5.24 TRASTUZUMAB
Powder for I.V. infusion 60 mg,
Powder for I.V. infusion 150 mg,
Powder for I.V. infusion 420 mg,
Kanjinti®, Amgen Australia Pty Ltd.

1 Purpose of Application

1.1 The minor submission sought a Section 100 (Efficient Funding of Chemotherapy Program), Authority Required (STREAMLINED) listing of a new biosimilar brand of trastuzumab (Kanjinti®).

2 Requested listing

2.1 The submission requested listing Kanjinti for all indications for which the reference brand Herceptin is currently PBS listed:

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

2.2 The sponsor requested restriction details and wording that are identical to the listings for the reference product, Herceptin (with the exception of wording to allow for the proposed application of biosimilar uptake drivers).

2.3 Due to the current Special Pricing Arrangement (SPA) in place for Herceptin, and the impending statutory price reductions with the listings of other biosimilar trastuzumab brands recommended by the PBAC at its March 2019 meeting, the sponsor did not provide a dispensed price for maximum quantity (DPMQ).

2.4 The item codes relating to the Herceptin SC brand are not sought for reimbursement.

2.5 The Herceptin and Kanjinti brands share two common presentations: 60 mg and 150 mg single vial strengths with powder for reconstitution with sterile water for IV administration. Kanjinti also has a 420 mg injection presentation which is not shared by Herceptin.

2.6 The minor submission noted that, since trastuzumab is listed as an EFC item, all presentations with the same authority level are captured by one PBS item code. Since the other TGA-approved biosimilar trastuzumab brands do not have a 60 mg vial presentation, the minor submission requested that an additional Administrative Note be included in the restriction stating that it is not appropriate to mix brands in a single infusion.

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

3 Background

3.1 The Kanjinti brand of trastuzumab was TGA approved on 8 January 2019 and was determined to be a biosimilar to the reference brand Herceptin. It was listed on the Australian Register of Therapeutic Goods (ARTG) on 16 May 2019.

3.2 Kanjinti is TGA approved with the same indications as the reference brand, Herceptin: early breast cancer, locally advanced breast cancer, metastatic breast cancer, and advanced gastric cancer.

3.3 The PBAC had not previously considered a submission for this brand of trastuzumab.

3.4 At its March 2019 meeting, the PBAC recommended the listing of two trastuzumab biosimilars, Ogivri (sponsor Alphapharm) and Ontruzant (sponsor MSD).

Biosimilar uptake measures

3.5 The minor submission requested Authority Required (STREAMLINED) listings across all item codes for Kanjinti. Herceptin has an Authority Required (Written) and Authority Required (Telephone) listing on the PBS.

3.6 The minor submission also requested that the restriction for Kanjinti include an Administrative note to encourage prescribing of this biosimilar brand for treatment naïve patients.

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

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 biosimilarity of Kanjinti compared to Herceptin. As a minor submission, no evaluation of the clinical evidence was undertaken.

Table 1: Trials and associated reports presented in the submission

Trial ID (Full Study No.)	Protocol title/publication title	Publication citation
Study 283 (LILAC) (20120283) (NCT01901146)	Randomized, Double-blind, Phase 3 Study Evaluating the Efficacy and Safety of ABP 980 Compared With Trastuzumab in Subjects With HER2-positive Early Breast Cancer	Clinical Study Reports Primary analysis: Data cut-off 5 May 2016 Report date: 06 June 2017 Supplementary primary analysis: Report date: 11 December 2017 Final analysis CSR addendum: Report date: 19 Jun 2017 *Refer Attachment 3*
	Main publication Efficacy and safety of ABP 980 compared with reference trastuzumab in women with HER2-positive early breast cancer (LILAC study): a randomised, double-blind, phase 3 trial	von Minckwitz G et al. Lancet Oncol. 2018; 19(7):987-998.
Study 119 (20130119)	Randomized, Single-blind, Single-dose, 3-arm, Parallel Group Study to Determine the Pharmacokinetic Equivalence of ABP 980 and Trastuzumab (Herceptin®) in Healthy Male Subjects	Clinical Study Report Report date: 3 April 2015 *Refer Attachment 3*
	Main Publication A randomized, single-blind, single-dose study evaluating the pharmacokinetic equivalence of proposed biosimilar ABP 980 and trastuzumab in healthy male subjects	Hanes et al. Cancer Chemother Pharmacol 2017; 79 (5): 881-888

Source: Table 2.1.1 of the submission, page 10

4.4 The clinical trials presented in the submission formed part of the sponsor's TGA documentation. They comprised one pivotal trial comparing Kanjinti to trastuzumab sourced from Europe (Herceptin) in women with HER2-positive early breast cancer, and one pharmacokinetic study in healthy adult male subjects to determine whether Kanjinti is biosimilar to FDA-licensed trastuzumab and EU-authorised trastuzumab.

4.5 Study 283 (LILAC) was a randomised, double-blind, phase 3 study evaluating the efficacy and safety of Kanjinti (ABP 980) versus Herceptin in patients with HER-2 positive EBC.

4.6 The co-primary efficacy endpoints were risk difference (RD) and risk ratio (RR) of pathological complete response (pCR), defined as the absence of invasive tumour cells in the breast tissue and in axillary lymph nodes regardless of ductal carcinoma in situ. A sensitivity analysis was conducted based on central laboratory evaluation of tumour samples. The 2-sided 90% confidence interval (CI) for both RD (-0.5%, 12.0%) and RR (0.993, 1.312) of the incidence of pCR were contained within the pre-specified equivalence margins (-13%, 13% and 0.76, 1.32, respectively). Based on this assessment, both non-inferiority and non-superiority margins were met. The TGA was therefore satisfied that Kanjinti was at least non-inferior to trastuzumab.

4.7 To further evaluate the efficacy between Kanjinti and trastuzumab, statistical assessments were conducted, which allowed for the incorporation of evidence from the PK similarity study (Study 119) into the analysis of data from the clinical similarity study (LILAC). In all populations analysed, the 90% CIs for RD of pCR and RR of pCR were within the pre-specified equivalence margins. The TGA was satisfied that results from these analyses support the clinical similarity (both non-inferiority and non-superiority) of Kanjinti to trastuzumab.

4.8 With respect to the secondary efficacy endpoints in LILAC, the RD and RR results were consistently numerically superior in the Kanjinti arm compared with the trastuzumab arm. The lower bound of the 90% CI for the RD was greater than -13% for all secondary efficacy endpoints. Similarly, the lower bound of the 90% CI for the RR was greater than 0.7585. The TGA was satisfied that these secondary efficacy results for both the RD and RR for the pCR, evaluated by both local and central laboratories, supported the primary analysis of the two co-primary efficacy endpoints. Furthermore, overall survival (OS) in the entire study was 99.7% (n = 363) in subjects initially randomised to Kanjinti (n = 364) and 98.6% (n = 356) in subjected initially randomised to trastuzumab (n = 361).

4.9 Based on the totality of the provided safety data, the TGA evaluator concluded that the safety profiles of Kanjinti and trastuzumab (sourced from Europe) were broadly similar, and that the observed numerical difference in adverse event rates between the two products were not clinically significant.

Clinical claim

4.10 The submission claimed that Kanjinti is non-inferior in terms of comparative effectiveness, and non-inferior in terms of comparative safety, to Herceptin.

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

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

Estimated PBS usage & financial implications

4.13 The submission stated that the PBS/RPBS will achieve approximately $60 - $100 million per year in savings by listing trastuzumab biosimilars, equivalent to approximately more than $100 million over six years. The sponsor stated that the availability of Kanjinti confers additional dose efficiencies compared to other biosimilars, i.e. it is currently the only biosimilar that has a 60 mg vial size (as does Herceptin), which has been estimated to potentially yield an incremental less than $10 million per year in savings.

4.14 As a minor submission, the financial estimates have not been independently evaluated.

4.15 Whilst the listing of the first biosimilar brand of a medicine reduces the overall PBS spend by the force of the statutory price reductions and subsequent price disclosure related price reductions, such reductions cannot be claimed by this subsequent brand of biosimilar. Further, the PBAC was of the view that it was not possible to accurately estimate whether prescribers would choose Kanjinti or any other biosimilar over the originator brand.

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

5 PBAC Outcome

5.1 The PBAC recommended the listing of trastuzumab (Kanjinti) as a biosimilar of trastuzumab (Herceptin) on a cost-minimisation basis for all of the indications for which Herceptin is PBS-listed.

5.2 The PBAC noted the TGA was satisfied that the two equivalence studies presented in the submission demonstrated clinical equivalence between Kanjinti 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 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.

5.4 Consistent with its March 2019 recommendation made at the time the first two biosimilar brands of trastuzumab were considered, the PBAC advised that all of the PBS-listed brands of trastuzumab should be made Authority Required (STREAMLINED) across all indications, with a change in wording to allow adjuvant or neoadjuvant treatment for early breast cancer, and to allow trastuzumab in combination with any platinum chemotherapy for advanced gastric cancer. The PBAC advised removal of the "locally advanced" indication and for the written authority requirement to remain for pertuzumab, trastuzumab emtansine and lapatinib in metastatic cancer. However, the PBAC requested the Department provide a discussion paper on the PBS restriction of the subcutaneous form of trastuzumab at an upcoming meeting

5.5 The PBAC did not recommend the inclusion of an Administrative Note that states it is not appropriate to mix brands in a single infusion, as such a note would not have legal effect. Furthermore, the PBAC noted that the other EFC listings do not include this note, and considered that allowing it for this listing could cause confusion with prescribers, suppliers and compounders. The PBAC noted that, under the *National Health Act*, it does not regulate the clinical practise of suppliers when administering or dispensing PBS medicines, but that the conditions of approval for pharmacists include requirements to:

(a) comply with the Pharmaceutical Society of Australia's Code of Ethics for Pharmacists 2017, as existing at the reference time; and

(b) comply with the Pharmaceutical Society of Australia's Professional Practice Standards 2017, as existing at the reference time, in relation to each patient…

(c) maintain a disciplined dispensing procedure that includes:

(i) attention to accuracy of product or ingredient selection; and

(ii) accuracy of calculations; and

(iii) application of accepted techniques for the preparation of pharmaceutical products; and

(iv) appropriate packaging and storage; and

(v) accuracy of final product; and

(vi) adequate information for the patient.

5.6 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. The PBAC suggested the Department could develop a set of biosimilar uptake drivers suitable for EFC medicines.

5.7 The extent of the savings claimed by the sponsor are uncertain and cannot be attributed to this brand of biosimilar trastuzumab alone. The PBAC recalled that it had recommended two trastuzumab biosimilars for listing at its March 2019 meeting and recommended that the Department ask the Medical Oncology Group of Australia (MOGA) to raise awareness amongst oncologists on the various biosimilar trastuzumab brands available on the PBS.

5.8 The PBAC reiterated its previous advice that trastuzumab should be exempt from the Early Supply Rule.

5.9 The PBAC reiterated its previous advice that trastuzumab is not suitable for prescribing by nurse practitioners.

5.10 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 Restriction to be finalised.

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

8 Sponsor's Comment

The sponsor had no comment.