

5.25 TRASTUZUMAB

Powder for I.V. infusion 150 mg, Herzuma[®], Celltrion Healthcare 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 (Herzuma[®]).

2 Requested listing

- 2.1 The submission requested listing Herzuma 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 (but requested streamlined listings across all item codes for Herzuma).
- 2.3 The requested dispensed price for maximum quantity (DPMQ) was calculated based on a 25% reduction in the Herceptin approved ex-manufacturer price (AEMP). Due to the complexity of these calculations, the sponsor requested that the calculated DPMQ be confirmed with the Department during the listing process.
- 2.4 The sponsor requested that Herzuma be 'a' flagged against the reference product.
- 2.5 The item codes relating to the subcutaneous form of Herceptin are not sought for reimbursement.
- 2.6 The Herceptin and Herzuma brands share one common presentation: a single vial with 150 mg powder for reconstitution with sterile water for IV administration. Unlike Herceptin, Herzuma does not have a 60 mg presentation.

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

3 Background

- 3.1 The Herzuma brand of trastuzumab was listed on the Australian Register of Therapeutic Goods (ARTG) on the 17 July 2018.
- 3.2 Herzuma was determined by the TGA to be a biosimilar to the reference brand Herceptin and is approved with the same indications: 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 sponsor requested Authority Required (STREAMLINED) listings across all item codes for Herzuma. Herceptin currently has an Authority Required (Written) and Authority Required (Telephone) listing on the PBS.

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 one head-to-head pivotal trial to support the biosimilarity of Herzuma 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
CT-P6 3.2 NCT02162667	A Phase 3, Double-Blind, Randomized, Parallel-Group, Active-Controlled Study to Compare the Efficacy and Safety of CT-P6 and Herceptin as Neoadjuvant and Adjuvant Treatment in Patients with HER2-Positive Early Breast Cancer	Clinical Study Report (17 April 2017) (CT-P6 3.2, 2017) <i>Refer Attachment 3</i>
	<u>Main publication</u> CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial.	Stebbing J, Baranau Y, Baryash V, Manikhas A, Moiseyenko V, Dzagnidze G, et al. <i>Lancet Oncol.</i> 2017;18(7):917-928 (Stebbing J, 2017).

Source: Table 2.2 of the submission, page 34

- 4.4 Study CT-P6 3.2 was a phase 3, double-blind, randomised, parallel-group, active-controlled study evaluating the efficacy and safety of Herzuma (CT-P6) versus Herceptin in patients with HER2-positive early breast cancer.
- 4.5 The primary efficacy endpoint was the pathological complete response (pCR) at the time of definitive surgery, defined as the absence of invasive tumour cells in the breast and axillary lymph nodes (regardless of ductal carcinoma in situ). For both the per-protocol set (PPS) and intent-to-treat (ITT) population, the proportion of patients achieving pCR in the Herzuma treatment group was similar to that in the Herceptin treatment group. The 95% CI for the estimate of treatment difference for both groups (-0.1238 – 0.0516 and -0.1198 – 0.0480 respectively) was entirely within the equivalence margin of ± 0.15 . The TGA was therefore satisfied that therapeutic equivalence had been met.
- 4.6 The secondary efficacy endpoints were: overall response rate (ORR), defined as the proportion of patients with a best overall response (BOR) of partial response (PR) or complete response (CR) as assessed by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1; breast conservation rate, measured as the proportion of patients who had Lumpectomy (breast conservation surgery); and other pCRs (pCR of the breast only (pCRB) and pCR without ductal carcinoma in situ (DCIS)). The TGA was satisfied that the results in terms of pCRB, pCR of breast and axillary nodes with absence of DCIS, breast conservation rate, and ORR supported the clinical claim that the efficacy of Herzuma is similar to that of Herceptin.
- 4.7 The number of patients who experienced at least one treatment-emergent serious adverse event (TESAE) was similar between the two treatment groups (263 [97.0%] and 265 [95.3%] in the Herzuma and Herceptin treatment groups, respectively). The TGA was satisfied that there were no notable differences between the two treatment groups and that, overall, Herzuma was well tolerated, with a safety profile similar to that of Herceptin.

Clinical claim

- 4.8 The submission claimed that Herzuma is non-inferior in terms of comparative effectiveness, and non-inferior in terms of comparative safety, to Herceptin.
- 4.9 The TGA was satisfied that the biosimilar brand was non-inferior in terms of both efficacy and safety compared to the reference brand.
- 4.10 The PBAC considered that the claim of non-inferior comparative effectiveness and non-inferior comparative safety was reasonable.

Estimated PBS usage & financial implications

- 4.11 The submission stated that the proposed listing of Herzuma is estimated to save the PBS/RPBS \$57.8 million in Year 1, increasing to \$66.5 million in Year 6.
- 4.12 As a minor submission, the financial estimates have not been independently evaluated.
- 4.13 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 Herzuma 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 (Herzuma) 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 clinical equivalence study presented in the submission demonstrated clinical equivalence between Herzuma 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

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“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 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.
- 5.6 The extent of the savings claimed by the sponsor are uncertain and cannot be attributed to this brand of biosimilar trastuzumab.
- 5.7 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.