



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Pertuzumab

Proprietary Product Name: Perjeta

Sponsor: Roche Products Pty Ltd

October 2013

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- 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 (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New biological entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	2 May 2013
<i>Active ingredient:</i>	Pertuzumab (rch ¹)
<i>Product name:</i>	Perjeta
<i>Sponsor's name and address:</i>	Roche Products Pty Limited 4-10 Inman Road Dee Why NSW 2099
<i>Dose form:</i>	Injection solution concentrate
<i>Strength:</i>	30 mg/mL
<i>Container:</i>	Vial
<i>Pack size:</i>	1 x 420 mg/14 mL single use vial
<i>Approved therapeutic use:</i>	Perjeta is indicated in combination with trastuzumab and docetaxel for patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease.
<i>Route of administration:</i>	Intravenous (IV) infusion
<i>Dosage (abbreviated):</i>	Dosage of Perjeta in combination with trastuzumab and docetaxel: The recommended initial dose of Perjeta is 840 mg, administered as a 60 min IV infusion, followed by, every 3 weeks, a 420 mg dose administered over 30-60 min.
<i>ARTG number:</i>	196218

Product background

Pertuzumab is a recombinant, humanised (rch), immunoglobulin (Ig) G1 kappa (κ) chain monoclonal antibody (MAb) that targets the human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2). The HER2 receptor is a transmembrane glycoprotein with intrinsic tyrosine kinase activity that has been implicated in the development of some breast cancers. Pertuzumab is the first in a new class of targeted cancer treatments called HER2 dimerisation inhibitors. By binding to the subdomain 2 epitope of the extracellular domain of HER2, pertuzumab prevents heterodimerisation of HER2 with other members of the HER family (HER1, HER3 and HER4) and blocks ligand-activated downstream signalling. Pertuzumab is also capable of activating antibody-dependent cell-mediated cytotoxicity (ADCC).

¹ rch denotes 'recombinant humanised'

This AusPAR describes the application by Roche Products Pty Ltd (the sponsor) to register Perjeta intravenous (IV) injection solution concentrate containing pertuzumab for the following indicated:

in combination with Herceptin and docetaxel for patients with HER2-positive metastatic (Stage IV) or unresectable locally recurrent breast cancer who have not received previous treatment or whose disease has relapsed after adjuvant therapy.

Pertuzumab was designated as an orphan drug by the TGA on 19 January 2012 for “*the treatment of patients with HER2-positive metastatic (Stage IV) or locally recurrent breast cancer*”. The sponsor estimates the prevalence of patients with HER2-positive metastatic breast cancer in Australia to be 1300 (that is, 535 incident population x 2.4 mean years overall survival).

Regulatory status

At the time this application was considered by the TGA, a similar application had been approved in the US (June, 2012), the European Union (EU, March 2013) and Switzerland (August 2012) and was under consideration in Canada and New Zealand.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Structure

Pertuzumab is a full length recombinant, humanised monoclonal antibody based upon the human IgG1(κ) framework sequence. It is composed of two light chains consisting of 214 amino acid residues, two heavy chains consisting of 448 or 449 amino-acid residues, and contains an N-linked oligosaccharide.

Pertuzumab has a total molecular weight of approximately 148,000 Da, excluding the oligosaccharide carbohydrate.

Manufacture

Acceptable information was provided on pertuzumab drug substance manufacturers and responsibilities. Cell banking processes are satisfactory.

All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Physical and chemical properties

Extensive characterisation of the physicochemical, biological and immunological properties of pertuzumab and confirmation of its purity was done using methods selected in accordance with ICH Topic Q6B *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (CPMP/ICH/365/96). The data indicate that pertuzumab has the structure expected of a recombinant humanised monoclonal antibody

expressed in Chinese hamster ovary (CHO) cells. Product variants and process-related impurities were quantified and were consistent with those described for several other monoclonal antibody products. Biological and immunological characterisation demonstrated that pertuzumab inhibits cell proliferation by blocking the association of HER2 with other members of the HER receptor family.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use, have been assessed.

Appropriate validation data have been submitted in support of the test procedures.

Stability data have been generated under real time/stressed conditions to characterise the stability/degradation profile of the substance and to establish a retest period shelf life. The real time data submitted support a shelf life of 36 months.

Drug product

Formulation

The pertuzumab drug product formulation is a stable formulation suitable for manufacturing, storage, transport and IV administration.

Pertuzumab drug product is manufactured as a liquid formulation in a configuration to deliver 420 mg per vial. The protein concentration of the bulk drug product, which is identical to the drug substance protein concentration, is 30 mg/mL. The drug product is sterile filtered and filled into 20 mL Type I glass vials. Each vial is stoppered with a 20 mm fluoro-resin laminated liquid-type rubber stopper and crimped with a 20 mm aluminium seal fitted with a flip-off plastic cap. Filling occurs in a Class 100/Grade A environment.

Specifications

Information was assessed on the composition of pertuzumab drug product. Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data indicate the product is photostable.

The proposed shelf life is 36 months when stored at 2°C–8°C.

Biopharmaceutics

During the development of pertuzumab a comprehensive strategy consisting of in vitro binding characterisation, antiproliferative activity and nonclinical pharmacokinetic (PK) studies demonstrated biocomparability of different generations of drug substance and drug product. Once biocomparability was demonstrated, no additional clinical biocomparability studies were conducted.

Advisory committee considerations

This application was noted at the 149th (December 2012) meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical and microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. The following evaluations were completed:

- Primary evaluation
- Endotoxin safety
- Viral/prion/transmissible spongiform encephalopathies (TSE) safety
- Container safety
- Sterility

Issues regarding manufacturing and quality were raised with the sponsor during the evaluation phases and have been resolved.

The quality evaluators recommend that Perjeta (pertuzumab, rch) concentrate for IV infusion 420 mg be approved with conditions of registration² relating to:

- Batch release testing
- Certified Product Details (CPDs)

III. Nonclinical findings

Introduction

Overall quality of the nonclinical dossier

The submitted nonclinical data were in general accordance with ICH Topic S9 *Nonclinical Evaluation for Anticancer Pharmaceuticals* (EMA/CHMP/ICH/646107/2008). A deficiency was that toxicity studies were only conducted in one species.³ This was justified on the basis of the ability of pertuzumab to bind to the HER2 receptor in the species used (cynomolgus monkeys). Although there was no evidence of major safety issues with pertuzumab this is still a deficiency in the submission. All pivotal repeat-dose toxicity and reproductive toxicity studies were compliant with Good Laboratory Practice (GLP) principles. For information relating to the primary pharmacology the submission relied entirely on published studies. Safety related studies were confined to repeat-dose toxicity studies conducted in one species (cynomolgus monkeys) and involved only small numbers of animals. These pivotal studies reached exposure levels that were in excess of expected human exposures. Because of the limited nature of the toxicity investigation it remains possible that the full range of safety issues has not been explored. This is not considered a major limitation, however, as the evidence provided does not suggest any major safety risks in adults.

² Specific details of these conditions are beyond the scope of the AusPAR.

³ Sponsor comment: The nonclinical safety evaluation was in accordance with Guideline EMA/ICH guideline S6 *Preclinical safety evaluation of biotechnology-derived pharmaceuticals*, CPMP/ICH/302/95)

Pharmacology

Primary pharmacology

Pertuzumab is a humanised monoclonal antibody developed to bind to HER2 receptors. These receptors are expressed in various human tumours, most notably in breast tumours. Binding of pertuzumab results in inhibition of receptor dimerisation, thereby inhibiting intracellular signalling via mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K) (Agus *et al.* 2002⁴) and causing cell growth arrest and apoptosis, respectively. By binding to HER2, pertuzumab blocks association with ligand-activated HER family members including epidermal growth factor receptor (EGFR, HER1), HER3 and HER4. Pertuzumab binds to an epitope distinct from that of trastuzumab (also an HER2 selective antibody). The ability of pertuzumab to block heregulin (HRG)-induced activation of the PI3K cell survival pathway is distinct from the activity of trastuzumab due to the difference in the binding site on the HER2 receptor of the two antibodies. Trastuzumab binds to subdomain IV of the extracellular domain of HER2 while pertuzumab binds to the domain II dimerisation arm of the receptor.

The HER2 receptors in humans and cynomolgus monkeys are very similar (sequence identity 99%) and pertuzumab binds to the two receptors with similar affinity (affinity constant, K_D , values (nM mean \pm standard error (SE)): human 0.80 ± 0.08 , cynomolgus monkey 0.53 ± 0.07). This similarity in the two receptors supports the use of the monkey as the animal model.

Pertuzumab also mediates antibody-dependent cellular cytotoxicity.

In vivo

Pertuzumab showed dose-related, single-agent anti-tumour activity in trastuzumab-sensitive and trastuzumab-resistant xenografts, and in a trastuzumab-resistant transgenic mouse model of breast cancer. The effective doses (that is, sufficient to cause significant inhibition of tumour growth) produced serum trough concentrations from 5 $\mu\text{g/mL}$ to 50 $\mu\text{g/mL}$. These may be compared to the clinical minimum concentration at steady state ($C_{\text{min,ss}}$) of 50.5 $\mu\text{g/mL}$ (according to the human population-PK Report 11-2998), suggesting the effective dose in these models is close to the expected clinical exposure.

Anti-tumour activity of pertuzumab given in combination with other anti-cancer agents was also investigated in xenograft models. Combinations of pertuzumab administered with the other agents (cisplatin, gemcitabine, erlotinib, irinotecan, paclitaxel, trastuzumab, bevacizumab and capecitabine) generally resulted in enhanced tumour growth inhibition relative to the effects of the single agents. This was the case regardless of the other agent's mode of action. There were some quantitative differences in the size of the effect with different agents and different tumour xenografts but the effect was consistent. Combining pertuzumab with trastuzumab (2 of the 3 agents to be used together in clinical practice) caused a marked increase in inhibition of tumour growth of KPL-4 breast xenografts. The combination was also more effective against Calu-3 NSCLC xenografts than either agent alone. Literature cited by the sponsor showed that the combination of trastuzumab and pertuzumab had a synergistic growth-inhibiting effect on BT474 breast cancer cells, which express high levels of HER2, underscoring the complementary mechanism of action of the two drugs (Nahta *et al.*, 2004⁵). Combination of pertuzumab and docetaxel was not investigated but the combination of pertuzumab and paclitaxel (another taxane) also gave

⁴ Agus DB, Akita RW, Fox WD, Lewis GD, Higgins B, Pisacane PI, *et al.* Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. *Cancer cell* 2002;2(2): 127-137.
Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. *Nature reviews. Cancer* 2009;9(7): 463-475.

⁵ Nahta R, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. *Cancer Res* 2004;64(7): 2343-2346.

enhanced inhibition of Calu-3 NSCLC xenografts. The proposed clinical combination of pertuzumab, trastuzumab and docetaxel was not investigated in these models.

Dedicated safety pharmacology studies were not conducted. Electrocardiography found no evidence of any effects of pertuzumab and there were no signs of central nervous system (CNS) or respiratory effects from the general observation of the animals in the 7- and 26-week repeat dose toxicity studies at plasma pertuzumab concentrations (7310 µg/mL) approximately 25 times the clinical maximum concentration (C_{max}).

Pharmacokinetics

The PK profile of pertuzumab was found to be comparable in mice, rats and monkeys, all showing a biphasic elimination profile fitted to a two-compartment model. The volume of distribution of the central compartment (V_c) for each species examined approximated the plasma volume, and steady state (SS) volume of distribution (V_{ss}) was approximately twice the V_c . The clearance (CL) ranged from 5 to 10 mg/day/kg, compared to the human CL 239 mL/day (or 4 mL/day/kg for a 60 kg person). All animals showed a short distribution half life ($t_{1/2\alpha}$ 0.07–1.6 days) in single dose studies followed by an elimination half life ($t_{1/2\beta}$) of between 8.9 and 15.7 days. In the human population PK report 11-2998 the median values for the distribution phase and the elimination phase half-lives were 1.5 and 17.2 days, respectively. Repeat-dose studies in monkeys revealed a non-linear relationship between dose and exposure in terms of area under the concentration-time curve (AUC). Following repeated dosing CL increased by approximately 30% when the dose was increased from 50 to 150 mg/kg. This increase in CL may be due to saturation of the neonatal Fc receptor (FcRn) salvage mechanism, which is understood to play a role in the maintenance of immunoglobulin plasma levels.

Tissue distribution was not studied *in vivo* but *in vitro* results of a tissue cross-reactivity study suggest tissue binding in monkeys and humans. Tissue cross-reactivity to pertuzumab was demonstrated in mammary gland, placenta, kidney, ureter, urinary bladder and prostate gland of both species, in addition to monkey sweat and sebaceous glands and human salivary glands and fallopian tube.

No metabolism studies were performed since pertuzumab is a member of a therapeutic class understood to be degraded into smaller peptides and individual amino acids.

Pharmacokinetic drug interactions

No PK drug interactions were found in a single study investigating interactions with bevacizumab in rats. Single IV bolus doses of 30 mg/kg pertuzumab and bevacizumab alone or in combination resulted in similar AUC values. The ratio of the geometric means for AUC over time zero to 14 days ($AUC_{0-14 \text{ days}}$) for pertuzumab alone or in combination was 83% (95% confidence interval (CI): 74–93%) and for bevacizumab it was 100% (95% CI: 85–118.5). Pharmacokinetic parameters calculated using a two-compartment model were similar for all three groups, indicating the lack of PK drug interactions between bevacizumab and pertuzumab.

Toxicology

Acute toxicity

No single-dose toxicity studies were conducted. No acute toxicity was observed in the repeat-dose toxicity studies in monkeys at doses up to 150 mg/kg IV. No mortality or acute reactions to pertuzumab were reported in rodents used in xenograft studies up to 180 mg/kg IV or 120 mg/kg by intraperitoneal (IP) injection.

Repeat-dose toxicity

GLP-compliant repeat-dose toxicity studies by the IV route were performed in one species, cynomolgus monkeys (up to 26 weeks). A single non-GLP compliant study was conducted in the same species using subcutaneous (SC) administration. Confining the toxicity studies to a single species was justified by the distribution of HER2 receptors which are not expressed in other laboratory species.

Relative exposure

Exposure ratios have been calculated based on animal:human plasma AUC ratios. C_{max} values for human and animal studies are also provided for comparison in the table below. The human reference value for C_{max} (289 $\mu\text{g}/\text{mL}$) is from clinical Study B016934, which included 61 patients receiving loading doses of 840 mg and subsequent 420 mg every 3 weeks (q3w) maintenance dosing. The AUC_{ss} (1757 $\mu\text{g}\cdot\text{day}/\text{mL}$) value is from population PK report 11-2998 which included 12 studies comprised of 444 patients and a dose range 2 to 25 mg/kg, which includes the pivotal Phase III study and the proposed clinical dose regimen of 840 mg plus 420 mg q3w maintenance dosing. The two pivotal repeat-dose GLP animal studies are included in the table (7 week and 26 week). Exposure measures of AUC for the seven week study were taken from the final week (days 42-48) as plasma concentrations would be approaching steady state values by this time given the terminal half-life in this species. For the 26 week study $AUC_{0-182\text{ day}}$ values were used.

Table 1. Relative exposure in repeat-dose toxicity studies

Species	Study duration	Dose (mg/kg/day)	C_{max} ($\mu\text{g}/\text{mL}$)	AUC_{0-21d}^{\dagger} ($\mu\text{g}\cdot\text{day}/\text{mL}$)	Exposure ratio [#]
Monkey (cynomolgus)	7 weeks	15	713	7857	4.5
		50	2210	23017	13
		150	5690	52599	30
	26 weeks	15	862	11206	6.4
		50	2820	32571	18
		150	7310	83405	47
Human (cancer patients)	Report 11-2998 (population PK; steady state)	840 mg (loading) 420 mg q3w (maintenance)	289*	1757	–

[#] = animal:human plasma AUC_{ss} ; * C_{max} value from StudyB016934 (report 1020161) [†] $AUC_{42-48} \times 3$ (7 week study), $AUC_{0-182\text{day}}/26 \times 3$ (26 week study), AUC_{ss} (human data)

The relative exposure level, in terms of AUC, reached a ratio of 47 in the 26 week study which is an acceptable comparative value given the toxicological profile. The C_{max} values were well above those seen in the clinical study achieving a ratio of 25. Since all animals exhibited diarrhoea even at the lowest doses tested in the repeat-dose studies, a no observed effect level (NOEL) was not determined.

Major toxicities

No major toxicities were identified in relation to pertuzumab exposure. No anti-therapeutic antibodies were detected in any of the animals in the two pivotal repeat-dose toxicity studies. The potential for cardiac effects was investigated in the two pivotal repeat-dose toxicity studies. No evidence of cardiotoxicity was found but the number of animals investigated was small particularly in the 26-week study. The nonclinical evaluation protocols were similar to those used in the toxicological evaluation of trastuzumab. No cardiotoxicity was detected in the nonclinical toxicity studies of trastuzumab but cardiotoxicity has subsequently been reported in clinical use, although this is possibly the result of use of other anti-cancer agents in conjunction with trastuzumab (Hudis, 2007⁶). At this stage the potential for similar cardiotoxicity with pertuzumab when used in conjunction with other agents has not been studied in any animal species.

The only consistent finding was diarrhoea which resulted in dehydration in some animals at all dose levels. Liquid/non-formed faeces persisted after the dosing period in a few instances. There were no associated pathological findings.

Genotoxicity

No genotoxicity studies were conducted. This was considered acceptable and in accordance with the relevant European Medicines Agency (EMA)/ICH guideline S6. *Preclinical safety evaluation of biotechnology-derived pharmaceuticals, CPMP/ICH/302/95*).

Carcinogenicity

No carcinogenicity studies were conducted. This is considered acceptable given the nature of the drug, the target patient group and relevant guidance (*Note for Guidance on Carcinogenicity: Testing for carcinogenicity of pharmaceuticals; CPMP/ICH/299/95; Note for guidance on nonclinical evaluation for anticancer pharmaceuticals* (EMEA/CHMP/ICH/646107/2008)).

Reproductive toxicity

One embryo-fetal development study was conducted in pregnant monkeys. Pertuzumab was embryotoxic and fetotoxic at all doses tested (loading dose 30-150 mg/kg and maintenance dose 10-100 mg/kg twice weekly) with severity increasing with dose. Dead or aborted fetuses occurred in all treated groups, compared with no fetal mortality in the vehicle control group. Surviving fetuses showed low fetal weight and consistent evidence of delayed kidney development (hypoplasia), oligohydramnios and other abnormalities (paw hyperextension and hyperflexion, clinodactyly, microtia, thin ventricular wall and small lung). Limb anomalies (paw hyperextension and hyperflexion, microtia, and clinodactyly) and small lung might be secondary to oligohydramnios.

All dams given pertuzumab had positive drug exposure during the period of fetal organogenesis (gestation day (GD) 20 to 50). Plasma pertuzumab concentrations (644-5360 µg/mL) were approximately 2-19 times the clinical C_{max} at the loading dose of 800 mg. As expected for an IgG antibody, pertuzumab crossed the placenta and was detected in fetal plasma. Ratios of fetal to maternal pertuzumab plasma concentration were similar across the dose levels (0.3-0.4 for the 10-100 mg/kg dose groups).

⁶ Hudis CA. Trastuzumab--mechanism of action and use in clinical practice. *N Eng J Med* 2007;357: 39-51.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2.⁷ This is not appropriate based on the embryofetal study findings in the submission. A more appropriate classification based on this information would be Pregnancy Category D.⁸

Blood compatibility

At concentrations up to 21.6 mg/mL (compare with the clinical C_{max} 0.289 mg/mL) pertuzumab did not cause haemolysis of cynomolgus monkey or human erythrocytes and was compatible with cynomolgus monkey and human serum and plasma.

Paediatric use

Pertuzumab is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Comments on the safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for pertuzumab detailed in the sponsor's draft Risk Management Plan (AusRMP V1.0, Section 7.1) are in general concordance with those of the nonclinical evaluator.

Nonclinical summary and conclusions

- The submitted nonclinical data were in general accordance with the EU/ICH guidelines (ICH S6 and S9) on the nonclinical evaluation of anticancer and biotechnology derived pharmaceuticals. All pivotal repeat-dose toxicity and reproductive toxicity studies were GLP-compliant. For information relating to the primary pharmacology the submission relied entirely on published studies. Safety related studies were confined to repeat-dose toxicity studies conducted in one species (cynomolgus monkeys) and involved only small numbers of animals. Cynomolgus monkeys are the only suitable species for these studies because pertuzumab binds to human HER2 and monkey ErbB2 with comparable affinity but does not bind to the rodent variant, ortholog neu. Exposures in the pivotal toxicity studies were in excess of expected human exposures. Because of the limited nature of the toxicity investigation it remains possible that the full range of safety issues has not been explored. This is not considered a major limitation however as the evidence provided does not suggest any major safety risks and the toxicology testing program for pertuzumab is not uncommon for humanised monoclonal antibodies.
- The mechanism of action of pertuzumab is derived from its affinity for HER2. Pertuzumab binds to human and cynomolgus monkey HER2 receptors with similar affinity (K_D values 0.80 and 0.53 nM, respectively). By binding to HER2, pertuzumab blocks association with ligand-activated HER family members including epidermal growth factor receptor (EGFR, HER1), HER3 and HER4. Pertuzumab binds to an epitope distinct from that of trastuzumab (also an HER2 selective antibody). Binding

⁷ Category B2: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.*

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

⁸ 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.*

of pertuzumab results in inhibition of receptor dimerisation thereby inhibiting intracellular signalling via MAP kinase and PI3K and causing cell growth arrest and apoptosis, respectively. The ability of pertuzumab to block HRG-induced activation of the PI3K cell survival pathway is distinct from the activity of trastuzumab due to the difference in the binding site on the HER2 receptor of the two antibodies. Trastuzumab binds to subdomain IV of the extracellular domain of HER2 while pertuzumab binds to the domain II dimerisation arm of the receptor. Pertuzumab also mediates antibody-dependent cellular cytotoxicity.

- Pertuzumab inhibited the growth of human derived tumour xenografts in mice at clinically relevant concentrations. When tested in combination with other anti-cancer agents the inhibition of tumour growth by pertuzumab was enhanced. This enhanced effect was seen regardless of the mechanism of action of the other agent. The combination of trastuzumab and pertuzumab has been shown to have a synergistic growth-inhibiting effect on BT474 breast cancer cells, which express high levels for HER2. Pertuzumab is proposed for use in combination with trastuzumab and docetaxel. Combination of pertuzumab and docetaxel was not investigated but the combination of pertuzumab and paclitaxel gave enhanced inhibition of Calu-3 NSCLC xenografts. Combining pertuzumab with trastuzumab (2 of the 3 agents to be used together in clinical practice) caused a marked increase in growth inhibition of KPL-4 breast xenografts. The combination was also more effective against Calu-3 NSCLC xenografts than either agent alone. There were no nonclinical studies investigating the combined effects of pertuzumab, trastuzumab and docetaxel.
- Tissue cross-reactivity studies in both cynomolgus monkeys and humans demonstrated that pertuzumab binding patterns corresponded to the pattern of HER/neu expression reported in the literature.
- No specific safety pharmacology studies were conducted. Observations of animals in the 7 and 26 repeat-dose toxicity studies in monkeys at plasma drug concentrations up to approximately 25 times the clinical C_{max} did not show any evidence of adverse effects in the CNS or respiratory systems or electrocardiogram (ECG) abnormalities.
- The nonlinear PK profile in cynomolgus monkeys was similar to that seen in humans. In monkeys a biphasic profile with an initial distribution phase of approximately one day followed by an elimination phase of approximately 10 days was seen, slightly shorter than the human values (1.5 and 17.2 days, respectively). The V_c in monkeys approximated the plasma volume, consistent with that in humans. Clearance appeared to increase with increasing dose in the repeat-dose studies in monkeys, with exposure levels (AUC) increasing in a less than dose-proportionate manner.
- No major toxicities were identified in repeat-dose toxicity studies at exposure levels approximately 48 times the human exposure ($AUC_{0-21days}$) over a 3 week period. The only consistent negative finding was diarrhoea which resulted in dehydration in some animals.
- Pertuzumab was shown to be embryotoxic and fetotoxic at all the dose levels tested in monkeys. The doses resulted in exposure levels 2-19 times than expected in clinical use, based on C_{max} . Surviving fetuses showed low fetal weight and consistent evidence of delayed kidney development (hypoplasia), oligohydramnios and other abnormalities. A NOEL for embryoletality and fetal abnormalities was not established.
- At concentrations up to 21.6 mg/mL (compare with clinical C_{max} 0.289 mg/mL) pertuzumab did not cause haemolysis of cynomolgus monkey or human erythrocytes and was compatible with cynomolgus monkey and human serum and plasma.

Recommendation

- Pertuzumab is clearly embryotoxic and fetotoxic at clinically relevant doses (2-19 times the clinical exposure based C_{max}) and surviving fetuses showed consistent evidence of delayed kidney development (hypoplasia, oligohydramnios and other abnormalities. For these reasons a Pregnancy Category D is recommended.
- There were no nonclinical studies with the combination of pertuzumab, trastuzumab and docetaxel. This nonclinical deficiency should not preclude the approval of the product provided the efficacy and safety of the combination has been adequately studied in the target patient population.
- The draft PI should be amended as recommended.⁹

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

Perjeta is proposed *for use in combination with Herceptin and docetaxel for patients with HER2-positive metastatic (Stage IV) or unresectable locally recurrent breast cancer who have not received previous treatment or whose disease has relapsed after adjuvant therapy.*

The sponsor's covering letter bases the clinical rationale for the submission on the unmet clinical need for therapies to treat HER2-positive metastatic breast cancer. The sponsor notes that HER2-positive breast cancer represents 15% to 20% of breast cancers and without treatment is associated with aggressive tumour growth and poor clinical outcomes. Furthermore, the sponsor comments that although Herceptin "represents a major advance in the treatment of HER2-positive metastatic breast cancer, almost all patients with HER2-positive metastatic breast cancer will eventually progress on Herceptin-based regimens, with median survival still approximately three years".

The sponsor's clinical rationale was acceptable to the clinical evaluator.

Scope of the clinical dossier

The submission contained the following clinical information:

- Module 5
 - 12 studies providing PK data and 1 study providing pharmacodynamic (PD) data;
 - 2 population PK analyses;
 - 1 pivotal efficacy/safety study;
 - 10 other efficacy/safety studies;
 - Other data, included 19 bioanalytical reports;
 - Literature references.
- Module 1
 - Letter of application; comprehensive table of contents; application forms; medicine information documents (proposed Australian draft PI and Consumer

⁹ Details of recommended revisions to nonclinical statements in the PI are beyond the scope of the AusPAR.

Medicine Information (CMI)), packaging and labelling; information about the experts; good manufacturing information; statement regarding individual patient data; overseas regulatory status; justification for not providing pharmaceutical studies; Risk Management Plan (RMP) proposed for Australia.

- Module 2
 - Clinical Overview; Clinical Summaries (Biopharmaceutics and Associated Analytical Methods; Clinical Pharmacology; Clinical Efficacy; Clinical Safety); references; and synopses of individual studies.

Paediatric data

The sponsor states that it has confirmation for a class waiver from the EMA for pertuzumab regarding the conduct of studies based on the proposed indication.

Good clinical practice

All studies are stated to have complied with the principles of good clinical practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

Individual studies

The submission included 12 individual clinical studies in approximately 480 patients with cancer that assessed the PK of pertuzumab administered as a single agent or in combination with other chemotherapeutic agents (see Table 2, below). There were no pertuzumab PK data in healthy subjects. The PK parameters in the individual studies were standard and were derived from serum concentrations (pertuzumab/trastuzumab) or plasma concentrations (chemotherapeutic agents) using non-compartmental analysis (NCA).

Table 2. Individual studies with pharmacokinetic data.

Study	Phase	Indication	Dose/Regimens	N/P K
Single-agent studies (pertuzumab)				
TOC2297g	Ia	Advanced solid tumours	Dose-escalation: 0.5, 2, 5, 10, and 15 mg/kg	21
JO17076	I	Advanced solid tumours	Dose-escalation: 5, 10, 15, and 25 mg/kg	18
TOC2689g	II	Advanced ovarian cancer	Cohort 1: 840 mg loading, then 420 mg q3w Cohort 2: 1050 mg q3w	61 62
BO16934	II	mBC, low HER2 expression	Arm A: 840 mg loading, then 420 mg q3w Arm B: 1050 mg q3w	40 37

Study	Phase	Indication	Dose/Regimens	N/PK
BO17004	II	HRPC, chemotherapy naive	Cohort 1: 840 mg loading, then 420 mg q3w Cohort 2: 1050 mg q3w	35 33
TOC2682g	II	CRPC, pre-treated with DOX	840 mg loading, then 420 mg q3w	40
TOC2572g	II	Advanced, recurrent NSCLC	840 mg loading, then 420 mg q3w	43
Combination-studies (pertuzumab plus various other chemotherapeutic agents)				
BO17003	Ib	Advanced solid tumours	PTZ: 1050 mg q3w + CAP: 825, 1000, 1250 mg/m ²	18
BO17021	Ib	Advanced solid tumours	PTZ: 1050 mg q3w + DOX: 60, 75 mg/m ² . PTZ: 840 mg loading, then 420 mg q3w + DOX: 75, 100 mg/m ²	19
WO20024	Ib	Advanced NSCLC	PTZ: 840 mg loading, then 420 mg q3w + ERL: 100, 150 mg/day	15
TOC3258g	II	Ovarian, peritoneal, or fallopian cancer, platinum resistant	PTZ: 840 mg loading, then 420 mg q3w + GEM: 800 mg/m ² GEM: alone	16 11
WOC20698 Pivotal	III	mBC HER2+	PBO: q3w + DOX: 75 mg/m ² for 6 cycles at least + TTZ: 8 mg/kg loading, then 6 mg/kg, q3w PTZ: 840 mg loading, then 420 mg q3w + DOX 75 mg/m ² for 6 cycles at least + TTZ: 8 mg/kg loading, then 6 mg/kg	17 20

PTZ = pertuzumab; TTZ = trastuzumab; DOX = docetaxel; GEM = gemcitabine; CAP = capecitabine; PBO = placebo; mBC = metastatic breast cancer; NSCLC = non-small cell lung cancer; CRPC = castrate resistant prostate cancer; HRPC = hormone resistant prostate cancer. N/PK = number of subjects used for PK analysis

Population-PK analyses

The submission included two population-PK analyses (Ng *et al.*, 2006¹⁰; and Report 11-2998). The preliminary analysis by Ng *et al.*, 2006 was based on the PK results from one

¹⁰ Ng CM *et al.* Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. *Pharm Res* 2006;23(6): 1275-1284.

Phase I study (TOC2297g), and two Phase II studies (TOC2689g; B016934). This study showed that the PK characteristics of pertuzumab were similar to those reported for other monoclonal IgG1 antibodies. The pivotal population-PK analysis was report 11-2998 which included PK data from all 12 Phase I/II/III clinical studies listed above in Table 2.

Evaluator's overall conclusions on pharmacokinetics

- The PK of pertuzumab have been reasonably well characterised in patients with a variety of malignant tumours. There were no PK studies with pertuzumab in healthy subjects.
- The two population-PK analyses in patients with cancer support the fixed, non-weight-based dosing regimen proposed for registration (Ng *et al.*, 2006; and Report 11-2998). In the pivotal population-PK analysis (Report 11-2998), data from 440 cancer patients were pooled from eleven Phase I/II studies and one Phase III study at pertuzumab doses ranging from 2 to 25 mg/kg. This dose range covered the pertuzumab 840 mg loading followed by 420 mg q3w IV dosing regimen proposed for the treatment of metastatic breast cancer. The population-PK analysis demonstrated that the data were best described by a two-compartment model with first order elimination from the central compartment. The population-PK analysis showed no statistically significant difference in either clearance or volume of the central compartment between the pivotal Phase III study (WO20698/TOC4129g) and the Phase I/II studies.
- In the population-PK analysis (Report 11-2998), the volume of distribution of pertuzumab was estimated to be 5.43 L (that is, V_c 3.07 L [1.2% SE] + V_p 2.36 L [3.5% SE]). The estimated V_c (3.07 L) approximates plasma volume (3L). Both V_c and the volume of the peripheral compartment (V_p) increased in patients with greater lean body weight. However, sensitivity analyses for estimated steady state C_{min} , C_{max} , and AUC at the proposed pertuzumab dosing regimen of 840/420 mg showed that the effect of lean body weight on these parameters was within the estimated inter-individual variability of these parameters in the overall population.
- In the population-PK analysis (Report 11-2998), the clearance of pertuzumab was estimated to be 0.239 L/day (2.1% SE), with a coefficient of variation of 34.5% (suggesting moderate inter-subject variability). Clearance decreased in patients with higher baseline serum albumin concentrations, and increased in patients with greater lean body weight. However, sensitivity analyses for estimated steady state C_{min} , C_{max} , and AUC at the proposed pertuzumab dosing regimen of 840/420 mg showed that the effects of serum albumin and lean body weight on these parameters were well within the estimated inter-individual variability of these parameters in the overall population. In the population-PK analysis (report 11-2998), the median terminal elimination half-life was 17.2 days (95% range: 7.8 to 32 days).
- There were no data in the submission investigating the metabolism of pertuzumab. However, it is expected that this large molecular weight (MW, approximately 148 kilo Daltons) protein will undergo catabolism to small peptides and individual amino acids. There were no data in the submission on renal excretion of pertuzumab. However, it can be predicted that pertuzumab will not undergo renal filtration due to its large MW.
- In Study B016934, a loading dose of 840 mg achieved trough and peak concentrations with the range of those observed at steady state by the second treatment cycle in women with metastatic breast cancer (n=40). Over 17 treatment cycles (approximately 1 year) a mean serum concentration of 289 µg/mL was reached with the 840/420 mg regimen and at the end of the cycles the mean serum concentrations dropped to approximately 100 µg/mL (Study B016934). In Study J017076, the observed accumulation ratio (that is, ratio = Cycle 3: Cycle 1, trough concentration) was 2.30 in Japanese patients. The population-PK analysis (Report 11-2998) showed

that about 92% of the population treated with the proposed pertuzumab fixed-dose regimen (840/420 mg) achieved trough serum concentrations > 20 µg/mL (target concentration) regardless of sex, weight or race (Japanese versus non-Japanese).

- There were no specific PK studies in patients with hepatic or renal impairment. However, as pertuzumab is not cleared by hepatic metabolism or renal excretion the absence of such studies is not considered to be a major issue. In the population-PK analysis (Report 11-2998), median steady state trough pertuzumab concentrations were comparable in patients with normal renal function and patients with mild and moderate renal impairment based on creatinine clearance (CrCL). However, there were only limited data on patients with severe renal impairment.
- There were no specific PK studies investigating the effects of pertuzumab in elderly patients (that is, ≥ 65 years of age). However, the population-PK analysis (Report 11-2998) showed that age did not significantly affect the PK of pertuzumab as regards clearance and the volumes of the central and peripheral compartments. Similarly, the population-PK analysis (Report 11-2998) showed that there was no difference between male and female patients, or between Japanese and non-Japanese patients as regards clearance and volumes of the central and peripheral compartments.
- There were no specific studies investigating the PK drug-drug interactions. However, there were five clinical studies with relevant PK interaction data. In the pivotal efficacy and safety study in patients with metastatic breast cancer (WO20698/TOC4129g), substudy 2 showed that there are unlikely to be significant PK interactions when pertuzumab, trastuzumab and docetaxel are administered at the proposed doses for the treatment of metastatic breast cancer. Other clinical combination studies in patients with cancer showed no significant PK interactions between pertuzumab and gemcitabine (TOC3258g), pertuzumab and capecitabine (BO17003), pertuzumab and docetaxel (BO17021), or pertuzumab and erlotinib (WO20024).
- In the pivotal Phase III study WO20698/TOC4129g, there were 11 (2.8%) patients out of 386 with evaluable anti-therapeutic antibody (ATA) data who tested positive at some time during or after treatment. There were data from two patients (one each in TOC2572g and WO20698/TOC4129g) suggesting that anti-pertuzumab antibodies might reduce pertuzumab serum concentrations. However, no definitive conclusions can be drawn from this limited data.

Pharmacodynamics

The submission included one study containing PD data (QT interval¹¹ data) in patients with metastatic breast cancer (WO20698/Substudy 2).

The substudy was designed to enrol a total of 50 ECG evaluable patients and at least 40 PK evaluable patients. The two treatment groups were the combination of pertuzumab, trastuzumab, and docetaxel (n=20) compared with the combination of placebo, trastuzumab, and docetaxel (n=17). A positive-control comparison drug (for example, moxifloxacin) is recommended in “thorough QT/QTc studies” to validate assay sensitivity. However, in this study a positive-control was not administered as the sponsor considered that the use of such a drug would not be ethical in a metastatic cancer patient population.

¹¹ QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate. To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval QTc is often calculated.

Pertuzumab or placebo was administered as an IV loading dose of 840 mg on Day 1 of Cycle 1, and then as a maintenance dose of 420 mg for subsequent q3w cycles. Trastuzumab was administered as an IV loading dose of 8 mg/kg on Day 2 of Cycle 1, and then as a maintenance dose of 6 mg/kg IV on Day 1 of subsequent cycles following pertuzumab. Docetaxel was administered as an IV dose of 75 mg/m² on Day 2, Cycle 1, following trastuzumab and then on Day 1 of subsequent cycles following trastuzumab.

The objectives of the ECG analyses were to assess the effect of pertuzumab on the change (Δ) from baseline in the QTc interval, calculated using both Fridericia's correction (Δ QTcF) and Bazett's correction (Δ QTcB), and to assess the effect of pertuzumab on other ECG parameters of heart rate, QT interval, PR interval, and QRS duration. Data consisted of 12-lead ECG measurements obtained in triplicate and sent to a central core cardiology laboratory, which produced a single dataset that was analysed by Genentech following unblinding of the main study. Statistical analysis of ECG data was guided by the Statistical Analysis Plan (SAP), dated 12 July, 2011.

Evaluator's overall conclusions on pharmacodynamics

The submission included one PD study investigating the relationship between QTcF prolongation and pertuzumab serum concentration in patients with metastatic breast cancer (WO20698; Substudy 2). During Cycle 3 of this study, the point estimate of $\Delta\Delta$ QTcF¹² for the 30-minute pre-infusion time-point and the immediately post-infusion time-point were greater than 5 ms, and the upper 90% CIs of the $\Delta\Delta$ QTcF were greater than 10 ms for all four time-points assessed. The results from Cycle 3 would give rise to regulatory concern in a "thorough QT/QTc study" (relevant note for guidance, CHMP/ICH/2/04¹³). However, the sponsor considers that these findings are attributable to random variability and not due to a drug effect.

The sponsor notes that the point estimates of Δ QTcF in Cycle 3 for pertuzumab were generally higher than the Δ QTcF for placebo, suggesting that the $\Delta\Delta$ QTcF values may have been inflated due to over-correction associated with the Δ QTcF of placebo. In addition, the sponsor comments that if post-baseline measurements of QTcF are regressed to the overall mean of about 413.3 ms, a difference would be observed in post-baseline changes between the pertuzumab (414.3 minus 410.7) and placebo groups (414.3 minus 420.0) of 9.3 ms, "lower than the value of 10 ms considered to important in thorough QTc studies. Thus it is unlikely pertuzumab causes $\Delta\Delta$ QTcF prolongation larger than those of clinical interest in thorough QTc studies". The sponsor's analysis was *post hoc* and not specified in the study protocol. In addition, the TGA adopted QT/QTc interval guidance document (CHMP/ICH/2/04) makes no mention of adjusting post-baseline changes in the QTcF by regressing them to the overall global mean. Furthermore, the QT/QTc guideline states that the threshold of regulatory concern "is around 5 ms as evidenced by an upper bound of the 95% CI confidence interval around the mean effect on QTc of 10 ms". It appears that the 10 ms referred to in the sponsor's *post hoc* analysis refers to the mean difference between the two treatment arms rather than the upper bound of the 95% CI of the mean. If this is the case, then the observed mean difference of 9.3 ms is greater than the mean difference of 5 ms, which is of regulatory concern in a "thorough QT/QTc study".

Overall, despite the observed upper bound of the 90% CI being > 10 ms for each of the four $\Delta\Delta$ QTcF point estimates in Cycle 3, and the point-estimates being > 10 ms for the 30-minute pre-infusion and the immediately post-infusion time points in this Cycle, no patients in the pertuzumab group (0/20) had QTcF values > 450 ms (compared with 2/16

¹² $\Delta\Delta$ denotes baseline-adjusted placebo-corrected values

¹³ EMA. ICH E14. *The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs*, 25 May 2005. Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (CHMP/ICH/2/04).

in the placebo group), and no patients in either group had QTcF values > 480 ms or > 500 ms. In addition, no patients in the pertuzumab group (0/20) had an increase in QTcF > 30 ms from baseline (compared with 2/17 in the placebo group), and no subjects in either treatment group had an increase in QTcF > 60 ms from baseline. The categorical results are reassuring and suggest that clinically significant increases in the QTcF are unlikely with pertuzumab.

Efficacy

Dosage selection for the pivotal studies

The protocol of the pivotal Phase III study (CLEOPATRA¹⁴) states that the dose of pertuzumab selected for investigation (that is, 840 mg loading, 420 mg maintenance q3w) was based on PK studies demonstrating similar PK observed across doses ranging from 2.0 to 15.0 mg/kg (140 mg to 1050 mg for a 70 kg patient). In addition, the protocol also states that the preliminary population-PK analysis showed that a two-compartment model adequately described the concentration-time data with a systemic serum clearance of approximately 0.24 L/day and a terminal half-life of approximately 17 days for a typical patient. Based on these data, a dosing interval of 3 weeks was recommended for the clinical studies. In the Phase II studies, a loading dose of 840 mg (followed by 420 mg q3w) was shown to be capable of attaining steady-state trough and peak concentrations by the second cycle. The preliminary population-PK analysis also showed that modelling data from Phase Ia and Phase II studies supported the use of fixed, non-weight based dosing. Additionally, there was no evidence that pertuzumab significantly affected the PK of co-administered chemotherapeutic agents docetaxel and capecitabine in Phase Ib studies.

Comment: The rationale for selection of the pertuzumab dosage regimen for the pivotal Phase III study is reasonable. Population-PK analysis involving data from all 12 PK studies included in the submission (Report-11-2998) supported the use of fixed-dose pertuzumab identified in the smaller, preliminary, population-PK analysis (Ng *et al.*, 2006). In addition, data from the pivotal Phase III PK Substudy confirmed that significant PK interactions between agents were unlikely for the pertuzumab, trastuzumab and docetaxel combination. However, data from the two, single-agent (pertuzumab) PK dose-escalation studies in patients with advanced solid tumours showed that the maximum tolerated dose (MTD) of pertuzumab was “not reached” at doses up to 15 mg/kg (that is, 1050 mg in a 70 kg person) in Study TOC2297g and 25 mg/kg (that is, 1750 mg in a 70 kg person) in Study JO1706. Consequently, these data raise some uncertainties about whether the dose selected for the pivotal study was the most appropriate dose. However, despite these reservation, the population-PK analysis (Report 11-2998) showed that about 92% of the population treated with the proposed pertuzumab fixed-dose regimen (840/420 mg) achieved trough serum concentrations > 20 µg/mL (target concentration) regardless of sex, weight or race (Japanese versus non-Japanese).

Studies providing evaluable efficacy data

The sponsor’s letter of application nominates the Phase III study (WO20698/CLEOPATRA) as the pivotal efficacy and safety study, with additional supportive data being provided by Studies WO20697/NEOSPHERE and BO17929 and a range of Phase I and II studies in patients with cancers of various types. The sponsor’s clinical overview identifies the Phase III study (WO20698/CLEOPATRA) as being pivotal, and two Phase II studies as being key supporting studies (WO20697/NEOSPHERE and BO17929). The submission included four studies in patients with breast cancer (see Table 3, below).

¹⁴ Clinical evaluation of pertuzumab and trastuzumab

Table 3. Breast cancer studies.

Protocol No.	Study Design	Population	Efficacy Parameters	Drug, Dose, Duration	No. of Patients Sex (M:F)
PIVOTAL STUDY					
Phase III – Combination therapy, HER2-positive breast cancer					
WO20698/ TOC4129g (CLEOPATRA)	A Phase III randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety of: Arm A: P1a+T+D vs Arm B: P1z+T+D	Patients with HER2-positive locally recurrent, unresectable and metastatic breast cancer (MBC) who have not received chemotherapy or biologic therapy for their advanced/metastatic disease.	IRF- assessed progression-free survival (PFS), overall survival (OS), investigator-assessed PFS, objective response rate (ORR), duration of response, time to symptom progression based on Quality of Life (QoL).	Pertuzumab: 420 mg every 3 weeks (q3w) (840 mg loading dose) or placebo q3w Trastuzumab: 6 mg/kg q3w (8mg/kg loading dose) Docetaxel: 75mg/m ² escalating to 100mg/m ² q3w. Treatment until progression	808 patients (2M: 806F): P1a+T+D : N= 408 P1z+T+D: N= 402
KEY SUPPORTING STUDIES:					
Phase II Studies – Combination therapy, HER2-positive breast cancer					
WO20697 (NEOSPHERE)	A Phase II randomized, open-label, four-arm study evaluating • A, T+D • B, P1z+T+D • C, P1z+T • D, P1z+D in the neoadjuvant setting.	Patients with locally advanced, inflammatory or early stage HER2-positive breast cancer scheduled to receive neoadjuvant therapy.	Neoadjuvant phase: Pathological complete response (pCR) rate, tumor response, clinical response rate, time to response, breast conserving surgery Adjuvant phase only: Disease-free survival, PFS	Neoadjuvant (4 cycles): Pertuzumab: 420 mg (840 mg loading dose) Trastuzumab: 6 mg/kg q3w (8mg/kg loading dose) Docetaxel: 75mg/m ² IV every 3 weeks	417 patients (0 M:417 F): Arm A (T+D): N=107 Arm B (P1z+T+D): N=107 Arm C (P1z+T): N = 107 Arm D (P1z+D): N= 96
BO17929	An exploratory, two-stage Phase II, single-arm study of efficacy and safety of pertuzumab and trastuzumab.	HER2-positive MBC patients who have progressed on trastuzumab-based therapy.	ORR and clinical benefit response (CBR) rate, PFS, TTP, duration of response, time to response, OS.	Pertuzumab: 420 mg (840 mg loading dose) q3w Trastuzumab: 2mg/kg qw (4mg/kg loading dose or 6 mg/kg q3w (8mg/kg loading dose)). Treatment until progression	95 patients (0M: 95F) Cohorts 1+2 (P1z+T): N = 68 Cohort 3 (P1z): N=28
Phase II Studies – Single agent, HER2-negative breast cancer					
BO16934	A Phase II, open-label, randomized, two-arm, multicenter study of efficacy and safety of two different doses of pertuzumab.	Patients with MBC with low expression of HER2, that has progressed during or after standard chemotherapy.	ORR, time to and duration of response, TTP.	Pertuzumab: 420 mg (840 mg loading dose) q3w OR 1050 mg q3w Treatment until progression	79 patients (0M : 79F) 420 mg P1z: N=41 1050 mg P1z: N = 38

5-FU 5-fluorouracil, CBR = clinical benefit response, D = docetaxel, IRF = independent review facility, ORR = objective response rate, OS overall survival, P1a = placebo, P1z = pertuzumab, PFS = progression-free survival; q3w = every three weeks, qw = every week, QoL = quality of life, T = trastuzumab, TTP = time to progression

In agreement with the sponsor's covering letter and clinical overview, it is considered that the submission includes one pivotal Phase III study (CLEOPATRA) supporting the application to register pertuzumab in combination with trastuzumab and docetaxel for the proposed indication. However, the two Phase II studies nominated by the sponsor as being the key supporting studies are considered to provide efficacy data of limited relevance to the submission. In these two Phase II studies in patients with breast cancer, the patient group and/or the pertuzumab treatment regimen differed from those being proposed and, consequently, the efficacy data from these two studies are not considered to be directly relevant to the application to register pertuzumab for the proposed indication. The pivotal study (CLEOPATRA) is reviewed and in view of the importance that the sponsor places on the two studies that it considers to be key supporting studies (WO20697/NEOSPHERE and BO17929) these two studies have also been reviewed.

One of the two Phase II studies (WO20697/NEOSPHERE) nominated by the sponsor as key supporting was undertaken in patients with locally advanced, inflammatory or early stage HER2-positive breast cancer scheduled to receive neoadjuvant therapy for four cycles prior to surgery, including pertuzumab in combination with trastuzumab, and docetaxel. This study can not be considered to directly support the pivotal study as the patient population (early stage breast cancer) and the treatment regimen (neoadjuvant) both differed from that being proposed.

The other of the two Phase II studies (BO17929) nominated by the sponsor as key supporting was an exploratory, single-arm study that evaluated the doublet combination of pertuzumab and trastuzumab in patients with HER2-positive metastatic breast cancer who had progressed while on trastuzumab based therapy. This study can not be considered to directly support the pivotal study as the treatment regimen differed from that being proposed for registration.

There was one Phase II study (BO16934) in patients with metastatic breast cancer with low HER2 expression that had progressed during or after standard chemotherapy that assessed two pertuzumab single-agent treatment regimens (see Table 3 above). However, the study can not be considered to directly support the pivotal study as the treatment regimen (single-agent pertuzumab) differed from that being proposed for registration.

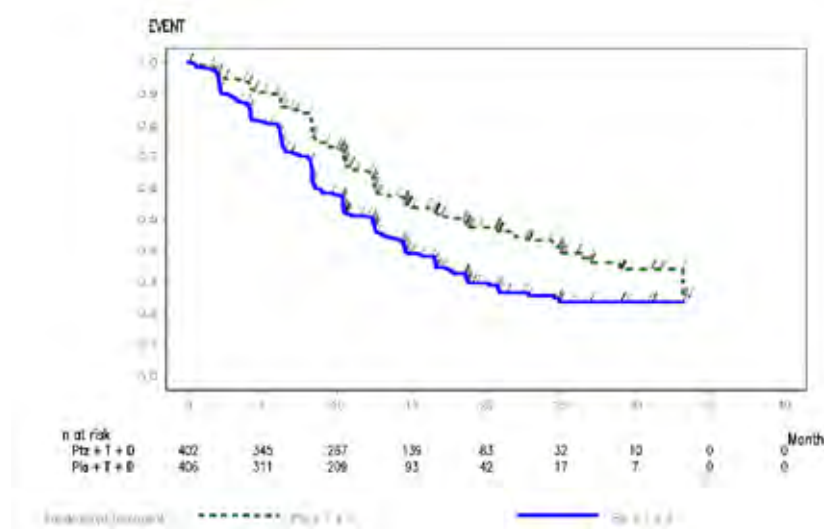
In addition to the four clinical efficacy and safety studies in patients with breast cancer summarised above in Table 3, the submission included 9 other Phase I and II studies with pertuzumab efficacy and safety data for other indications. However, these studies are not considered to provide supportive efficacy data as the patient populations included cancers other than breast cancer and the pertuzumab dosage regimens did not include the triplet combination proposed for registration. In these studies, pertuzumab as monotherapy demonstrated little efficacy, while pertuzumab in combination with other chemotherapeutic agents showed variable efficacy depending on the indication.

Evaluator's conclusions on clinical efficacy for metastatic breast cancer

The submitted data included four studies with efficacy data for pertuzumab in patients with breast cancer (see Table 3 above for details), and nine additional studies with efficacy data for pertuzumab in patients with other cancers. Of the four breast cancer studies, it is considered that one of the studies includes pivotal efficacy data (CLEOPATRA), while the other three studies are considered not to provide direct supportive efficacy data because the indication and/or the pertuzumab dosing regimens differ from those being proposed for approval. The nine studies in patients with indications other than breast cancer are considered not to include supportive efficacy data.

The pivotal Phase III study (CLEOPATRA) is considered to have satisfactorily demonstrated that the combination of pertuzumab in combination with trastuzumab and docetaxel (Ptz+T+D) for the treatment of the proposed patient population results in a clinically meaningful increase in progression-free survival (PFS) compared with the combination of placebo in combination with trastuzumab and docetaxel (Pla+T+D). In this study, both the primary efficacy endpoint (PFS) and the secondary endpoint (overall survival, OS) are consistent with the endpoints recommended in the TGA adopted *Guideline on the evaluation of anticancer medicinal products in man* (CPMP/EWP/205/95/Rev.3/Corr, Dec 2005). The study showed that the median duration of the independent review facility (IRF)-assessed PFS (primary efficacy endpoint) was 6.1 months longer in the Ptz+T+D arm (18.5 months) than in the T+D arm (12.4 months), and that the risk of a PFS event (disease progression or death) was reduced 38% in the Ptz+T+D arm relative to the Pla+T+D arm (hazard ratio (HR) = 0.62 [95% CI: 0.51, 0.75], $p < 0.0001$). The Kaplan-Meier analysis showed that the IRF-assessed PFS curves began to separate in favour of the Ptz+T+D arm at about 2 to 3 months following initiation of treatment, with separation being maintained throughout the remainder of the observation period (see Figure 1). The difference in IRF-assessed PFS was not only statistically significant, but is also considered to be clinically meaningful. The observed improvement in the observed median duration of the IRF-assessed PFS in the Ptz+T+D arm compared with the Pla+T+D (relative increase 49%, absolute increase 6.1 months) was greater than the estimated increase used to power the study (relative increase 33%, absolute difference 3.5 months).

Figure 1. CLEOPATRA - Kaplan-Meier curves of IRF-assessed progression-free survival.



The robustness of the observed result in favour of the Ptz+T+D arm compared with the Pla+T+D arm was supported by the six sensitivity analyses of PFS, the univariate and multivariate Cox regression analyses of the PFS, and the subgroup PFS analyses. Furthermore, the result of the secondary efficacy endpoint analysis of investigator-assessed PFS was consistent with the results of the primary efficacy endpoint analysis of IRF-assessed PFS.

In addition to investigator-assessed PFS, other key secondary efficacy endpoint analyses also supported the efficacy of the Ptz+T+D combination compared with the Pla+T+D combination. The analysis of OS favoured the Ptz+T+D arm over the Pla+T+D arm (96 deaths versus 69 deaths, respectively, HR = 0.64 [96% CI: 0.47, 0.88], $p = 0.0053$), but the estimated HR did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets α -spending function¹⁵ for this interim analysis (HR ≤ 0.603 , $p \leq 0.0012$). Consequently, the observed survival benefit in favour of the Ptz+T+D arm relative to the Pla+T+D arm was deemed to be not statistically significant. However, the Kaplan-Meier analysis showed that the survival curves began to separate in favour of the Ptz+T+D arm at about 10 months. The median length of follow-up for survival was estimated to be 19.3 months in both treatment arms, but the median time to death had not been reached in either treatment arm at the time of data cut-off. Furthermore, at the time of the analysis only 43% (165/385) the prespecified number of deaths had occurred.

The overall response rate (ORR) was higher in the Ptz+T+D arm than in the Pla+T+D arm (80.2% versus 69.3%, respectively), but the observed statistically significant difference between the two arms (10.8% [95% CI: 4.2, 17.5]; $p=0.0011$) was deemed to be exploratory rather than confirmatory due to the pre-specified fixed-sequence testing hierarchy. This hierarchy (IRF-assessed PFS \rightarrow OS \rightarrow ORR) specified that confirmatory testing should stop if the statistical the analysis of the OS was found to be negative.

The duration of the IRF-assessed objective response was assessed in the 233 patients in the Pla+T+D arm and 275 patients in the Ptz+T+D arm and showed that objective response was maintained for an estimated additional 33.5 weeks in patients receiving Ptz+T+D compared with Pla+T+D. The median duration of response in the Pla+T+D arm was 54.1 weeks (range: 5, 135 weeks) and 87.6 weeks (range: 7, 137) in the Ptz+T+D arm; HR = 0.66 (95% CI: 0.51, 0.85). The Functional Assessment of Cancer Therapy–Breast (FACT-B) analysis showed that time to symptom progression in both treatment arms was

¹⁵ A method used in the analysis of group sequential design studies

similar and represented about 6 treatment cycles (18.3 weeks, Pla+T+D versus 18.4 weeks, Ptz+T+D).

The two breast cancer studies identified by the sponsor as providing key supporting efficacy data were WO20697/NEOSPHERE and B017929. However, as discussed above neither of these two studies are considered to provide direct supportive efficacy data as the indication and/or the pertuzumab dosing regimen differed from those being proposed.

In WO20697/NEOSPHERE, the efficacy of a triplet combination including pertuzumab, trastuzumab and docetaxel as neoadjuvant therapy (four cycles) was compared with three doublet combinations for the treatment of female patients with locally advanced, inflammatory or early stage, HER2-positive breast cancer. The study showed that the proportion of patients with pathological complete response (pCR) was significantly greater in patients treated with pertuzumab, trastuzumab and docetaxel (n=107) compared with trastuzumab plus docetaxel (n=107): 45.8% versus 29.0%, respectively; difference 16.8% (95% CI: 3.5, 30.1); p=0.0141. In addition, the pCR in the pertuzumab and docetaxel arm (n=96) was significantly lower than in the pertuzumab, trastuzumab and docetaxel arm (n=107): 24.0% versus 45.8%, respectively; difference -21.8% (95% CI: -35.1, -8.5); p=0.0030.

In Study B017929, a doublet combination of pertuzumab plus trastuzumab (n=66) showed ORR (24.2%) and clinical benefit response (CBR, 50.0%) results defined by the sponsor to be clinically meaningful in patients with trastuzumab insensitive advanced metastatic HER2-positive breast cancer.

In Study B016934, single-agent pertuzumab therapy (840/420 mg or 1050 mg) in women with metastatic breast cancer with low expression of HER2 resulted in only 2 out of 41 patients (4.9%) in the 840/420 mg arm achieving a partial response and no patients out of 37 achieving a partial response in the 1050 mg arm.

In summary, it is considered that the submission to register pertuzumab for the proposed indication and the proposed dosage regimen is supported by only one pivotal Phase III study (CLEOPATRA). However, there is a relevant TGA adopted guidance document¹⁶ indicating that submissions can be supported by only one pivotal study provided that the study is particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality and internal consistency. Overall, it is considered that the pivotal Phase III study (CLEOPATRA) meets the required criteria for submissions supported by one pivotal study and supports the registration of the proposed pertuzumab treatment regimen for the proposed indication.

Safety

Studies providing evaluable safety data

The key safety data in the submission comes from the pivotal Phase III efficacy and safety study (CLEOPATRA). This study included 407 patients treated with Ptz+T+D for the proposed indication compared with 397 patients exposed to Pla+T+D.

Supportive safety data comes from an integrated summary from a total of 1412 patients exposed to pertuzumab. These 1412 patients included:

- 514 patients exposed to pertuzumab, trastuzumab and docetaxel (Ptz+T+D) in patients with metastatic breast cancer from the pivotal Phase III study (CLEOPATRA);

¹⁶ *Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study*. CPMP/EWP/2330/99, 31 May 2001

n=407), and in patient with early stage breast cancer from the neoadjuvant treatment Phase II study (WO20697; n=107);

- 191 patients exposed to pertuzumab and trastuzumab (Ptz+T) in patients with breast cancer from Phase II study WO20697 (n=108) and Phase II study BO17929 (n=83);
- 386 patients exposed to pertuzumab monotherapy in Phase II studies using fixed-dose regimens of 420/840 mg or 1050 mg; and
- 321 patients exposed to pertuzumab in Phase I dose escalation studies.

An overview of the key safety from the integrated database is summarised below in Table 4. Overall, adverse events (AEs) associated with the pertuzumab, trastuzumab, and docetaxel (Ptz+T+D) combination arm in the pivotal Phase III study (CLEOPATRA) occurred more frequently than with pertuzumab in the remainder of the safety database. However, exposure to pertuzumab was greater in the Ptz+T+D arm of CLEOPATRA than in the other studies, and this might account for the differences between this study and the Phase I/II studies. The safety profile of the Ptz+T+D combination from the Phase II Study WO20697 was consistent with the safety profile of this combination from CLEOPATRA. The safety data from the all pertuzumab treated patient population (n=1412) have been reviewed, as have the safety data from the integrated data base relating to AEs of particular interest. Interpretation of the integrated pertuzumab safety database is complicated by the fact that in this database pertuzumab has been either combined with various chemotherapeutic agents (primarily in doublet regimens) or administered as a single-agent.

Table 4. Summary of the integrated safety database.

Safety Parameter	Patients Experiencing Event								
	WO20698/TOC4129g		WO20697				BO17929	Single Agent Ptz	All Ptz-Treated Pts
	Pla+T+D n=397	Ptz+T+D n=407	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T n=83	Ptz n=386	Various n=1412
Any AE	98.5%	99.9%	98.1%	98.1%	72.2%	98.9%	95.2%	94.3%	95.8%
Grade ≥ 3	72.8%	74.2%	72.9%	62.6%	6.5%	70.2%	18.1%	40.2%	53.3%
Related AE	96.2%	97.3%	97.2%	96.3%	67.6%	97.9%	79.5%	76.2%	86.9%
AE→disc	27.7%	29.2%	0	0.9%	1.9%	2.1%	3.6%	7.3%	12.9%
AE→int/mod	53.1%	60.0%	34.6%	32.7%	14.8%	43.6%	15.7%	11.9%	33.9%
AE→Rx	92.9%	95.6%	86.9%	79.4%	52.8%	84.0%	78.3%	81.1%	85.2%
SAE	26.2%	34.4%	16.8%	10.3%	3.7%	17.0%	14.5%	26.9%	25.7%
AE→death	2.5%	2.0%	0	0.9%	0	0	1.2%	1.3%	1.6%
Death on Trt	3.0%	2.5%	0	0.9%	0	0	2.4%	7.8%	4.5%
Death, PD	0.8%	0.2%	0	0	0	0	0	7.0%	2.9%
Death, other	2.3%	2.2%	0	0.9%	0	0	2.4%	0.8%	1.6%

NB: patients may appear in more than one group/column. Dark grey columns data for patients treated with Ptz+T+D (proposed licensed treatment regimen); Mid grey columns data for patients treated with Ptz+T; Pale grey columns data for patients treated with single agent pertuzumab; AE→disc = any AE leading to discontinuation of one or more study drugs; AE→int/mod = any AE leading to dose interruption/ modification; AE→Rx = any AE requiring treatment; AE→death = AE with outcome, death (that is, Grade 5 AE; Death on Trt = all deaths within 42 days of last treatment; Death, PD = deaths due to progressive disease (a subset of deaths within 42 days of last treatment); Death, other = deaths due to causes other than progressive disease (a subset of deaths within 42 days of last treatment)).

Summary of evaluator's overall conclusions on clinical safety

A summary of the general safety findings appears in this section. Details of AEs, including analyses based on various AE categories, are found in section 7 of the Extract from the CER (Attachment 2 of this AusPAR). See also *First round assessment of risks* and *Second round assessment of risks*, below.

The pivotal safety data in this submission are from the pivotal Phase III efficacy and safety study (CLEOPATRA). In this study, safety data from 407 patients treated with pertuzumab in combination with trastuzumab and docetaxel (Ptz+T+D) were compared with 397 patients treated with placebo in combination with trastuzumab and docetaxel (Pla+T+D).

Overall, the data are considered to show that the safety profile of the Ptz+T+D combination is inferior to that of the Pla+T+D combination. However, despite the difference in the safety profile of the two treatment combinations the data are considered to have satisfactorily established the safety of Ptz+T+D for the proposed indication.

In addition to the pivotal safety data from CLEOPATRA, the submission also included an integrated safety database containing supportive safety data on 1412 patients with various types of cancer treated with pertuzumab as a single agent and in doublet and triplet combinations. Overall, the safety profile of pertuzumab from the integrated database is considered to be consistent with the safety profile of pertuzumab observed in CLEOPATRA.

In CLEOPATRA, exposure to pertuzumab is considered sufficient to adequately characterise the safety of the Ptz+T+D combination for the proposed indication. The median number of cycles was 18 (range: 1, 56) for the Ptz+T+D arm compared with 15 (range: 1, 50) for the Pla+T+D arm. By Cycle 16, 62% (252/407) of patients who had commenced treatment with Ptz+T+D were still receiving treatment compared with 47% (188/397) of patients who had commenced treatment with Pla+T+D. The difference between the two arms was due to a greater number of early withdrawals from study treatment in the Pla+T+D arm, primarily resulting from a higher incidence of patients with progressive disease in the Pla+T+D arm. Post-hoc Kaplan-Meier analysis showed that median time on treatment to a PFS event was 18.1 months in the Ptz+T+D arm and 11.8 months in the Pla+T+D arm.

Overview of commonly occurring adverse events by body system

The overall incidence of AEs occurring in patients during the treatment period was balanced between the treatment arms (98.5%, Pla+T+D versus 99.8%, Ptz+T+D), although the total number of AEs reported in the Ptz+T+D arm was higher than in the Pla+T+D arm (6048 versus 5300).

The system organ classes (SOCs) in which the most common AEs ($\geq 10\%$ of patients in either treatment arm) were reported (Pla+T+D versus Ptz+T+D) included:

- General Disorders and Administration Site Conditions (81.9% versus 83.3%): most frequently fatigue (36.8% versus 37.6%), asthenia (30.2% versus 26.0%), peripheral oedema (30.0% versus 23.1%), mucosal inflammation (19.9% versus 27.8%), pyrexia (17.9% versus 18.7%) and oedema (12.6% versus 11.3%).
- Skin and Subcutaneous Tissue Disorders (78.6% versus 83.3%): most frequently alopecia (60.5% versus 60.9%), rash (24.2% versus 33.7%), nail disorder (22.9% versus 22.9%), pruritus (10.1% versus 14.0%) and dry skin (4.3% versus 10.6%).
- Gastrointestinal Disorders (76.1% versus 84.0%): most frequently diarrhoea (46.3% versus 66.8%), nausea (41.6% versus 42.3%), vomiting (23.9% versus 24.1%), constipation (24.9% versus 15.0%), stomatitis (15.4% versus 18.9%), abdominal pain (12.3% versus 14.0%) and dyspepsia (12.1% versus 12.0%).
- Blood and Lymphatic System Disorder (62.7% versus 69.0%): most frequently neutropenia (49.6% versus 52.8%), anaemia (18.9% versus 23.1%), leukopenia (20.4% versus 18.2%) and febrile neutropenia (7.6% versus 13.8%).
- Nervous System Disorders (61.2% versus 65.6%): most frequently peripheral neuropathy (20.2% versus 21.1%), headache (16.9% versus 20.9%), dysgeusia (15.6%

versus 18.4%), peripheral sensory neuropathy (14.1% versus 12.0%), dizziness (12.1% versus 12.5%) and paraesthesia (10.1% versus 9.1%).

- Musculoskeletal and Connective Tissue Disorders (61.2% versus 59.5%): most frequently myalgia (23.9% versus 22.9%), arthralgia (16.1% versus 15.5%), pain in extremity (11.8% versus 15.2%), and back pain (11.6% versus 13.5%).
- Infections and Infestations (56.2% versus 61.7%): most frequently upper respiratory tract infection (13.4% versus 16.7%) and nasopharyngitis (12.8% versus 11.8%).
- Respiratory, Thoracic and Mediastinal Disorders (48.1% versus 48.6%): most frequently cough (18.6% versus 21.4%) and dyspnoea (15.6% versus 14.0%).
- Metabolism and Nutrition Disorders (38.0% versus 40.0%): most frequently decreased appetite (26.4% versus 29.2%).
- Eye Disorders (23.7% versus 32.2%): most frequently increased lacrimation (13.9% versus 14.0%).

Cardiac disorders (SOC) occurred marginally more frequently in patients in the Pla+T+D arm (16.4%) than in the Ptz+T+D arm (14.5%). The most common cardiac disorder AEs (Pla+T+D versus Ptz+T+D) were left ventricular dysfunction (LVD, 8.3% versus 4.4%), tachycardia (3.0% versus 2.5%), palpitations (2.5 versus 2.7%), and pericardial effusion (1.5% versus 1.2%). None of the other cardiac disorder AEs occurred in more than 1% of patients in either of the two treatment arms.

Renal and urinary disorders (SOC) occurred more frequently in patients in the Ptz+T+D arm (10.6%) than in the Pla+T+D arm (7.6%), primarily due to the increased incidence of dysuria (5.4% versus 2.3%, respectively). None of the other renal and urinary disorder AEs occurred in more than 1% of patients in either of the two treatment arms. There was no difference between the two arms in the proportion of patients with increased "blood creatinine" (1.5%, Ptz+T+D versus 0.7%, Pla+T+D).

Hepatobiliary disorders (SOC) occurred in a similar proportion of patients in both treatment arms (2.3%, Pla+T+D versus 2.5%, Ptz+T+D), and no hepatobiliary AEs occurred with an incidence of more than 1% in patients in either of the two treatment arms. Increases in hepatic transaminase AEs occurred with similar frequencies in both treatment arms.

The total number of deaths reported at the study cut-off date was greater in the Pla+T+D arm (n=94, 23.7%) than in the Ptz+T+D arm (n=69, 17.0%). The most frequent cause of death was progressive disease, and this occurred notably more frequently in the Pla+T+D arm (n=81, 20.4%) than in Ptz+T+D arm (n=57, 14.0%). Deaths due to AEs were reported in a similar proportion of patients in the Pla+T+D arm (n=10, 2.5%) and the Ptz+T+D arm (n=8, 2.0%).

Serious adverse events (SAEs) occurred more frequently in the Ptz+T+D arm (34.4%) than in the Pla+T+D arm (26.2%). The most frequently reported SAEs were system organ class "blood and lymphatic system" disorders (16.0% of patients in the Ptz+T+D arm versus 10.6% of patients in the Pla+T+D arm), mainly due to a higher incidence of febrile neutropenia in the Ptz+T+D arm (11.3%) than in the Pla+T+D arm (5.0%); and "infections and infestations" (10.8% of patients in the Ptz+T+D arm versus 7.3% of patients in the Pla+T+D arm). The proportion of patients in both treatment arms with SAEs was generally comparable for all other SOCs and no other SOC included more than 5% of patients with SAEs in either treatment arm.

Adverse events that resulted in interruption or dose modification of any of the three study medications were reported more frequently in patients in the Ptz+T+D arm (60.0%) than in the Pla+T+D arm (53.1%).

The AE profile of Ptz+T+D in patients aged ≥ 65 years differs from that in patients aged < 65 years. The main differences were: greater incidence of SAEs in the older age group; greater incidence of total deaths and deaths due to other causes (that is, other than progressive disease) occurring 42 days after last treatment in the older age group; greater incidence of Grade ≥ 3 infusion associated reactions (IARs) in the older age group; greater incidence of diarrhoea (all grades and grade ≥ 3) in the older age group; greater incidence of febrile neutropenia and rash in the younger age group in the Ptz+T+D arm; and greater incidence of congestive heart failure (CHF) and left ventricular ejection fraction (LVEF) decline in the older age group in the Pla+T+D arm, and lowest incidence of CHF and LVEF decline in the older age group in the Ptz+T+D arm.

The AE profile was notably inferior in Asian patients treated with Ptz+T+D than White patients treated with this combination, and the AE profile in Asian patients treated with Pla+T+D was also inferior to that of White patients treated with this combination. There was no investigation of AEs in the Asian population based on region of origin (for example, Chinese, Japanese, and Korean).

First round benefit-risk assessment

First round assessment of benefit

The pivotal Phase III study (CLEOPATRA) has satisfactorily demonstrated that treatment of the proposed patient population with pertuzumab in combination with trastuzumab and docetaxel results in a statistically significant and clinically meaningful improvement in the duration of IRF-assessed PFS of 6.1 months compared with placebo in combination with trastuzumab and docetaxel (median IRF-PFS 18.5 and 12.4 months, respectively). The risk of experiencing a PFS event (disease progression or death) was reduced by 38% in patients treated with Ptz+T+D compared with Pla+T+D (HR = 0.62 [95% CI: 0.51, 0.75], $p < 0.0001$). The Kaplan-Meier analysis showed that the IRF-assessed PFS curves began to separate in favour of the Ptz+T+D arm at about 2 to 3 months after initiation of treatment, with separation being maintained throughout the remainder of the observation period. The IRF-assessed PFS was the primary efficacy endpoint in CLEOPATRA, and the treatment benefit of Ptz+T+D compared with Pla+T+D seen in this analysis was also observed in the secondary efficacy endpoint analysis of investigator assessed PFS.

In addition to investigator-assessed PFS, other key secondary efficacy endpoint analyses also supported the benefit of the Ptz+T+D combination compared with the Pla+T+D combination for the treatment of the proposed patient population. There was an OS benefit in favour of the Ptz+T+D combination compared with the Pla+T+D combination (69 versus 96 deaths, respectively; HR = 0.64 [96% CI: 0.47, 0.88], $p = 0.0053$). However, the estimated HR did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets α -spending function for the interim OS analysis (HR ≤ 0.603 , $p \leq 0.0012$). Consequently, the observed OS benefit in favour of Ptz+T+D relative to Pla+T+D was deemed to be not statistically significant. The Kaplan-Meier analysis showed that the survival curves began to separate in favour of the Ptz+T+D arm at about 10 months. The median length of follow-up for survival was estimated to be 19.3 months in both treatment arms, but the median time to death had not been reached in either treatment arm at the time of data cut-off. Furthermore, at the time of the OS analysis only 43% (165/385) the prespecified number of deaths had occurred.

The ORR analysis showed a benefit for patients treated with the Ptz+T+D combination compared with the Pla+T+D combination (80.2% versus 69.3%, respectively; difference = 10.8% [95% CI: 4.2, 17.5]; $p = 0.0011$). However, the statistically significant result must be considered to be exploratory rather than confirmatory, as the interim analysis of OS

(preceding analysis in the pre-specified testing hierarchy of IRF-assessed PFS → OS → ORR) was deemed not statistically significant.

The duration of the IRF-assessed objective response was assessed in the 233 patients in the Pla+T+D arm and 275 patients in the Ptz+T+D arm and showed that objective response was maintained for an estimated additional 33.5 weeks in patients receiving Ptz+T+D compared with Pla+T+D. The median duration of response in the Pla+T+D arm was 54.1 weeks (range: 5, 135 weeks) and 87.6 weeks (range: 7, 137) in the Ptz+T+D arm; HR = 0.66 (95% CI: 0.51, 0.85). The FACT-B analysis showed that time to symptom progression in both treatment arms was similar and represented about 6 treatment cycles (18.3, Pla+T+D versus 18.4 weeks, Ptz+T+D).

First round assessment of risks

The risks of treatment with pertuzumab in combination with trastuzumab and docetaxel for the proposed indication are considered to be greater than those with placebo in combination with trastuzumab and docetaxel. However, despite the increased risks with the triplet combination it is considered that the submission has satisfactorily established the safety of the regimen for treatment of the proposed indication. The risks of treatment described below relate to those identified in the pivotal Phase III study (CLEOPATRA), unless otherwise stated.

In CLEOPATRA, nearly all patients treated with Ptz+T+D (99.8%) experienced at least one AE (all grades), as did patients treated with Pla+T+D (98.5%). The most commonly occurring AEs (all grades) reported with an incidence of ≥ 20% in the Ptz+T+D arm (versus Pla+T+D arm) were diarrhoea (66.8% versus 46.3%), alopecia (60.9% versus 60.5%), neutropenia (52.8% versus 49.6%), nausea (42.3% versus 41.6%), fatigue (37.6% versus 36.8%), rash (33.7% versus 24.2%), decreased appetite (29.2% versus 26.4%), mucosal inflammation (27.8% versus 19.9%), asthenia (26.0% versus 30.2%), vomiting (24.1% versus 23.9%), peripheral oedema (23.1% versus 30.0%), anaemia (23.1% versus 18.9%), myalgia (22.9% versus 23.9%), nail disorder (22.9% versus 22.9%), cough (21.4% versus 18.6%), and peripheral neuropathy (21.1% versus 20.2%).

While AEs occurred commonly in both treatment arms, they appeared to be manageable by dose interruptions/modifications rather than discontinuation of treatment with pertuzumab and trastuzumab. In addition, AEs also appeared to have been frequently managed by standard symptomatic and/or supportive treatments: for example, diarrhoea (“AE to monitor”¹⁷) requiring treatment (46.2%, Ptz+T+D versus 23.2%, Pla+T+D); rash (“AE to monitor”) requiring treatment (29.2%, Ptz+T+D versus 20.2%, Pla+T+D); leukopenia (“AE to monitor”) requiring treatment (37.8%, Ptz+T+D versus 33.2%, Pla+T+D).

According to the protocol, if pertuzumab/placebo or trastuzumab were discontinued due to toxicity then all three study drugs had to be discontinued and the patient was withdrawn from the study. AEs resulting in discontinuation of pertuzumab and trastuzumab treatment (excluding events that led to discontinuation of docetaxel only) occurred in a similar proportion of patients in the two treatment arms (5.3%, Pla+T+D versus 6.1%, Ptz+T+D). Dose interruption or modification was the term used to describe slowing down, temporary interruption or discontinuation of the current infusion, or reduction or delay of the subsequent dose (dose reductions were only allowed for

¹⁷ Selected “adverse events to monitor” were prospectively defined to address specific safety topics. These events were based on clinical and nonclinical data for pertuzumab, and the safety profile established for trastuzumab, monoclonal antibodies in general and potential effects associated with HER receptor inhibition. The database search was based on SMQs, as far as available, or prospectively defined Roche-standardised adverse event grouped terms (AEGTs).

docetaxel). AEs resulting in dose interruption or modification were reported more frequently in patients in the Ptz+T+D arm (60.0%) than in the Pla+T+D arm (53.1%).

Adverse events (all grades) occurring in at least 5% of patients in either treatment arm and at least 5% more frequently in the Ptz+T+D arm (versus the Pla+T+D arm) were diarrhoea (66.8% versus 46.3%), rash (33.7% versus 24.2%), mucosal inflammation (27.8% versus 19.9%), febrile neutropenia (13.8% versus 7.6%), and dry skin (10.6% versus 4.3%). However, treatment discontinuations of pertuzumab and trastuzumab due to these events (excluding discontinuations of docetaxel only for these events) occurred in less than 1% of patients in either treatment arm. Dose interruptions/modifications (Pla+T+D versus Ptz+T+D) for diarrhoea were 1.8% versus 5.4%, and for febrile neutropenia were 5.0% versus 7.6%. The proportion of patients in the Ptz+T+D arm was $\geq 2\%$ to $< 5\%$ higher for a large number of AEs, with the majority of these events being Grade 1 or 2 in severity.

Grade ≥ 3 AEs (that is, grades 3, 4, or 5) were reported in a similar proportion of patients in the Ptz+T+D arm (74.2%) and in the Pla+T+D arm (72.8%). The most frequently reported Grade ≥ 3 AEs were SOC “blood and lymphatic tissue disorders” (59.0%, Ptz+T+D versus 54.2%, Pla+T+D arm). The difference was predominantly due to the higher incidence in patients in the Ptz+T+D arm (versus Pla+T+D arm) of neutropenia (48.9% versus 45.8%) and febrile neutropenia (13.8% versus 7.6%), while leukopenia occurred more frequently in the Pla+T+D arm than in the Ptz+T+D arm (14.6% versus 12.3%).

There was no increased risk of death during treatment due to AEs in the Ptz+T+D arm compared with the Pla+T+D arm. However, the risk of other SAEs was greater in the Ptz+T+D arm (34.4%) than in the Pla+T+D arm (26.2%). The most frequently reported SAEs were SOC “blood and lymphatic system” disorders (16.0%, Ptz+T+D versus 10.6%, Pla+T+D arm), mainly due to a higher incidence of febrile neutropenia in the Ptz+T+D arm (11.3%) than in the Pla+T+D arm (5.0%). Following SOC “blood and lymphatic system disorders”, the next most frequently reported SAEs were SOC “infections and infestations” (10.8%, Ptz+T+D versus 7.3%, Pla+T+D). However, no particular SOC “infection and infestations” SAE accounted for the difference in incidence between the two arms, and individual SAEs accounted for no more than 2% of patients in either arm.

Patients in the Ptz+T+D arm did not have an increased risk of experiencing SOC “cardiac disorders” compared with patients in Pla+T+D arm (14.5% versus 16.4%, respectively), and the incidence of LVD was similar in the two arms (1.0% versus 1.8%, respectively). However, the inclusion criteria for CLEOPATRA required patients to have a LVEF of $\geq 50\%$ and the exclusion criteria excluded patients with prior history of congestive heart failure (any New York Heart Association (NYHA) grading), symptomatic decreases in LVEF to $< 50\%$ during prior trastuzumab treatment, conditions that could impair left ventricular function, clinically significant cardiovascular disease, or cumulative prior anthracycline exposures to $> 360 \text{ mg/m}^2$ of doxorubicin (or equivalent). There were no marked differences in ECG abnormalities (included QT prolongation) between the two treatment arms.

The risk of drug related hepatic disorders (“AE to monitor”) was similar in patients in the two treatment arms (9.6%, Ptz+T+D versus 10.1%, Pla+T+D). The risk of LFT abnormalities (defined as $\text{AST} > 5 \times \text{ULN}$ or $\text{ALT} > 5 \times \text{ULN}$ or total bilirubin $> 2 \times \text{ULN}$) was low in patients in both treatment arms (3.7%, Ptz+T+D versus 2.0%, Pla+T+D). There were no definite cases of drug induced hepatotoxicity meeting Hy’s law criteria in either treatment arm. SOC “hepatobiliary disorders” occurred in a similar proportion of patients in both treatment arms (2.3%, Pla+T+D versus 2.5%, Ptz+T+D), and no AEs (PT) occurred with an incidence of more than 1% in patients in either of the two arms. However, CLEOPATRA excluded patients with impaired liver function (exclusion criteria in this context were: $\text{TBL} > \text{ULN}$ (unless the patient had documented Gilbert’s syndrome), AST or $\text{ALT} > 2.5 \times \text{ULN}$, AST or $\text{ALT} > 1.5 \times \text{ULN}$ with concurrent serum alkaline phosphatase

> 2.5 × ULN. Serum alkaline phosphatase may have been > 2.5 × ULN only if bone metastases were present and AST and ALT < 1.5 × ULN), and there are no safety data in patients with hepatic impairment. SOC “renal and urinary disorders” occurred more commonly in patients in the Ptz+T+D arm (10.6%) than in the Pla+T+D arm (7.6%), due to the increased incidence of dysuria (5.4% versus 2.3%). However, increases in creatinine levels were reported infrequently in both treatment arms (about 1.5% of patients in each of the arms), but CLEOPATRA excluded patients with serum creatinine > 2 mg/dL.

In the first treatment cycle (day 1), when placebo and pertuzumab were administered alone, 19.2% of patients given pertuzumab experienced an AE on the day of the infusion compared with 14.6% of patients given placebo, while reactions during the infusion occurred in 3.9% and 2.0% of patients, respectively. The majority of patients (84% in each arm) received pre-medication prior to infusion of any study medication (including docetaxel), with corticosteroids (77% to 78%) and 5-HT₃ antagonists (59% to 60%) being the most common classes of pre-medications received. Other pre-medications used by at least 10% of patients were antihistamines (47% to 49%), histamine H₂-receptor antagonists (31% to 32%) and analgesics (19% to 22%). Colony stimulating factor (described as a ‘pre-medication’) was used in 3.9% of patients in the Pla+T+D arm and 5.0% of patients in the Ptz+T+D arm.

The risk of hypersensitivity/anaphylaxis (“AE to monitor”), all grades, was similar in patients in the Ptz+T+D (10.8%) and Pla+T+D (9.1%) arms, as was the incidence of Grade ≥ 3 events (2.0%, Ptz+T+D versus 2.5%, Pla+T+D). The proportion of patients positive for pertuzumab anti-therapeutic antibodies post-baseline was lower in the Ptz+T+D arm (2.8%, 11/386) than in the Pla+T+D arm (6.2%, 23/372).

Overall, the risks of Ptz+T+D treatment are greater in patients aged ≥ 65 years compared with patients < 65 years, and in Asian patients compared with “White” patients.

First round assessment of benefit-risk balance

The benefit-risk balance of pertuzumab in combination with trastuzumab and docetaxel, given the proposed usage, is favourable. In CLEOPATRA, the pertuzumab, trastuzumab and docetaxel combination resulted in a statistically significant and clinically meaningful increase in time to progression free events (disease progression or death due to any cause) of 6.1 months compared with the placebo, trastuzumab, and docetaxel combination. Based on the hazard ratio, the pertuzumab, trastuzumab and docetaxel combination reduced the risk of a PFS event by 28%¹⁸ (95% CI: 25%, 49%), relative to the placebo, trastuzumab, and docetaxel combination. The risk of experiencing a PFS event was 47.5% with the pertuzumab, trastuzumab and docetaxel combination compared with 59.6% with the placebo, trastuzumab, and docetaxel combination. The risks of experiencing commonly occurring AEs (all grades), AEs Grade ≥ 3, and SAEs were greater with the pertuzumab, trastuzumab and docetaxel combination than with the placebo, trastuzumab, and docetaxel combination. However, the observed toxicities were not unexpected and were manageable using standard methods employed in oncological clinical practice (for example, dose interruptions/modifications; symptomatic and/or supportive treatment).

First round recommendation regarding authorisation

It is recommended that pertuzumab in combination with trastuzumab and docetaxel at the proposed dosage be approved for the treatment of patients with HER2-positive metastatic (Stage IV) or unresectable locally recurrent breast cancer who have not received previous treatment or whose disease has relapsed after adjuvant therapy.

¹⁸ Sponsor comment: the correct % for reduced risk of PFS is 38%

Clinical questions

Pharmacodynamics

Question: In the QTc substudy of the pivotal trial, in discussing the results of the analysis involving regression to the mean it is stated that the observed value of 9.3 ms for the difference between the QTcF post-baseline values of pertuzumab and placebo after being regressed to the global mean was “lower than the value of 10 ms considered to be important in thorough QTc studies. Thus it is unlikely pertuzumab causes $\Delta\Delta\text{QTcF}$ prolongation larger than those of clinical interest in thorough QTc studies”. However, the TGA adopted QT/QTc interval guidance document (CHMP/ICH/2/04) makes no mention of adjusting post-baseline changes in the QTcF by regressing them to the overall global mean. Furthermore, the relevant QT/QTc guideline states that the threshold of regulatory concern “is around 5 ms as evidenced by an upper bound of the 95% CI confidence interval around the mean effect on QTc of 10 ms”. It appears that the 10 ms difference referred to in the sponsor’s regression to the overall mean analysis refers to the mean difference between the two treatment arms rather than the upper bound of the 95% CI of the mean. If this is the case, then the observed mean difference of 9.3 ms is greater than the mean difference of 5 ms which is of regulatory concern in a “thorough QT/QTc study”. Please clarify the matter.

Indication

The proposed indication is “*Perjeta is indicated in combination with Herceptin and docetaxel for patients with HER2-positive metastatic (Stage IV) or unresectable locally recurrent breast cancer who have not received previous treatment or whose disease has relapsed after adjuvant therapy*”.

It is recommended that the trade name Herceptin be changed to the generic name trastuzumab.

Since Perjeta is an orphan-designated drug with approval in the USA, it is open to the Delegate to register the drug without referral to the Advisory Committee on Prescription Medicines (ACPM). However, the US indication¹⁹ is more restrictive than that proposed since it does not include unresectable locally recurrent breast cancer.

The sponsor was asked to justify the proposed indication with reference to the populations in the trials, numbers of subjects and outcomes in the metastatic breast cancer and unresectable locally recurrent breast cancer subgroups. What is the role of radiotherapy in unresectable locally recurrent breast cancer?

Second round evaluation of clinical data submitted in response to questions

The clinical evaluator’s review of the sponsor’s responses to the two clinical questions arising following the first round clinical evaluation of the submission (see above) is presented below. The evaluator reviewing the sponsor’s responses to the clinical questions was the same clinical evaluator who undertook the first round evaluation of the submission.

¹⁹ The FDA approved Perjeta (pertuzumab) *in combination with trastuzumab and docetaxel for the treatment of HER2-positive late stage (metastatic) breast cancer for patients who have not received prior treatment with anti-HER2 therapy or chemotherapy* (FDA News Release, 8 June 2012).

Question on pharmacodynamics***Sponsor's response***

See Attachment 2 of this AusPAR for full details of the sponsor's response to this question.

Evaluator's assessment

The sponsor states that the $\Delta\Delta\text{QTcF}$ of 9.3 ms referred to in the pharmacodynamics question was not a difference between the post-baseline QTc values of pertuzumab and placebo but was the pre-treatment baseline difference between the pertuzumab and placebo arms. However, this is not at all clear from the following sentence in the report for WO206968B/substudy 2: "[f]urther, if post-BL measurements of QTcF regressed to the global overall mean of about 414.3 ms, a difference would be observed in post-BL changes (that is, a $\Delta\Delta\text{QTcF}$ would be observed) between the pertuzumab and placebo groups of about $(414.3-410.7) - (414.3-420.0) = 9.3$ ms". This sentence appears to suggest that a post-baseline difference between pertuzumab and placebo would be 9.3 ms "if post-BL measurements of QTcF regressed to the overall mean of 413.3 ms". The origin of the 9.3 ms value remains confusing. Consequently, it would appear to be prudent to discard the reference to the 9.3 ms value based on calculation by the method defined by the sponsor as "regressed to the overall mean". However, the data from WO206968B/substudy 2 gave rise to concern as it showed that in Cycle 3 the $\Delta\Delta\text{QTcF}$ immediately post-infusion was 8.41 ms (90% CI: -2.58, 19.39) greater in the pertuzumab arm than in the placebo arm, with the upper 90% CI for both post infusion doses being > 10 ms. It is agreed that the data from Cycle 1 showed that the $\Delta\Delta\text{QTcF}$ was < 5 ms and the upper 90% CI was < 10 ms.

In order to clarify the clinical relevance of the QT data the sponsor summarised the key results of WO206968B/substudy 2 and concluded that pertuzumab does not have a clinically relevant effect on QTcF and other ECG parameters in patients with HER2-positive metastatic breast cancer when combined with trastuzumab and docetaxel.

The evaluator agrees with the sponsor and considers that review of the totality of the ECG data suggests that clinically significant increases in QTcF are unlikely with the proposed triplet combination in patients with metastatic breast cancer. The first round evaluation of WO206968B/substudy 2 is consistent with the sponsor's conclusions.

Question relating to the proposed indication.***Sponsor's response***

Roche agrees to change 'Herceptin' to 'trastuzumab' throughout the PI.

Roche acknowledges that the number of patients with unresectable, locally recurrent disease included in the pivotal WO20698/TOC4129g (CLEOPATRA) study was very low. This is because investigators were discouraged from including any patient in the study with potentially curable disease. It was considered more appropriate for such patients to receive standard loco-regional and systemic therapy, including neoadjuvant therapy if appropriate. Since high response rates were anticipated with trastuzumab and docetaxel (with or without pertuzumab), only patients with locally recurrent disease that was considered unlikely to become resectable after systemic treatment were encouraged to enter the study.

Roche acknowledges that there is an important role for radiotherapy in patients with unresectable, locally recurrent disease. However, many patients with unresectable, locally recurrent disease have already received radical radiotherapy as part of their primary treatment. Moreover, radiotherapy cannot control occult systemic disease which may be present.

Roche considers that there is no biological reason to believe that patients with locally recurrent, inoperable disease will respond differently to pertuzumab, compared to

patients with metastatic disease. In general, treatments that are effective for patients with metastatic breast cancer are also effective in patients with locally recurrent, unresectable disease, and treatment guidelines may group these patients together, along with patients with locally advanced breast cancer (see for example, Cardoso *et al*, 2011²⁰; Cardoso *et al*, 2012²¹; Carlson *et al*, 2012²²). Moreover, the WO20697 (NEOSPHERE) study indicates clearly that pertuzumab improves the efficacy (pathological complete response [pCR] rate) of trastuzumab and docetaxel in patients with locally advanced (that is, non-metastatic) disease. A substantial and statistically significant improvement in efficacy was seen in these patients (pCR rate for Ptz+T+D = 45.8% versus 29.0% for T+D; difference between arms = 16.8%; CI: 3.5-30.1%; p=0.0141). This is in line with the improvement in efficacy seen in the WO20698/TOC429g (CLEOPATRA) study overall (HR = 0.62 for IRF-assessed PFS; CI 0.51, 0.75; p < 0.0001; improvement in median IRF-assessed PFS of 6.1 months).

As seen in the WO20698/TOC4129g study and the WO20697 study, the toxicity of Ptz+T+D was manageable in patients with metastatic or non-metastatic disease, and so Roche considers that the likely benefits of Ptz+T+D outweigh the risks in patients with locally recurrent, unresectable disease, just as they do in patients with metastatic disease. Overall, therefore, Roche considers that the indication for pertuzumab should reflect the entry criteria for the pivotal study and that patients with locally recurrent unresectable disease should not be denied the benefits of pertuzumab. Although the approved US indication for pertuzumab does not include unresectable locally recurrent disease, the above rationale was acceptable to EU regulators and the EU indication is expected to include patients with unresectable, locally recurrent breast cancer.

Evaluator's assessment

Following the first round assessment of the submitted data it was recommended that pertuzumab in combination with trastuzumab and docetaxel be approved for the treatment of patients with HER2-positive metastatic (Stage IV) or unresectable locally recurrent breast cancer who have not received previous treatment or whose disease has relapsed after adjuvant therapy. This was the indication initially proposed by the sponsor and remains the sponsor's proposed indication

However, the FDA has approved Perjeta in combination with trastuzumab and docetaxel for the treatment of HER2-positive patients only with metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. In contrast, the Committee for Medicinal Products for Human Use (CHMP) of the EMA recently recommended the granting of marketing authorisation for Perjeta for use in combination with trastuzumab and docetaxel in adult 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 (EMA Website, Summary of Opinion, 13 December 2012).

In view of the question from the TGA relating to the indication, the sponsor's response, the approved FDA indication and the recent CHMP recommendation relating to the indication, the relevant data in the original submission relating to the treatment population has been re-examined. Following this re-examination, it is considered that the indication for Perjeta in combination with trastuzumab and docetaxel should be restricted to patients with HER2-positive breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

²⁰ Cardoso F, et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2011;22(6): 25-30.

²¹ Cardoso F, et al. 1st International consensus guidelines for advanced breast cancer (ABC 1). *Breast* 2012;21(3):242-252

²² Carlson RW, et al. NCCN Practice Guidelines in Oncology. Breast Cancer. Version 2. 2012: <http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf>

Review of the data suggests that there is a strong argument to restrict the indication to patients with HER2-positive metastatic breast cancer as very few patients in the total population in CLEOPATRA were categorised as having unresectable, locally recurrent disease. In the Pla+T+D arm, 8 out of 406 patients (2.0%) had unresectable, locally recurrent disease and the corresponding number in the Ptz+T+D arm was 11 out of 402 patients (2.7%). Of the 19 patients in the total study population with unresectable, locally recurrent disease, 7 actually had metastases noted on their baseline disease assessment (2 in the Pla+T+D arm and 5 in the Ptz+T+D arm). In the total study population in CLEOPATRA, almost all patients had metastases at study entry (98.0% in the Pla+T+D arm and 97.3% in the Ptz+T+D arm). CLEOPATRA (WO20698/TOC4129g) was the only study in the breast cancer clinical program that included patients with unresectable, locally recurrent breast cancer (see the summary table immediately below). NEOSPHERE (WO20697) included patients with locally advanced disease treated with one of the four regimens (including Ptz+T+D) but in the **neoadjuvant** setting.

Table 5. Breast cancer distribution in the clinical trial program.

	HER2-positive							HER2-negative		
	WO20698/TOC4129g (MBC)		WO20697 (EBC/LABC)				B017929 (MBC)		B016934 (MBC)	
	Pla+T+D	Ptz+ T +D	T + D	Ptz+T+D	Ptz+T	Ptz+D	Cohorts 1 and 2 Ptz+T	Cohort 3 Ptz Ptz+T	Ptz (420 mg)	Ptz (1050mg)
Breast Cancer Type: N	405	401	107	107	107	96	66	29	41	38
Locally Recurrent ^a	8 (2.0)	11 (2.7)		0	0	0	0	0	0	0
Metastatic Disease ^b	397 (98.0)	390 (97.3)	0	0	0	0	66 (100.0)	29 (100)	41 (100.0)	38 (100)
Inflammatory	10 (2.5)	6 (1.5)	7 (6.5)	10 (9.3)	7 (6.5)	5 (5.2)	0	0	0	0
Locally Advanced	0	0	36 (33.6)	32 (29.9)	35 (32.7)	31 (32.3)	0	0	0	0
Operable (EBC)	0	0	64 (59.8)	65 (60.7)	65 (60.7)	60 (62.5)	0	0	0	0

Note: In this table, the total number of patients with locally recurrent or metastatic disease in the Pla+T+D and Ptz+T+D arms (405 and 401, respectively) is less than the number of randomised patients in the study (406 and 402, respectively). This suggests that baseline breast cancer status was unknown in a 1 patient in each treatment arm.

a = Includes *de novo*, locally advanced disease with no prior resection. Some patients also had metastases.

b = Includes inflammatory disease in the metastatic setting.

In CLEOPATRA, the statistical analysis was undertaken on the total study population. Subgroup analysis on patients with unresectable, locally recurrent breast cancer would not have been meaningful due to the small number of patients with this condition in the study (that is, 19 out of 808 randomised patients; 2.4%). Therefore, it is likely that the statistically significant efficacy results observed in CLEOPATRA were driven exclusively by the patients with metastatic disease. Furthermore, 7 of the 19 patients with unresectable, locally recurrent breast cancer appear to have had metastatic disease at baseline and would presumably have met metastatic disease treatment criteria. This leaves 12 patients (1.5%) in the study population with unresectable, locally recurrent disease without metastases. Consequently, it can be argued that a separate study should be undertaken in patients with unresectable, locally recurrent breast cancer without metastases in order to establish the efficacy of the proposed regimen in this patient group.

The sponsor argues that there is no biological reason to believe that patients with locally advanced recurrent, inoperable disease will respond differently to pertuzumab compared to patients with metastatic disease. The sponsor also notes that, in general, treatments that are effective for patients with metastatic breast cancer are also effective in patients with locally recurrent, unresectable disease, and treatment guidelines may group these patients together, along with patients with locally advanced breast cancer. The sponsor also notes that the results of NEOSPHERE clearly show that pertuzumab improves the efficacy (pathological complete response [pCR] rate) of trastuzumab and docetaxel in

patients with locally advanced (that is, non-metastatic) disease. However, NEOSPHERE was conducted in neoadjuvant setting in treatment-naïve women with operable, locally advanced HER-2 breast cancer. Consequently, the results from NEOSPHERE are not necessarily relevant to women with unresectable, locally recurrent disease who may or may not have undergone prior adjuvant therapy. There were no data on pCR from CLEOPATRA as this end point was not evaluated in this study.

It is noted that both the FDA and CHMP indications are worded to include patients who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease, while the proposed Australian indication is worded to include patients who have not received previous treatment or have relapsed after adjuvant therapy. However, the FDA or CHMP and Australian wordings are basically describing the same patient population. The protocol excluded patients with a history of anti-cancer therapy for metastatic breast cancer (with the exception of one prior hormonal regimen for metastatic breast cancer, which had to be stopped prior to randomisation). Anti-cancer therapy for metastatic breast cancer included any EGFR or anti-HER2 agents or vaccines, cytotoxic chemotherapy, or more than one prior hormonal regimen for metastatic breast cancer. Therefore, in accordance with the protocol it is recommended that the wording of the indication should refer to patients who have not received previous anti-HER2 therapy or chemotherapy for metastatic disease.

Following consideration of the characteristics of the patient population included in CLEOPATRA the following indication is recommended:

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

Second round benefit-risk assessment

Second round assessment of benefit

The benefits of treatment in the total study patient population in CLEOPATRA are described below. However, it is considered that the benefits should be interpreted as referring to patients with metastatic HER2-positive breast cancer who have not been previously treated with trastuzumab or chemotherapy for metastatic breast cancer. The number of patients in CLEOPATRA with unresectable, locally recurrent breast cancer in the total treatment population (2.4% [n=19]) is considered to be too small to adequately assess the benefits in this patient population. In addition, of the 19 patients with unresectable, locally recurrent breast cancer, 7 had metastatic disease noted at baseline leaving 12 patients (1.5%) patients with unresectable, locally recurrent breast cancer without metastases.

The pivotal Phase III study (CLEOPATRA) satisfactorily established that treatment of the study population with pertuzumab in combination with trastuzumab and docetaxel resulted in a statistically significant and clinically meaningful improvement in the duration of IRF-assessed PFS of 6.1 months compared with placebo in combination with trastuzumab and docetaxel (median IRF-PFS 18.5 and 12.4 months, respectively). The risk of experiencing a PFS event (disease progression or death) was reduced by 38% in patients treated with Ptz+T+D compared with Pla+T+D (HR = 0.62 [95% CI: 0.51, 0.75], p<0.0001). The Kaplan-Meier analysis showed that the IRF-assessed PFS curves began to separate in favour of the Ptz+T+D arm at about 2 to 3 months after initiation of treatment, with separation being maintained throughout the remainder of the observation period. The IRF-assessed PFS was the primary efficacy endpoint in CLEOPATRA, and the treatment benefit of Ptz+T+D compared with Pla+T+D seen in this analysis was also observed in the secondary efficacy endpoint analysis of investigator assessed PFS.

In addition to investigator-assessed PFS, other key secondary efficacy endpoint analyses also supported the benefit of the Ptz+T+D combination compared with the Pla+T+D combination in the study population. There was an OS benefit in favour of the Ptz+T+D combination compared with the Pla+T+D combination (69 versus 96 deaths, respectively; HR = 0.64 [96% CI: 0.47, 0.88], $p = 0.0053$). However, the estimated HR did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets α -spending function for the interim OS analysis (HR ≤ 0.603 , $p \leq 0.0012$). Consequently, the observed OS benefit in favour of Ptz+T+D relative to Pla+T+D was deemed to be not statistically significant. The Kaplan-Meier analysis showed that the survival curves began to separate in favour of the Ptz+T+D arm at about 10 months. The median length of follow-up for survival was estimated to be 19.3 months in both treatment arms, but the median time to death had not been reached in either treatment arm at the time of data cut-off. Furthermore, at the time of the OS analysis only 43% (165/385) the prespecified number of deaths had occurred.

The ORR analysis showed a benefit for patients in the study population treated with the Ptz+T+D combination compared with the Pla+T+D combination (80.2% versus 69.3%, respectively; difference = 10.8% [95% CI: 4.2, 17.5]; $p=0.0011$). However, the statistically significant result must be considered to be exploratory rather than confirmatory, as the interim analysis of OS (preceding analysis in the pre-specified testing hierarchy of IRF-assessed PFS \rightarrow OS \rightarrow ORR) was deemed not statistically significant.

The duration of the IRF-assessed objective response was assessed in 233 patients in the Pla+T+D arm and 275 patients in the Ptz+T+D arm and showed that objective response was maintained for an estimated additional 33.5 weeks in patients receiving Ptz+T+D compared with Pla+T+D. The median duration of response in the Pla+T+D arm was 54.1 weeks (range: 5, 135 weeks) and 87.6 weeks (range: 7, 137) in the Ptz+T+D arm; HR = 0.66 (95% CI: 0.51, 0.85). The FACT-B analysis showed that time to symptom progression in both treatment arms was similar and represented about 6 treatment cycles (18.3, Pla+T+D versus 18.4 weeks, Ptz+T+D).

In pre-specified subgroup analyses, IRF-assessed PFS in the both the de nova ($n=432$) and prior adjuvant/neoadjuvant ($n=376$) treatment groups was greater in the Ptz+T+D arm relative to the Pla+T+D arm: HR (de novo group) = 0.63 (95% CI: 0.49, 0.82); HR (adjuvant or neoadjuvant group) = 0.61 (95% CI: 0.46, 0.81). In post-hoc exploratory subgroup analyses of IRF-assessed PFS undertaken post-database lock, in the subgroup of patients who had received trastuzumab ($n=88$) the HR was 0.62 (95% CI: 0.35, 1.07), and in the subgroup of patients in the prior neoadjuvant/adjuvant treatment group that did not include trastuzumab ($n=288$) the HR was 0.60 (95% CI: 0.43, 0.83). The pre-specified subgroup and exploratory subgroup analyses of IRF-assessed PFS support the primary efficacy analysis.

Second round assessment of risks

The risks of treatment in the total study population in CLEOPATRA are described below. However, for the reasons outlined above under *Second round assessment of benefits* (first paragraph) it is considered that the risks of treatment with Perjeta in combination with trastuzumab and docetaxel observed in CLEOPATRA relate primarily to patients with HER2-positive metastatic breast cancer not previously treated with trastuzumab or chemotherapy for metastatic breast disease. The last three paragraphs in this second round assessment of risks expand on the information provided in the first round assessment of risks relating to patients with pertuzumab anti-therapeutic antibodies (ATAs).

In CLEOPATRA, nearly all patients treated with Ptz+T+D (99.8%) experienced at least one AE (all grades), as did patients treated with Pla+T+D (98.5%). The most commonly occurring AEs (all grades) reported with an incidence of $\geq 20\%$ in the Ptz+T+D arm

(versus Pla+T+D arm) were diarrhoea (66.8% versus 46.3%), alopecia (60.9% versus 60.5%), neutropenia (52.8% versus 49.6%), nausea (42.3% versus 41.6%), fatigue (37.6% versus 36.8%), rash (33.7% versus 24.2%), decreased appetite (29.2% versus 26.4%), mucosal inflammation (27.8% versus 19.9%), asthenia (26.0% versus 30.2%), vomiting (24.1% versus 23.9%), peripheral oedema (23.1% versus 30.0%), anaemia (23.1% versus 18.9%), myalgia (22.9% versus 23.9%), nail disorder (22.9% versus 22.9%), cough (21.4% versus 18.6%), and peripheral neuropathy (21.1% versus 20.2%).

While AEs occurred commonly in both treatment arms, they appeared to be manageable by dose interruptions/modifications rather than discontinuation of treatment with pertuzumab and trastuzumab. In addition, AEs also appeared to have been frequently managed by standard symptomatic and/or supportive treatments: e.g., diarrhoea (“AE to monitor”) requiring treatment (46.2%, Ptz+T+D versus 23.2%, Pla+T+D); rash (“AE to monitor”) requiring treatment (29.2%, Ptz+T+D versus 20.2%, Pla+T+D); leukopenia (“AE to monitor”) requiring treatment (37.8%, Ptz+T+D versus 33.2%, Pla+T+D).

If pertuzumab/placebo or trastuzumab were discontinued due to toxicity then all three study drugs had to be discontinued and the patient was withdrawn from the study. AEs resulting in discontinuation of pertuzumab and trastuzumab treatment (excluding events that led to discontinuation of docetaxel only) occurred in a similar proportion of patients in the two treatment arms (5.3%, Pla+T+D versus 6.1%, Ptz+T+D). Dose interruption or modification was the term used to describe slowing down, temporary interruption or discontinuation of the current infusion, or reduction or delay of the subsequent dose (dose reductions were only allowed for docetaxel). AEs resulting in dose interruption or modification were reported more frequently in patients in the Ptz+T+D arm (60.0%) than in the Pla+T+D arm (53.1%).

AEs (all grades) occurring in at least 5% of patients in either treatment arm and at least 5% more frequently in the Ptz+T+D arm (versus the Pla+T+D arm) were diarrhoea (66.8% versus 46.3%), rash (33.7% versus 24.2%), mucosal inflammation (27.8% versus 19.9%), febrile neutropenia (13.8% versus 7.6%), and dry skin (10.6% versus 4.3%). However, treatment discontinuations of pertuzumab and trastuzumab due to these events (excluding discontinuations of docetaxel only for these events) occurred in less than 1% of patients in either treatment arm. Dose interruptions/modifications (Pla+T+D versus Ptz+T+D) for diarrhoea were 1.8% versus 5.4%, and for febrile neutropenia were 5.0% versus 7.6%. The proportion of patients in the Ptz+T+D arm was $\geq 2\%$ to $< 5\%$ higher for a large number of AEs, with the majority of these events being Grade 1 or 2 in severity.

Grade ≥ 3 AEs (that is, grades 3, 4, or 5) were reported in a similar proportion of patients in the Ptz+T+D arm (74.2%) and in the Pla+T+D arm (72.8%). The most frequently reported Grade ≥ 3 AEs were SOC “blood and lymphatic tissue disorders” (59.0%, Ptz+T+D versus 54.2%, Pla+T+D arm). The difference was predominantly due to the higher incidence in patients in the Ptz+T+D arm (versus Pla+T+D arm) of neutropenia (48.9% versus 45.8%) and febrile neutropenia (13.8% versus 7.6%), while leukopenia occurred more frequently in the Pla+T+D arm than in the Ptz+T+D arm (14.6% versus 12.3%).

There was no increased risk of death during treatment due to AEs in the Ptz+T+D arm compared with the Pla+T+D arm. However, the risk of other SAEs was greater in the Ptz+T+D arm (34.4%) than in the Pla+T+D arm (26.2%). The most frequently reported SAEs were SOC “blood and lymphatic system” disorders (16.0%, Ptz+T+D versus 10.6%, Pla+T+D arm), mainly due to a higher incidence of febrile neutropenia in the Ptz+T+D arm (11.3%) than in the Pla+T+D arm (5.0%). Following SOC “blood and lymphatic system disorders”, the next most frequently reported SAEs were SOC “infections and infestations” (10.8%, Ptz+T+D versus 7.3%, Pla+T+D). However, no particular SOC “infection and infestations” SAE accounted for the difference in incidence between the two arms, and individual SAEs accounted for no more than 2% of patients in either arm.

Patients in the Ptz+T+D arm did not have an increased risk of experiencing SOC “cardiac disorders” compared with patients in Ptz+T+D arm (14.5% versus 16.4%, respectively), and the incidence of LVD was similar in the two arms (1.0% versus 1.8%, respectively). However, the inclusion criteria for CLEOPATRA required patients to have a LVEF of $\geq 55\%$ and the exclusion criteria excluded patients with prior history of congestive heart failure (any NYHA grading), symptomatic decreases in LVEF to $< 50\%$ during prior trastuzumab treatment, conditions that could impair left ventricular function, clinically significant cardiovascular disease, or cumulative prior anthracycline exposures to $> 360 \text{ mg/m}^2$ of doxorubicin (or equivalent). There were no marked differences in ECG abnormalities (included QT prolongation) between the two treatment arms.

The risk of drug related hepatic disorders (“AE to monitor”) was similar in patients in the two treatment arms (9.6%, Ptz+T+D versus 10.1%, Pla+T+D). The risk of LFT abnormalities (defined as AST $> 5 \times \text{ULN}$ or ALT $> 5 \times \text{ULN}$ or total bilirubin $> 2 \times \text{ULN}$) was low in patients in both treatment arms (3.7%, Ptz+T+D versus 2.0%, Pla+T+D). There were no definite cases of drug induced hepatotoxicity meeting Hy’s law criteria in either treatment arm. SOC “hepatobiliary disorders” occurred in a similar proportion of patients in both treatment arms (2.3%, Pla+T+D versus 2.5%, Ptz+T+D versus), and no AEs (PT) occurred with an incidence of more than 1% in patients in either of the two arms. However, CLEOPATRA excluded patients with impaired liver function (exclusion criteria in this context were: TBL $> \text{ULN}$ (unless the patient had documented Gilbert’s syndrome), AST or ALT $> 2.5 \times \text{ULN}$, AST or ALT $> 1.5 \times \text{ULN}$ with concurrent serum alkaline phosphatase $> 2.5 \times \text{ULN}$. Serum alkaline phosphatase may have been $> 2.5 \times \text{ULN}$ only if bone metastases were present and AST and ALT $< 1.5 \times \text{ULN}$), and there are no safety data in patients with hepatic impairment. SOC “renal and urinary disorders” occurred more commonly in patients in the Ptz+T+D arm (10.6%) than in the Pla+T+D arm (7.6%), due to the increased incidence of dysuria (5.4% versus 2.3%). However, increases in creatinine levels were reported infrequently in both treatment arms (about 1.5% of patients in each of the arms), but CLEOPATRA excluded patients with serum creatinine $> 2 \text{ mg/dL}$.

In the first treatment cycle (day 1), when placebo and pertuzumab were administered alone, 19.2% of patients given pertuzumab experienced an AE on the day of the infusion compared with 14.6% of patients given placebo, while reactions during the infusion occurred in 3.9% and 2.0% of patients, respectively. The majority of patients (84% in each arm) received pre-medication prior to an infusion of any study medication (including docetaxel), with corticosteroids (77% to 78%) and 5-HT₃ antagonists (59% to 60%) being the most common classes of pre-medications received. Other pre-medications used by at least 10% of patients were antihistamines (47% to 49%), histamine H₂-receptor antagonists (31% to 32%) and analgesics (19% to 22%). Colony stimulating factor (described as a ‘pre-medication’) was used in 3.9% of patients in the Pla+T+D arm and 5.0% of patients in the Ptz+T+D arm.

The risk of hypersensitivity/anaphylaxis (“AE to monitor”), all grades, was similar in patients in the Ptz+T+D (10.8%) and Pla+T+D (9.1%) arms, as was the incidence of Grade ≥ 3 events (2.0%, Ptz+T+D versus 2.5%, Pla+T+D).

Overall, the risks of Ptz+T+D treatment are comparable in patients aged < 65 years and ≥ 65 years, while the risks Ptz+T+D are greater in Asian patients compared with “White” patients.

In CLEOPATRA, the proportion of patients positive for pertuzumab anti-therapeutic antibodies (ATA) post-baseline was lower in the Ptz+T+D arm (2.8%, 11/386) than in the Pla+T+D arm (6.2%, 23/372). A conservative approach was taken to calculating the incidence of ATA so that any patient confirmed to have an ATA positive sample after dosing was considered positive for ATA, regardless of baseline status. In the Pla+T+D arm, 2 patients positive for ATA experienced events described by the investigator as hypersensitivity reactions (during a pamidronate infusion in 1 patient, and during

docetaxel infusions on 3 occasions in 1 patient). Most of the patients in the Pla+T+D arm identified as ATA positive continued to receive treatment after ATA were first detected.

In the Ptz+T+D arm, 1 patient positive for ATA experienced a serious Grade 4 anaphylactic reaction resulting in discontinuation of study medication. However, this event occurred on Study Day 2 (T and D administration), and no AEs were reported on Study Day 1 (P administration), suggesting that the reaction was not due to pertuzumab. In addition, the patient did not have detectable ATA at baseline suggesting that the reaction was not related to ATA. Two (2) other patients experienced AEs described by the investigator as “hypersensitivity” and “drug hypersensitivity” reactions. However, both patients continued on Ptz+T+D treatment following detection of ATA without further hypersensitivity reactions, suggesting that the observed events might have been infusion-related reactions rather than hypersensitivity reactions due to ATA.

Exploratory post-hoc analyses were performed of IRF-assessed PFS and ORR in patients with at least one post-baseline ATA assessment. The results of these analyses are summarised in the table at the end of this section. The IRF-PFS and the ORR were both lower in the ATA-positive treatment arms compared with the ATA-negative treatment arms. However, these results should be interpreted cautiously due to the small number of patients in both ATA-positive treatment arms compared with the ATA-negative treatment arms, and the presence of ATA-positive patients in the Pla+T+D arm. In addition, the 95% CIs for the point estimates in the ATA-positive arms for both treatments were very wide for both the IRF-PFS and the ORR indicating marked intersubject variability for these outcomes. Individual IRF-assessed PFS data for each patient showed that several of the ATA-positive patients in the Ptz+T+D arm achieved prolonged disease control, and there was no clear temporal association between a positive ATA and IRF-assessed progressive disease. Similarly, the sponsor reports that individual ATA-positive patients in the Pla+T+D arm achieved prolonged disease control despite the presence of detectable ATA, with no clear relationship between the development of ATA positivity and IRF-assessed PD. In addition, exploration of confounding risks for disease progression or death in the patients in the post-hoc analyses was not undertaken. Overall, the results for the efficacy outcomes based on ATA status are of interest, but it is difficult to draw meaningful conclusions about the clinical relevance of the observations based on the data.

Table 6. Summary of efficacy by ATA status

	Pla+T+D arm		Ptz+T+D arm	
	ATA -ve	ATA +ve	ATA -ve	ATA +ve
n	349	23	375	11
IRF-PFS (median in months)	12.5	6.3	18.7	12.5
95% CI	[10; 14]	[4; 17]	[16; 25]	[2; 14]
ORR	73.2%	45.0%	81.7%	45.5%
95% CI	[67.7; 78.1]	[23.1; 68.5]	[77.1; 85.7]	[16.7; 76.6]

ORR = Objective response rate; IRF-PFS = progression-free survival according to IRF

Second round assessment of benefit-risk balance

The benefit-risk balance is considered favourable for pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2-positive metastatic breast cancer in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. The data on patients with unresectable, locally recurrent breast cancer are too limited to allow for an adequate benefit-risk balance assessment for this patient group to be undertaken.

Second round recommendation regarding authorisation

It is recommended that pertuzumab in combination with trastuzumab and docetaxel be approved for the treatment of HER2-positive metastatic breast cancer in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

It is recommended that approval should not extend to patients with unresectable, locally recurrent breast cancer as the pivotal study (CLEOPATRA) was undertaken almost exclusively in patients with metastatic breast cancer (97.4%; n=787). Furthermore, of the 19 patients with unresectable, locally recurrent disease included in CLEOPATRA, 7 had metastases noted on baseline disease assessment. Therefore, it can be inferred that the statistically significant efficacy results in favour of the proposed treatment regimen observed in the pivotal study were driven by patients with metastatic breast cancer. The number of patients in CLEOPATRA with unresectable, locally recurrent disease is too small to undertake a statistically meaningful subgroup analysis comparing the proposed and control treatment regimens in this patient population. Furthermore, based on the small number of patients with unresectable, locally recurrent disease in CLEOPATRA no meaningful benefit-risk balance assessment can be made in this patient population.

It is recommended that the indication be changed to:

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

The clinical evaluator also recommended various revisions to the PI; details of these are beyond the scope of the AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an Australian RMP Version 1.0 dated March 2012 (data lock point 28 November 2011) which was reviewed by the TGA's Office of Product Review (OPR). A summary of the RMP is shown in Table 7.

Table 7. Summary of Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important identified risks		
Exacerbation of chemotherapy/docetaxel-associated neutropenia	Routine	Routine
Infusion-associated reactions	Routine	Routine
Hypersensitivity/Anaphylaxis	Routine	Routine

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important potential risks		
Oligohydramnios	Routine	Routine
Interstitial lung disease (ILD)	Routine	None
Important missing information		
Patients with hepatic impairment	Routine	Routine
Patients with renal impairment	Routine	Routine
Patients with cardiovascular impairment	Routine	Routine
Male patients	Routine	None
Pregnant women	Routine	Routine
Lactating women	Routine	Routine

Safety specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the Office of Scientific Evaluation and the clinical aspects of the SS by the Office of Medicines Authorisation, the summary of the Ongoing Safety Concerns as specified in *Summary of Ongoing Safety Concerns* of the Aus RMP is as follows:

Table 8. Summary of the Ongoing Safety Concerns

Important Identified Risks	Exacerbation of chemotherapy/docetaxel-associated neutropenia
	Infusion-associated reactions
	Anaphylaxis/ Hypersensitivity reactions
Important Potential Risks	Oligohydramnios*
	Interstitial lung disease (ILD)

*Oligohydramnios has not been reported in patients treated with pertuzumab but occurred in cynomolgus monkeys administered pertuzumab and in pregnant women treated with trastuzumab. Due to age, prior adjuvant treatment, concurrent chemotherapy, the advanced stage of disease and poor prognosis in the patient population, the Sponsor assesses the likelihood of pregnancies to be low.

OPR reviewer's comments:

The *Summary of the Risk Management Plan* of the Aus RMP listed the following as areas of important missing information, which should also be included in the *Summary of Ongoing Safety Concerns* of the Aus RMP:

- Patients with hepatic impairment
- Patients with renal impairment
- Patients with cardiovascular impairment
- Male patients
- Pregnant women
- Lactating women

Pursuant to the evaluation of the non-clinical and clinical aspects of the SS, the above summary of the Ongoing Safety Concerns is considered acceptable with the addition of the abovementioned list of important areas of missing information, unless additional concerns are raised by the nonclinical and/or clinical evaluator(s).

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed for all ongoing safety concerns. It is also stated in the *Summary of Safety Concern and Planned Pharmacovigilance Actions* of the Aus RMP that “*reports of ILD, regardless of the source of reporting, will be followed up based on an internal checklist (analogous to the ILD “Guided Questionnaire” for HERCEPTIN – refer to HERCEPTIN AusRMP Annex 6 – Guided Questionnaires) in order to received detailed documentation....*”, which can be considered to be an enhanced or additional pharmacovigilance activity.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

There is no objection to the proposed use of a targeted checklist for the important potential risk ‘ILD’ that is similar to the ILD Guided Questionnaire for Herceptin.

A Pregnancy Registry is to be implemented as part of the post-marketing requirement imposed by the US FDA. It is recommended that the sponsor provides clarification as to whether a similar pregnancy registry will be implemented in Australia.

The proposed pharmacovigilance plan is otherwise considered acceptable, unless additional concerns are raised by the clinical and/or non-clinical evaluator(s).

Risk minimisation plan

The *Risk Minimisation Plan* part of the Aus RMP indicated that no additional risk minimisation activities are proposed.

OPR reviewer's comment:

This is considered acceptable as it is expected that this product will be used under the supervision of a healthcare professional who is experienced in cancer treatment, unless additional concerns are raised by the clinical and/or nonclinical evaluator(s).

Risk minimisation activities

Routine risk minimisation activities are proposed for all ongoing safety concerns except for the important potential risk ‘interstitial lung disease’ and area of missing information ‘male patients’, whereby no risk minimisation activity is proposed.

OPR reviewer's comment:

It is acceptable at this stage that only routine risk minimisation activities are proposed for all ongoing safety concerns, unless additional concerns are raised by the clinical and/or nonclinical evaluator(s). However, it is unclear why routine risk minimisation activity is not required for the important potential risk 'interstitial lung disease' as no justification is provided. It is recommended that the sponsor provides an acceptable justification for this.

The *Summary of the Risk Management Plan* of the Aus-RMP indicated that no routine risk minimisation activity is required for the area of missing information 'male patients'. This is acceptable at this stage as it is expected that very few male patients will be prescribed Perjeta given the proposed indication sought for in this submission. Furthermore, the following statement is already included under the *Precautions – Use in pregnancy* section of the draft Australian PI: "...female partners of male patients of child bearing potential should use effective contraception while receiving Perjeta and for 6 months following the last dose of Perjeta".

Summary of recommendations

The OPR provides the recommendation in the context that the submitted RMP is supportive to the application, with amendments as stated below and under the provision that no additional safety concerns are raised by the clinical and/or nonclinical evaluator(s):

It is recommended that the Delegate considers the following:

- Safety Concerns:
 - To request the sponsor to commit to including the following safety concerns in *Table 25 Summary of Ongoing Safety Concerns* in the next update to the RMP:
 - § Patients with hepatic impairment
 - § Patients with renal impairment
 - § Patients with cardiovascular impairment
 - § Male patients
 - § Pregnant women
 - § Lactating women
- Pharmacovigilance activities:
 - To request the sponsor to provide a copy of the ILD checklist for Perjeta that is intended for use in the Australian market, when available.
 - To request the sponsor to clarify if a pregnancy registry will be implemented in Australia. If not, the sponsor should provide a commitment that the safety information from the planned US based Pregnancy Registry will also be communicated to the TGA and state the expected milestone(s) for reporting.
- Risk Minimisation activities:
 - To request the sponsor to provide an acceptable justification for why routine risk minimisation activity is not required for the important potential risk 'interstitial lung disease'.
 - To request the inclusion of information in the draft Australian PI relating to
 - § contraindicated in patients with known hypersensitivity to pertuzumab, Chinese hamster ovary cell proteins or to any other component of the product.

§ other precautionary statements that may be considered.²³

Outstanding issues

Following receipt of the RMP evaluation report, the sponsor provided TGA with satisfactory response to matters outlined in the above recommendations.

Recommendation regarding registration

If this application is approved, it is recommended the Delegate consider implementing revisions to the PI as recommended by the RMP evaluator.

It is recommended that the following should be imposed as conditions of registration:

- Implement Australian Risk Management Plan Version 1.0 dated March 2012 (data lock point 28 November 2011) and any future updates as a condition of registration.
- Provide TGA with periodic safety update reports (PSURs) in accordance with the usual requirements for applications of this type.

VI. Overall conclusion and risk/benefit assessment

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

Background

Pertuzumab is a recombinant humanised monoclonal antibody that inhibits dimerisation of the HER2 protein, which blocks downstream intracellular signalling in the MAP kinase and PI3K pathways, arrests cell growth and causes apoptosis. It is claimed that pertuzumab complements trastuzumab since the two medicines act at different regions of the HER2 receptor.

A relevant European Guideline adopted by TGA is *Guideline on the Evaluation of Anticancer Medicinal Products in Man* (CPMP/EWG/205/95).

The indication under consideration as requested by the sponsor is:

Perjeta is indicated in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic (Stage IV) or unresectable locally recurrent breast cancer who have not received previous treatment or whose disease has relapsed after adjuvant therapy.

Quality

- Pertuzumab was well-characterised and stable. All outstanding biological and quality control issues have been addressed. The application was noted at the 149th (December 2012) meeting of the PSC.
- There have been some problems with manufacture resulting in low pertuzumab production and supply shortages overseas. This is under investigation by the sponsor.
- The evaluator supported registration subject to Batch Release conditions to ensure product consistency, and submission of Certified Product Details

²³ Details of recommended revisions to the PI are beyond the scope of the AusPAR.

Nonclinical

- The combination of pertuzumab and trastuzumab significantly increased anti-tumour activity in HER2-overexpressing breast xenograft models compared with pertuzumab alone.
- The safety studies were limited to cynomolgus monkeys due to the nature of the drug. There were no major toxicities. Pertuzumab exposure based on AUC was up to 47 times that expected clinically.
- In the reproductive study cynomolgus monkeys, pertuzumab was embryo- and fetotoxic at plasma concentrations 2-19 times the clinical C_{max} at the loading dose of 800 mg. Effects included fetal death, low fetal weight, delayed kidney development, oligohydramnios and limb abnormalities. Pregnancy category D is recommended.
- The evaluator supported registration.

Clinical

Pharmacokinetics

- In the pivotal population-PK analysis (Report 11-2998) in 440 cancer patients from 11 Phase I-II trials and the Phase III trial at pertuzumab doses of 2-25 mg/kg, PK were linear, the estimated volume of distribution was 5.4 L, clearance 0.24 L/day and median terminal elimination half-life 17 days. The PK analysis supported the fixed, non-weight-based dose proposed for registration.
- Pertuzumab is a large molecular weight protein which is expected to be catabolised to small peptides and amino acids. Clearance is unlikely to be affected by renal or hepatic impairment. The PK analysis showed that dose adjustments are not required in mild to moderate renal impairment; however, the data in severe renal impairment were limited.
- A substudy of the pivotal Phase III trial (WO20698/TOC4129g) showed that PK interaction between pertuzumab, trastuzumab and docetaxel is unlikely at the proposed doses.
- In the Phase III trial, 11 (2.8%) of 386 evaluable subjects were positive for anti-pertuzumab antibodies. The significance of anti-pertuzumab antibodies was unclear at the present time.

Pharmacodynamics

- A substudy of the pivotal Phase III trial (WO20698/Substudy 2) showed that pertuzumab caused a small increase in the QTcF interval during cycle 3 of treatment. Twenty subjects received pertuzumab in combination with trastuzumab and docetaxel and 17 subjects received placebo in combination with trastuzumab and docetaxel. No subject in either group had QTcF > 480 ms or increases in QTcF > 60 ms, which suggests clinically significant increases in QTcF are unlikely.

Efficacy

- The pivotal study (WO20698/CLEOPATRA) was a global, randomised, double-blind trial in patients with HER2-positive metastatic or locally recurrent unresectable breast cancer. The majority of subjects (98.5%) had metastatic disease. Patients had not had previous treatment for advanced disease. The treatments were pertuzumab plus trastuzumab and docetaxel or placebo plus trastuzumab and docetaxel. The doses

were pertuzumab 840 mg/kg IV loading then 420 mg/kg IV q3w, trastuzumab 8 mg/kg IV loading then 6 mg/kg IV q3w and docetaxel 75 mg/m² IV q3w for at least six cycles. The docetaxel dose could be increased to 100 mg/m² at the investigator's discretion. Treatment was continued until disease progression or unacceptable toxicity.

- The mean age of subjects was 54 years, range 22-89 years. Subjects required baseline LVEF \geq 50% and ECOG²⁴ performance status 0 or 1. Most subjects (84%) had premedication, commonly corticosteroids and 5-HT₃ antagonists. The primary endpoint was PFS assessed independently using RECIST²⁵ criteria.
- The addition of pertuzumab to trastuzumab and docetaxel significantly increased PFS by a median 6.1 months (Table 9). Sensitivity and subgroup analyses were supportive. Overall survival results were immature. 165 patients (20%) had died at the time of the analysis. The final analysis is due after 385 deaths (estimated in late 2013). The overall response rate was greater with pertuzumab than control. There was no significant difference in the time to symptom progression.
- The median duration of treatment was 13.1 months (range 0.1-38.0 months) in the pertuzumab group and 10.8 months (range 0.1-34.6 months) in the placebo group. The median follow-up was 17.7 months in the pertuzumab group and 16.8 months in the placebo group. The study has been published.²⁶
- Two other studies of combination therapy involving pertuzumab in HER2-positive breast cancer patients (WO20697 and BO17929) were not directly relevant.

Table 9. CLEOPATRA – Efficacy Results – data cut-off 13 May 2011.

	Pertuzumab + Trastuzumab+ Docetaxel n=402	Placebo+ Trastuzumab + Docetaxel n=406	Hazard Ratio or Difference [95% CI]	p-value ³
PFS median (months)	18.5	12.4	HR 0.62 ² [0.51, 0.75]	p<0.0001
Overall Survival median (months)	NR	NR	HR 0.64 [0.47, 0.88]	p=0.0053 ⁴
Overall Response Rate (ORR) ¹	80.2%	69.3%	Diff 10.8% [4.2%, 17.5%]	p=0.0011 ⁵

¹ Complete Response Rate + Partial Response Rate assessed independently using RECIST.

² Stratified by prior treatment (none, adjuvant, neoadjuvant) and region (Europe, North America, South America, Asia). ³ Log-Rank test. ⁴ Did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets

²⁴ Eastern Cooperative Oncology Group; see Appendix 1 of the Extract from the CER (Attachment 2 of this AusPAR) for a full definition.

²⁵ Response evaluation criteria in solid tumors; see Appendix 2 of the Extract from the CER (Attachment 2 of this AusPAR) for a full definition.

²⁶ Baselga J *et al.* Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. *N Eng J Med* 2012; 366: 109-19.

α -spending function (HR \leq 0.603, $p \leq$ 0.0012).⁵ Mantel-Haenszel χ^2 Test; exploratory due to testing hierarchy: PFS→OS→ORR. NR – Not Reached. NA – Not Applicable.

Safety

- The primary safety data is from the CLEOPATRA trial in which 407 subjects were exposed to pertuzumab and 397 to placebo, both in combination with trastuzumab and docetaxel. The median duration of treatment was 18 months in the pertuzumab group and 12 months in the placebo group.
- An integrated summary of safety of 1,412 subjects exposed to pertuzumab from several trials including CLEOPATRA was also submitted. Interpretation of this data was complicated because pertuzumab was combined with various chemotherapeutic agents. Generally, the incidence of AEs with pertuzumab was lower in the integrated summary than in CLEOPATRA; however, pertuzumab exposure was also lower in the integrated trials. The Delegate focussed on the CLEOPATRA trial.
- In the CLEOPATRA trial, common AEs with a higher incidence with pertuzumab than placebo were diarrhoea (67% versus 46%), rash (34% versus 24%) and mucosal inflammation (28% versus 20%), febrile neutropenia (14% versus 8%) and dry skin (11% versus 4%). The majority of subjects in each arm of the trial (84%) received a premedication, usually corticosteroids (78%), 5-HT₃ antagonists (60%) and antihistamines (48%).
- There was a higher incidence of SAEs with pertuzumab than placebo (34% versus 26%), which was mostly accounted for by the higher incidence of febrile neutropenia. Discontinuations due to AEs were similar with pertuzumab and placebo (6.1% versus 5.3%). However, dose interruption or modification was more frequent with pertuzumab than placebo (60% versus 53%). Deaths due to AEs were of similar incidence in the two treatment groups: 8 (2%) in the pertuzumab group and 10 (2.5%) in the placebo group. Deaths were mostly due to cardiovascular causes or infection.
- Cardiac AEs were not increased with pertuzumab: 15% pertuzumab versus 16% placebo. However, the trial excluded patients with cardiac disease or risk.

Clinical evaluator's recommendation

The evaluator recommended restricting the indication to *treatment of metastatic breast cancer* (due to few subjects with locally recurrent disease) and to *patients who had not received anti-HER2 therapy or chemotherapy for metastatic disease* (in line with the trial population).

Risk management plan

- The Safety Specification was acceptable to the clinical and nonclinical evaluators.
- The evaluator requested that: *the sponsor include 'interstitial lung disease' as an adverse reaction. In the CLEOPATRA trial, the incidence was 2.2% with pertuzumab and 1.5% with placebo.* The Delegate considered the data were inconclusive due to confounding.
- The RMP was acceptable.
- The evaluator recommended the implementation of the RMP and provision of PSURs as conditions of registration.

Risk-benefit analysis

Delegate considerations

The efficacy of pertuzumab in combination with trastuzumab and docetaxel in the proposed indication is based on the pivotal CLEOPATRA study. Trastuzumab and docetaxel is a standard treatment. Addition of pertuzumab significantly increased PFS by a median 6.1 months which is clinically meaningful. There was a trend to increased OS with pertuzumab; however, the data were immature. The majority of subjects had metastatic disease; only 12 (1.5%) had unresectable, locally recurrent disease.

The addition of pertuzumab to trastuzumab and docetaxel resulted in significantly increased diarrhoea, rash, mucosal inflammation, febrile neutropenia and dry skin. Adverse events were managed with premedication, dose reduction and other symptomatic treatment.

The Delegate supported the clinical evaluator in limiting the indication to treatment of metastatic breast cancer and to patients who had not received anti-HER2 therapy or chemotherapy for metastatic disease.

Proposed action

The Delegate proposed to approve the application for the following indication:

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

Approval would be subject to finalisation of the PI²⁷ and to the following conditions of registration:

- Submission of the final analysis of OS from the CLEOPATRA study when available.
- Implementation of Australian RMP Version 1.0 dated March 2012 (data lock point 28 November 2011) and any future updates.
- Provision of PSURs in accordance with usual requirements for applications of this type.
- Batch release conditions as specified by the TGA Office of Laboratories and Scientific Services
- Certified Product Details as specified by the TGA Office of Laboratories and Scientific Services

Request for advice from ACPM

The Delegate sought general advice on this application from the ACPM and in particular requested the ACPM address the following:

1. Has the efficacy of pertuzumab in the proposed indication been satisfactorily established in view of the lack of mature overall survival data?
2. Should the indication be restricted to metastatic disease in view of only 12 subjects with locally advanced disease²⁸ in the CLEOPATRA trial?
3. Is the benefit-risk balance of pertuzumab favourable in the proposed indication?

²⁷ Details of revisions to the PI are beyond the scope of the AusPAR.

²⁸ In the CER, these 12 patients are described as having 'unresectable, locally recurrent disease without metastases'.

Response from sponsor

Roche Products Pty Limited concurs with the Delegate's proposed action to approve the application for the following indication:

“PERJETA is indicated in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic (Stage IV) breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease”

The Sponsor agrees with the majority of the changes proposed for the PI.

Roche's responses to the delegate's questions submitted to ACPM for advice

1. Has the efficacy of pertuzumab in the proposed indication been satisfactorily established in view of the lack of mature overall survival data?

The sponsor believes the efficacy of pertuzumab has been established in the proposed indication based on the primary analysis of the pivotal Phase III study CLEOPATRA. The improvement in median PFS of 6.1 months (from 12.4 to 18.5 months) seen in the Perjeta treated group (HR of 0.62; $p < 0.0001$) represents a substantial and clinically relevant improvement in PFS over current standard of care treatment. And, although at the time of primary efficacy analysis, OS did not meet the pre-specified boundary and was not considered statistically significant, the interim OS data showed a strong trend suggestive of a survival benefit in favour of the Perjeta treated group (HR of 0.64, $p = 0.0053$).

In reference to “the lack of mature OS data”, as communicated to the TGA on the 03 Jul 2013, updated OS data from a second interim OS analysis became available after submission. These data were not officially submitted for evaluation, but the TGA was informed of the un-blinding of the study and notified that this updated OS analysis was now considered the final OS analysis.

This analysis was performed following a protocol amendment and included type I error control in order to allow appropriate statistical inference. The results (HR = 0.66; 95%CI: 0.52, 0.84; $p = 0.0008$) met the criteria for demonstrating a statistically significant improvement in OS and confirmed the conclusions of the primary analysis. Therefore this analysis is considered the final OS analysis (since the study has met its survival objective; any future survival analyses will be descriptive only).

Therefore, in response to this question, in line with the updated analysis and as per the recently approved EU Summary of Product Characteristics (SmPC), the sponsor proposes to update the Perjeta PI (*Clinical trials* section) with the updated OS results as follows (proposed revisions shown as struck-out text and in blue font);

Table 10. Excerpt from Table on Summary of efficacy from CLEOPATRA study (Clinical trials)

Parameter	Placebo + trastuzumab + docetaxel (n=406)	PERJETA + trastuzumab + docetaxel (n=402)	HR (95% CI)	p-value
Secondary Endpoints:				
Overall Survival (second Interim)			0.64 [0.47;0.88]	0.0053, NS
No. of patients with an event*	96(23.6) 154 (37.9%)	69 (17.2) 113 (28.1%)	0.66	± 0.0008*
Median months	37.6	Not reached	[0.52;0.84]	

* Second interim overall survival analysis performed one year after the primary analysis: the p-value met the O'Brien Fleming stopping boundary of the Lan DeMets alpha spending function for the interim analysis ($p \leq 0.0138$). The result was therefore statistically significant.

~~†NS: Not significant – the HR and p-value did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets alpha spending function for the interim analysis of overall survival (HR ≤ 0.603 , $p \leq 0.0012$). The interim analysis result is therefore not statistically significant and is only deemed exploratory~~

2. Should the indication be restricted to metastatic disease in view of only 12 subjects with locally advanced disease²⁹ in the CLEOPATRA trial?

The sponsor accepts the changes to the indication proposed by the clinical evaluator and supported by the Delegate.

3. Is the benefit-risk balance of pertuzumab favourable in the proposed indication?

As per above, the sponsor believes the pivotal trial clearly demonstrates a positive benefit–risk ratio for Perjeta and trastuzumab, combined with docetaxel, for the treatment of patients with HER2-positive metastatic or locally recurrent, unresectable breast cancer (the proposed indication).

A second interim analysis of OS available subsequent to submission further supports the primary analysis. Top level results are described below;

- Because of the fixed-sequence testing hierarchy implemented for secondary endpoints, the primary result for IRF-assessed ORR, which was deemed exploratory in the primary analysis, can now be considered statistically significant.
- The updated analysis of investigator-assessed PFS was highly consistent with those from the primary analysis. (HR =0.69; increase in median PFS of 6.3 months (from 12.4 months versus. 18.7 months).
- The observed HR ratio for OS was statistically significant and clinically meaningful (HR = 0.66; 95%CI: 0.52, 0.84; p = 0.0008).
- The safety profile, including the cardiac toxicity profile, of the Perjeta combination regimen was comparable to that of the control arm, apart from a higher incidence of Grade 1–2 diarrhoea, rash, pruritus, mucosal inflammation, dry skin, Grade 3–4 febrile neutropenia, and all grade VTEs.
- The additional safety data do not show evidence of any cumulative toxicity or late appearing toxicity, particularly regarding cardiac disorders.

The magnitude of clinical benefit and the acceptable safety profile in this study update provide further confirmation of the positive benefit-risk ratio of treatment with Perjeta and trastuzumab with docetaxel in patients with HER2-positive metastatic or locally recurrent, unresectable breast cancer.

However, as per above, the Sponsor agrees to restrict the indication to patients with metastatic HER2-positive breast cancer who have not been previously treated with trastuzumab or chemotherapy for metastatic breast cancer, excluding unresectable locally recurrent disease. The benefit-risk ratio of Perjeta combination treatment in these patients is clearly supported by the clinical evaluator (extracts from the CER reproduced below).

"... it is considered that the benefits should be interpreted as referring to patients with metastatic HER2-positive breast cancer who have not been previously treated with trastuzumab or chemotherapy for metastatic breast cancer .."

"The benefit-risk balance is considered favourable for pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2-positive metastatic breast cancer in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. The data on patients with unresectable, locally recurrent breast cancer are too limited to allow for an adequate benefit-risk balance assessment for this patient group to be undertaken"

²⁹ In the CER, these 12 patients are described as having 'unresectable, locally recurrent disease without metastases'

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered this product to have an overall positive benefit-risk profile for the Delegate's proposed indication;

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

The ACPM agrees with the Delegate that there were insufficient data to support the indication in the locally advanced disease state.³⁰

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Perjeta concentrate injection vial containing pertuzumab rch 30 mg/mL, indicated for:

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

Specific conditions applying to this therapeutic good

- The implementation of Australian RMP Version 1.0 dated March 2012 (data lock point 28 November 2011) and any future updates agreed with the TGA Office of Product Review.

and conditions³¹ relating to:

- Provision of PSURs to the TGA
- Batch release assessments by the TGA
- Provision of acceptable Certified Product Details
- Supply of Perjeta labelled with a 3-year shelf life until Perjeta labelled with a 2-year shelf life becomes available and is registered.

³⁰ This committee considered that: *'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.'* In the CER, these 12 patients are described as having 'unresectable, locally recurrent disease without metastases'

³¹ Specific details of these conditions and of general conditions of registration are beyond the scope of the AusPAR.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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