5.27 TRASTUZUMAB, Powder for I.V. infusion 60 mg, Powder for I.V. infusion 150 mg, Trazimera®, Pfizer Australia Pty Ltd

1 Purpose of Application

1.1 The minor submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for a new biosimilar brand of trastuzumab (Trazimera®), hereafter referred to as Trazimera.

2 Requested listing

2.1 The submission requested the listing of Trazimera for the same indications for which the reference brand, Herceptin®, is currently PBS listed, specifically:

- HER2-positive early, locally advanced and metastatic breast cancer (MBC)
- HER2-positive metastatic gastric cancer (MGC)

2.2 The sponsor requested Trazimera be 'a' flagged against the reference product Herceptin.

2.3 The Trazimera and Herceptin brands share two common presentations: a 60 mg vial with powder for injection for infusion and a 150 mg vial with powder for injection for infusion.

2.4 The item codes relating to the Herceptin SC (subcutaneous injection) brand were not sought for reimbursement.

2.5 The submission proposed identical restriction wording to Herceptin and all other listed brands of trastuzumab, and an Authority Required (STREAMLINED) listing across all item codes. Due to the length of the proposed restrictions they have not been reproduced here.

2.6 The Sponsor requested Authority Required (STREAMLINED) listings across all indications and treatment phases to encourage biosimilar uptake, while retaining physician and patient choice. This is in line with the PBAC's recommendation at its July 2019 meeting that all PBS-listed brands of trastuzumab should be made Authority Required (STREAMLINED) across all indications (Trastuzumab (Kanjinti) Public Summary Document, July 2019 PBAC Meeting, item 5.4). As of 1 October 2019, all of the trastuzumab listings on the PBS are Authority Required (STREAMLINED).

2.7 The PBAC has previously noted that the biosimilar uptake driver of applying a lower authority level to the biosimilar brand cannot be given effect for EFC medicines, and suggested that the Department could develop a set of biosimilar uptake drivers suitable for EFC medicines (Trastuzumab (Kanjinti) Public Summary Document, July 2019 PBAC Meeting, item 5.6).

For more detail on PBAC's view, see section 5 PBAC outcome

3 Background

Registration status

3.1 Trazimera was TGA registered on 18 July 2019 and was determined to be biosimilar to the reference brand Herceptin.

3.2 Trazimera is TGA approved for the same indications as Herceptin: early breast cancer, locally advanced breast cancer, metastatic breast cancer, and advanced gastric cancer.

Previous PBAC considerations

3.3 Trazimera has not previously been considered by the PBAC.

3.4 At the March 2019 PBAC meeting two trastuzumab biosimilar medicines (Ogivri® and Ontruzant®) were recommended for listing for the same indications for which Herceptin is currently PBS listed.

3.5 At the July 2019 PBAC meeting two additional biosimilar medicines, Kanjinti® and Herzuma®, were recommended for listing for the same indications for which Herceptin is currently PBS listed.

3.6 As of 1 November 2019, Ogivri and Herzuma are PBS-listed, and Kanjinti and Ontruzant are yet to be listed.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

4.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

4.3 The minor submission presented the following clinical trials to support the claim of biosimilarity of Trazimera to the reference product Herceptin.

4.4 As a minor submission, no independent evaluation of the clinical evidence was undertaken.

Table 1: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
B3271002	A Phase 3 Randomized, Double-Blind Study of PF-05280014 Plus Paclitaxel Versus Trastuzumab Plus Paclitaxel for the First-Line Treatment of Patients with HER2-Positive Metastatic Breast Cancer Description: Randomised, double blind, clinical comparability study in women with metastatic HER2+ breast cancer (n=707)	Clinical study report Published 21 July 2017
	Main publications: PF-05280014 (a trastuzumab biosimilar) plus paclitaxel compared with reference trastuzumab plus paclitaxel for HER2-positive metastatic breast cancer: a randomised, double-blind study.	Pegram M, Bondarenko I, Zorzetto M et al. Br J Cancer. 2019 Jan;120(2):172-182
	Population pharmacokinetics of PF-05280014 (a trastuzumab biosimilar) and reference trastuzumab (Herceptin®) in patients with HER2-positive metastatic breast cancer. Cancer Chemother Pharmacol.	Chen X, Li C, Ewesuedo R et al. 2019; 84(1): 83–92.
	Additional citations: A randomized, double-blind study of PF-05280014 (a potential trastuzumab biosimilar) vs trastuzumab, both in combination with paclitaxel, as first-line treatment for HER2-positive metastatic breast cancer.	Pegram M, Tan-Chiu E, Freyman A, et al. *Ann Oncol* 2017; 28(suppl_5).
	A phase 3 randomized, double-blind trial comparing PF-05280014 + paclitaxel vs. trastuzumab + paclitaxel for treatment of HER2+ metastatic breast cancer patients.	Ewesuedo R, Barker K.B., Taylor C.T. et al. Cancer Research. Conference: 36th Annual CTRC-AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Publication 73 (24 SUPPL. 1) (no pagination), 2013. Date of Publication: 15 Dec 2013.
B3271004	A Randomized, Double-Blind Pharmacokinetic Study Of PF-05280014 plus Taxotere® and Carboplatin versus Herceptin® plus Taxotere® and Carboplatin for the Neoadjuvant Treatment of patients with Operable HER2-Positive Breast Cancer. Description: Randomised, double blind, clinical comparability study in women with operable HER2+ breast cancer (n=226)	Clinical study report Published 26 January 2017

Trial ID/First Author	Protocol title/ Publication title	Publication citation
	Main publication: Neoadjuvant PF-05280014 (a potential trastuzumab biosimilar) versus trastuzumab for operable HER2+ breast cancer.	Lammers P, Dank M, Masetti R, et al. British Journal of Cancer 2018: 119:266–273.
	Additional citations: A randomized, double-blind study of PF-05280014 (a potential biosimilar) vs trastuzumab, both given with docetaxel (D) and carboplatin (C), as neoadjuvant treatment for operable human epidermal growth factor receptor 2-positive (HER2+) breast cancer.	Lammers P, Dank M, Masetti R, et al. *Ann Oncol* 2017;28(suppl_5)
	A Phase III Randomized, Double-Blind Trial Comparing PF-05280014 + Docetaxel and Carboplatin vs. Trastuzumab + Docetaxel and Carboplatin for Neoadjuvant Treatment of Operable HER2+ Breast Cancer.	Jacobs I, Coiro J, Hilton F, et al. Published at San Antonio Breast Cancer Symposium, 2014.

Supporting Evidence		
B3271001 (REFLECTIONS B327-01)	Phase 1, Double Blind, Randomized, Parallel-Group, Single-Dose, 3-Arm, Comparative Pharmacokinetic Study of PF-05280014 and Trastuzumab Sourced From US and EU Administered to Healthy Male Volunteers. Description: Double-blind, three parallel-arm, single dose pharmacokinetic study in healthy male volunteers (n=105)	Clinical study report Published 27 February 2013
	Main publication: A randomized phase 1 pharmacokinetic trial comparing the potential biosimilar PF-05280014 with trastuzumab in healthy volunteers Additional citations: Immunogenicity assessment of PF-05280014, a potential biosimilar to trastuzumab, in healthy subjects Phase I pharmacokinetics trial comparing PF-05280014 and trastuzumab in healthy volunteers (reflections B327-01).	Yin D, Barker KB, Li R, et al. Br J Clin Pharmacol 2014; 78(6):1281-90. Yin D, Cai CH, Taylor C.T, et al. European Journal of Cancer. Conference: European Cancer Congress 2013, ECC 2013. Amsterdam Netherlands. Conference Publication: 49 (SUPPL. 2) (pp S176-S177), 2013. Date of Publication: September 2013. Ricart A.D., Zacharchuk C., Reich S.D.A et al. Cancer Research. Conference: 35th Annual CTRC-AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Publication: 72 (24 SUPPL. 3) (no pagination), 2012. Date of Publication: 15 Dec 2012.
B3271006	Phase 1, Double-Blind, Randomized, Parallel-Group, Single-Dose, 2-Arm, Safety Study of PF-05280014 and Trastuzumab Sourced From the US Administered to Healthy Male Volunteers. Description: Double blind single dose safety study in healthy male volunteers (n= 162)	Clinical Study Report Published 8 July 2014

Source: Table 2.1.1 of the submission, pages 8 and 9

Study B3271002

4.5 This was a randomised, double-blind, clinical comparability study of Trazimera versus Herceptin-EU in female patients with metastatic HER2-positive breast cancer.

4.6 The primary efficacy endpoint was the percentage of patients in each group with complete response or partial response based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 by week 25 and confirmed based on blinded central radiology review by week 33. The ORR analysis confirmed similarity between Trazimera and Herceptin-EU.

4.7 The secondary endpoints included one-year progression-free survival (PFS) and overall survival (OS), duration of response (DOR), safety, population pharmacokinetics and immunogenicity. No clinically meaningful or statistically significant differences were observed in the secondary efficacy endpoint for PFS rate, duration of response and OS rate. The study supported biosimilarity of Trazimera to the reference biological medicine in terms of efficacy.

4.8 Based on the safety analysis of clinical data from up to approximately 1 year after randomisation, the incidence of treatment emergent adverse events (TEAEs) for both treatment groups were similar.

Study B3271004

4.9 This was a randomised, double-blind, non-inferiority trial of Trazimera versus Herceptin-EU as neo-adjuvant therapy in 226 adult, female patients with operable HER2-positive breast cancer.

4.10 The primary efficacy endpoint was the percentage of patients in the per protocol (PP) population with steady state Ctrough (lowest drug concentration before administration of the next dose) >20µg/ml.

4.11 Secondary efficacy endpoints included pathological complete response (pCR), ORR, safety and immunogenicity. Efficacy results for pCR and ORR were comparable for the per protocol population between treatment groups.

4.12 No clinically significant imbalance was observed between Trazimera and trastuzumab-EU for safety parameters. The percentage of patients was similar between treatment arms for AEs (Trazimera: 96.5%; trastuzumab-EU: 94.6%) and SAEs (Trazimera: 6.2%; trastuzumab-EU: 5.4%)

Study B3271001

4.13 A comparative clinical pharmacokinetic, phase 1, double-blind, randomised, parallel-group, single-dose, three-arm study of Trazimera and trastuzumab sourced from US (trastuzumab-US/Herceptin-US) and EU (trastuzumab-EU/Herceptin-EU) administered to healthy male volunteers.

4.14 The primary objective was to demonstrate the pharmacokinetic similarity of Trazimera to trastuzumab-US and trastuzumab-EU. The secondary objectives were to evaluate the safety, tolerability, and immunogenicity of Trazimera, trastuzumab-US, and trastuzumab-EU.

4.15 The evaluation of individual subject serum concentration-time data demonstrated that all 3 products (Trazimera, trastuzumab-US, and trastuzumab-EU) exhibited similar profiles, with mean serum concentration-time profiles superimposable.

Study B3271006

4.16 A single dose safety study (specific study of pyrexia) with the primary endpoint of the study was to compare relative risk of an abnormal elevated body temperature with

Trazimera versus Herceptin-US. The rate in the Trazimera arm (6.3%) was lower than that seen in the Herceptin-US arm (13.8%) (Relative risk 0.455, 90% CI: 0.198, 1.057). These findings supported that the higher incidence of fever seen in study B3271001 could be attributable to random variation in a small sample size.

4.17 The sponsor requested to extrapolate the results of the trials to all approved Herceptin indications, including metastatic breast cancer and metastatic gastric cancer.

Clinical claim

4.18 The submission claimed non-inferior comparative effectiveness and non-inferior comparative safety of Trazimera compared with Herceptin.

4.19 The TGA was satisfied that the biosimilar brand was non-inferior in terms of both efficacy and safety compared to the reference brand.

4.20 The PBAC considered that the claim of non-inferior comparative effectiveness and comparative safety was reasonable.

Economic analysis

4.21 The minor submission proposed listing on the basis of cost-minimisation of Trazimera compared with Herceptin. The equi-effective doses were estimated to be identical based on product information documents for both Trazimera and Herceptin.

4.22 The submission proposed pricings identical to Herceptin and other currently listed biosimilar trastuzumab medicines.

Table 2: Requested price for Trazimera (trastuzumab)

Presentation	AEMP
60 mg vial x 1	$213.29
150 mg vial x 1	$533.22

Source: Minor Submission, table 1.3.1 page 6

Estimated PBS usage & financial implications

4.23 The minor submission estimated there to be no financial implications to the PBS as the Sponsor expects Trazimera to only substitute for Herceptin and other biosimilar trastuzumab products, all of which have the same price.

5 PBAC Outcome

5.1 The PBAC recommended the listing of trastuzumab (Trazimera) as a biosimilar brand of trastuzumab (Herceptin) on the basis that it should only be available under special arrangements under Section 100 (Efficient Funding of Chemotherapy) on a cost-minimisation basis for all of the indications for which Herceptin is PBS-listed.

5.2 The PBAC noted that the TGA was satisfied that the two equivalence studies presented in the submission demonstrated clinical equivalence between Trazimera and Herceptin. The PBAC also noted the TGA's conclusion that the safety data from the

trials did not show clinically significant differences in any of the safety outcomes assessed.

5.3 The PBAC noted that the biosimilar uptake driver of applying a lower authority level to the biosimilar brand cannot be given effect for EFC medicines. Further, the PBAC noted that all PBS listed trastuzumab products are now Authority Required (STREAMLINED) across all indications, which is the lowest level of authority that can be applied to EFC drugs.

5.4 The PBAC recalled its advice from the July 2019 meeting that the Department develop a set of biosimilar uptake drivers suitable for EFC medicines as the current biosimilar uptake drivers cannot be applied to EFC medicines.

5.5 The PBAC noted that EFC medicines are governed by the *National Health (Efficient Funding of Chemotherapy) Special Arrangement 2011*, and that Section 33(2) allows substitution of brands under the same item code.

5.6 The PBAC noted that trastuzumab is not included on the list of PBS-listed drugs suitable for prescribing by nurse practitioners.

5.7 The PBAC noted that trastuzumab is exempt from the Early Supply Rule.

5.8 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

6 Recommended listing

6.1 Add new brand to PBS items: 10383L/10401K; 10391X/10402L; 10581X/10589H; 10588G/10597R; 4632T/7264H; 4639E/7265J; 4650R/7266K; 4703M/7267L.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

8 Sponsor's Comment

The sponsor had no comment.