2017; 34(10): 2210-2231.

Pharmacokinetics

Study B030185

This dose finding (healthy male volunteers) and dose confirmation (women with early breast cancer) study found that:

- a dose of pertuzumab 600 mg SC (whether in healthy volunteers or early breast cancer patients) provided similar $C_{\text{trough,ss}}$ and area under the concentration-time curve (AUC) to a 420 mg IV dose;
- the PK of pertuzumab SC was dose proportional in healthy male volunteers for doses of 400, 600 and 1200 mg;
- a loading dose of 1200 mg pertuzumab SC would achieve comparable exposure to an 840 mg loading dose of the IV product;
- inclusion of rHuPH20 at three studied doses (667, 1000 or 2000 U/mL) resulted in:
 - no meaningful change in trastuzumab or pertuzumab PK
 - no quantifiable systemic exposure of rHuPH20
- there was no apparent drug-drug interaction between pertuzumab and trastuzumab when the two antibodies were delivered SC co-mixed (no impact of trastuzumab on the PK of pertuzumab and no impact of pertuzumab on the PK of trastuzumab).

Based on the PK and safety findings of Study B030185, in addition to previous clinical experience with rHuPH20, the Phesgo SC doses chosen for evaluation in the FEDERICA trial were a loading dose of pertuzumab 1200 mg plus trastuzumab 600 mg (with rHuPH20 2000 U/mL) and a every three weeks maintenance dose of pertuzumab 600 mg plus trastuzumab 600 mg (with rHuPH20 2000 U/mL).

The FEDERICA trial

In the FEDERICA trial, the PK of pertuzumab and trastuzumab were compared when given SC (as Phesgo SC, with dosing as above) versus IV (as separate products), in combination with chemotherapy to patients with early breast cancer. The Phesgo SC dose used in the pivotal study was a loading dose of pertuzumab 1200 mg plus trastuzumab 600 mg and a maintenance dose of pertuzumab 600 mg plus trastuzumab 600 mg every three weeks. The SC dosing regimen used in the FEDERICA trial was selected based on PK data from the Phase Ib dose finding (healthy male volunteers) and dose confirmation (early breast cancer) study (Study B030185).

The primary endpoint (non-inferiority of C_{trough} serum pertuzumab at end of Cycle 7) was met, with a geometric mean ratio (geometric mean ratio (GMR): $C_{\text{trough,ss SC}}/C_{\text{trough,ss IV}}$) of 1.22 (90% CI: 1.14, 1.31). The lower limit of the confidence interval was above the pre-specified non-inferiority margin of 0.8.

Non-inferiority of trastuzumab exposure (a key secondary endpoint) was also met, with a GMR of 1.33 (90% CI; 1.24, 1.43) for trastuzumab $C_{\text{trough,ss SC}}/C_{\text{trough,ss IV}}$.

All patients in the Phesgo SC arm and 99% of patients in the comparator IV arm had Cycle 7 pertuzumab C_{trough} values above 20 $\mu\text{g/mL}$, which was determined to be the minimum effective concentration target of pertuzumab identified from nonclinical mouse xenograft models and early clinical response data.

Exploratory PK results indicated steady state exposures (as measured by geometric mean area under the concentration-time curve for 21 days ($\text{AUC}_{21\text{d}}$)) were similar with Phesgo SC compared to IV dosing:

- For pertuzumab: 2440 $\mu\text{g/mL}\cdot\text{day}$ for both the Phesgo SC and comparator arms, giving a GMR area under the concentration-time curve for the subcutaneous route

(AUC_{SC})/area under the concentration-time curve for the intravenous route (AUC_{IV}) of 1.00 (90% CI: 0.96, 1.05)

- For trastuzumab: 1730 µg/mL·day for the Phesgo SC arm and 1670 µg/mL·day for the comparator IV arm, giving a GMR AUC_{SC}/AUC_{IV} of 1.04 (90% CI: 0.99, 1.09).

Another exploratory analysis showed that mean maximum concentration (C_{max}) (Cycle 7) for both pertuzumab and trastuzumab were greater (around 50% higher) following IV administration compared to SC administration. Median Cycle 7 time to maximum concentration (T_{max}) was 3.82 days for pertuzumab and 3.85 days for trastuzumab with Phesgo SC dosing.

Population pharmacokinetics data

A PopPK/exposure-response analysis (Report 1098192) based on data from the FEDERICA trial was submitted. The PK of pertuzumab were described by a two-compartment model with first-order absorption. No clinically meaningful effect on pertuzumab exposure was seen with co-variables of weight, baseline albumin, Asian/non-Asian patients, age, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, Eastern Cooperative Oncology Group (ECOG) performance status,²⁷ clinical breast cancer stage or hormone receptor (estrogen receptor (ER)/progesterone receptor (PR)) status. The PopPK model was considered appropriate to use for exposure simulations and to evaluate exposure-response relationships after Phesgo SC administration in the FEDERICA trial.

The same report showed that observed trastuzumab exposure after Phesgo SC administration in the FEDERICA trial was in keeping with simulated exposures after Phesgo SC administration predicted using the previously developed trastuzumab population PK model from the HANNAH trial (Report 12-0215v2), which was reviewed by the TGA as part of the Herceptin SC submission. These findings indicate that pertuzumab has no effect on the PK of trastuzumab when the two drugs are co-administered in the Phesgo SC formulation.

Pharmacodynamics

Efficacy

A secondary endpoint in the FEDERICA trial was the proportion of patients who achieved a total pathological complete response (tpCR) (that is, absence of invasive neoplastic cells in the breast and axillary lymph nodes). The non-inferiority margin of -12.5% for tpCR was not justified, and no multiplicity adjustments were made for this endpoint. The tpCR rate was comparable between the two arms in the intent-to-treat (ITT);²⁸ population: 59.5% in the IV comparator arm and 59.7% in the Phesgo SC arm, resulting in a difference (SC minus IV) of 0.15% (95% CI: -8.67, 8.97). Exploratory subgroup analyses across

²⁷ ECOG Performance Status: The **Eastern Cooperative Oncology Group (ECOG)** has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

- 0 - Fully active, able to carry on all pre-disease performance without restriction
- 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
- 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
- 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
- 5 - Dead

²⁸ Randomised clinical trials analysed by the **intent-to-treat (ITT)** approach provide the unbiased comparisons among the treatment groups. In the ITT population, none of the patients are excluded and the patients are analysed according to the randomisation scheme.

multiple, pre-specified, clinically relevant subgroups showed no meaningful difference in the tpCR rates between the two treatment arms.

Exploratory exposure-response analyses did not identify a clinically meaningful relationship between pertuzumab exposure and tpCR for patients with EBC in the FEDERICA trial. The United States Food and Drug Administration (FDA) noted a review concern, but concluded that no definitive conclusions were warranted. Full details of the FDA subgroup analysis by weight quartiles is available in the public FDA review document.²⁹ This exploratory analysis is not considered a barrier to registration.

Safety

The exposure-response analyses did not identify any clinically meaningful relationships between pertuzumab exposure and safety endpoints (grade ≥ 3 adverse events (AE), cardiac toxicity, serious adverse events (SAE), grade ≥ 3 diarrhoea, grade ≥ 3 neutropenia, injection/infusion-related reactions (IRR) within 24 hours of HER2 treatment related to pertuzumab-trastuzumab FDC for SC use, or hypersensitivity/anaphylaxis related to pertuzumab-trastuzumab FDC for SC use) for patients with early breast cancer in the FEDERICA trial.

Immunogenicity

The treatment-emergent incidence of anti-drug antibodies (ADA) to pertuzumab and to trastuzumab in the FEDERICA trial was comparable in both treatment arms. Exploratory analyses indicated that the occurrence of ADA to pertuzumab in Phesgo SC treated patients had no clinically meaningful impact on the PK of pertuzumab, efficacy (tpCR) or administration related reactions.

The small absolute number of trastuzumab ADA-positive patients in both the Phesgo SC arm and the comparator arm precludes clinically meaningful conclusions relating to the impact of ADAs to trastuzumab on the PK of trastuzumab, efficacy or safety.

The small number of anti-rHuPH20 antibody positive patients in Phesgo SC arm precludes clinically meaningful conclusions relating to the impact of antibodies to anti-rHuPH20 on the efficacy or safety of Phesgo SC.

Efficacy

Efficacy of pertuzumab plus trastuzumab in the treatment of early breast cancer and metastatic breast cancer has been previously established.¹⁹ The submitted dossier for Phesgo SC provides adequate support for bridging to the same efficacy data.

The submitted data from the FEDERICA trial would not support a stand-alone assessment of efficacy for Phesgo SC, but is considered supportive.

Safety

The safety profile of pertuzumab plus trastuzumab in the treatment of early breast cancer and metastatic breast cancer has been previously established.¹⁹ The submitted dossier for Phesgo SC provides adequate support for bridging to the same safety data, as well as *de novo* safety data.

The FDA review document summarises the safety profile of Phesgo SC as follows:²⁹ The report also outlines one adverse event of administration via the wrong route.²⁹

²⁹ Center for Drug Evaluation and Research NDA/BLA Multi-disciplinary Review and Evaluation BLA 761170 Phesgo (Pertuzumab and Trastuzumab Solution for Subcutaneous Injection), January 2020. Available from the FDA website.

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.³⁰

Risk-benefit analysis

Delegate's considerations

Route of administration dosing errors and risk minimisation

Conditions in clinical trials generally involve more intense medical supervision than real world conditions. Despite this, a route-of-administration dosing error was seen in the pivotal trial. The PI will be reviewed with regards to risk minimisation around this.

Indication wording

The proposed Australian metastatic indication includes '*or locally recurrent unresectable.*' This differs both from what has been approved by the FDA and from the current approved Australian indication for Perjeta, but is reflective of the indication that has been approved by the European Medicines Agency (EMA), both for pertuzumab and for Phesgo SC.¹⁹

The reason that the Australian indication for Perjeta based on data from the CLEOPATRA trial was limited to patients with metastatic disease was that there were a limited number of patients with locally advanced disease enrolled. This was 19 patients according to the PI for Perjeta,¹⁹ and 12 patients according to the ratified minutes from Meeting 290 (5 April 2013) of the Advisory Committee on Prescription Medicines (ACPM).³¹ The decision Delegate for pertuzumab, which was being registered for the first time in Australia, asked the following question of the ACPM, with the juxtaposed response:³²

'Should the indication be restricted to metastatic disease in view of only 12 subjects with locally advanced disease in the CLEOPATRA trial?'

'Despite the theoretical support for efficacy in locally advanced disease, there are insufficient numbers of patients (only 12 patients) which provided very limited data to support the indication.'

At that time, evidence of pertuzumab efficacy was limited to early phase data, and randomised studies of pertuzumab in EBC had not been completed.

In 2021, the limited evidence of efficacy in locally advanced disease available from the small number of such patients enrolled in the CLEOPATRA trial is supported by the extensive evidence of efficacy of pertuzumab in non-metastatic settings that has since been generated. The inclusion of patients with locally advanced, unresectable disease in the Australian metastatic indication for Phesgo SC is acceptable, despite this not being specified at present in the Australian PI for pertuzumab.

³⁰ The sponsor must still comply with routine product vigilance and risk minimisation requirements.

³¹ The Advisory Committee on Prescription Medicines (ACPM) has since been superseded by the Advisory Committee on Medicines (ACM).

³² TGA, Australian Public Assessment Report for Pertuzumab, October 2013. Available at: <https://www.tga.gov.au/auspar/auspar-pertuzumab-rch>.

Companion diagnostics

New companion diagnostic policy has come into effect in Australia.³³ Minor modifications to the PI text will be proposed by the Delegate in line with those that have recently been made for other cancer medications.

Proposed action

The Delegate proposes to approve the registration of the product, subject to agreement on an acceptable PI document.

Advisory Committee considerations³⁴

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Phesgo SC (pertuzumab/trastuzumab) 1200 mg/15 mL pertuzumab and 600 mg/15 mL trastuzumab; 600 mg/10 mL pertuzumab and 600 mg/10 mL trastuzumab, solution for injection, vial, indicated for:

Early breast cancer (EBC)

Phesgo is indicated in combination with chemotherapy for the:

- *neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either > 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer*
- *adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence*

Select patients for therapy based on a validated test.

Metastatic breast cancer (MBC)

Phesgo is indicated in combination with docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Select patients for therapy based on a validated test.

Specific conditions of registration applying to these goods

- This approval does not impose any requirement for the submission of periodic safety update reports (PSURs). The sponsor should note that it is a requirement that all

³³ TGA, IVD Companion Diagnostics, Guidance on Regulatory Requirements, 14 February 2020. Available at: <https://www.tga.gov.au/publication/ivd-companion-diagnostics>

³⁴ The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

existing requirements for the submission of PSURs as a consequence of the initial registration or subsequent changes must be completed.

- Laboratory testing and compliance with Certified Product Details
 - All batches of Phesgo SC supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
 - When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results <http://www.tga.gov.au/ws-labs-index> and periodically in testing reports on the TGA website.
- For all injectable products the PI must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Phesgo SC approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
<https://www.tga.gov.au>