

**5.22 BEVACIZUMAB,
Solution for I.V. infusion 100 mg in 4 mL
Solution for I.V. infusion 400 mg in 16 mL,
Bevaciptin[®],
Cipla Australia Pty Ltd**

1 Purpose of Submission

- 1.1 The Category 3 submission sought a Section 100 Efficient Funding of Chemotherapy (EFC) Program Unrestricted Benefit listing of the bevacizumab biosimilar Bevaciptin[®] under the same conditions as the PBS-listed bevacizumab biosimilar Mvasi[®].

2 Background

Registration status

- 2.1 Bevaciptin was Therapeutic Goods Administration (TGA) registered on 2 November 2021 and was determined to be a biosimilar to the reference brand of bevacizumab, Avastin[®]. Bevaciptin has the same indications as Avastin and Mvasi.

Previous PBAC consideration

- 2.2 The biosimilar bevacizumab product Mvasi was recommended for Pharmaceutical Benefits Scheme (PBS) listing in November 2020 and was listed in June 2021. The two bevacizumab biosimilar products, Zirabev[®] and Abevmy[®], were recommended by the Pharmaceutical Benefits Advisory Committee (PBAC) in July 2020 and November 2021 respectively. They are not yet listed on the PBS.
- 2.3 Bevaciptin has not been considered by the PBAC.

Current status

- 2.4 Mvasi is the only brand of bevacizumab currently listed on the PBS. The originator brand Avastin was delisted at the request of its sponsor, Roche Products Pty Ltd, at the same time the biosimilar brand Mvasi was listed on 1 June 2021 as an unrestricted listing.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Requested listing

- 3.1 The submission requested listing Bevaciptin solution for I.V. infusion 100 mg in 4 mL and solution for I.V. infusion 400 mg in 16 mL under the same circumstances as the existing unrestricted listings of Mvasi.

- 3.2 The submission requested that Bevaciptin and Mvasi be treated as equivalent ('a'-flagged) to each other for the purpose of substitution. As EFC medicines are governed by the *National Health (Efficient Funding of Chemotherapy) Special Arrangement 2011* and subsection 33(2) allows substitution of brands with the same chemotherapy drug, Bevaciptin and Mvasi will be treated as equivalent to each other.

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

- 4.1 The submission nominated bevacizumab solution for I.V. infusion 100 mg in 4 mL and bevacizumab solution for I.V. infusion 400 mg in 16 mL (Avastin and Mvasi) as the main comparators. This was appropriate noting that the PBAC recommended listing Mvasi on a cost-minimisation basis to Avastin in November 2020.

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item.

Consumer comments

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

Clinical studies

- 5.3 The submission presented the following clinical studies:

Table 1. Clinical studies of Bevaciptin (bevacizumab biosimilar)

Study	Objective(s)	Design	Treatments	Subjects
MB02-A-02-17	The primary objective was to investigate and compare the PK profiles of bevacizumab biosimilar (MB02 - BEVACIPTIN), US-Avastin and EU-Avastin to establish bioequivalence. The study also compared other PK parameters and the safety profiles and immunogenicity of Bevaciptin, US and EU-Avastin	Phase I Multicentre (UK), Double blind, randomised, parallel arm, comparator	Single dose of 3 mg/kg MB02, US-Avastin or EU-Avastin administered by i.v. infusion	Healthy male subjects Randomised: 114 subjects MB02: 38 US-Avastin: 38 EU-Avastin: 38
MB02-A-05-18	As above	Phase I Single centre (Germany), Double blind, randomised,	As above	Healthy male subjects Randomised: 115 subjects

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		parallel arm, comparator		MB02: 38 US-Avastin: 38 EU-Avastin: 38
MB02-A-04-18	The primary objective was to demonstrate PK similarity by the Area under the concentration time curve extrapolated to infinity (AUC(0-∞)) between the 2 study arms, bevacizumab biosimilar MB02 (Bevaciptin) and EU-Avastin. This study also compared other PK parameters and the safety profiles and immunogenicity of MB02 and EU-Avastin	Phase I Single centre (Japan), Double blind, randomised, parallel arm, comparator	Single dose of 3 mg/kg MB02 or EU-Avastin administered by i.v. infusion	Healthy male subjects Randomised: 48 subjects MB02: 24 EU-Avastin: 24
BEVZ92-A-01-13	The primary objective was to compare the PK profile of bevacizumab biosimilar BEVZ92* (Bevaciptin) and EU-Avastin, both administered in combination with fluorouracil, leucovorin and oxaliplatin (FOLFOX) or fluorouracil, leucovorin and irinotecan (FOLFIRI). Additional PK parameters, safety profiles, immunogenicity, ORR, and PFS were also examined	Phase I Open label, randomised, parallel arm, comparator	5 mg/kg BEVZ92 or EU-Avastin administered in combination with FOLFOX or FOLFIRI by i.v. infusion once every two weeks Treatment was administered until disease progression, unacceptable toxicity or withdrawal of consent Maximum duration BEVZ92 arm = 88 weeks (44 cycles) Avastin arm= 122 weeks (61 cycles)	Subjects with metastatic CRC Randomised: 142 subjects BEVZ92: 71 EU-Avastin: 71
MB02-C-02-17	The primary objective was to compare ORR of bevacizumab biosimilar (MB02) (Bevaciptin) and EU-Avastin in patients with NSCLC receiving concomitant carboplatin and paclitaxel. The study also evaluated safety profile, immunogenicity, and other efficacy parameters (PFS and OS) of MB02 (Bevaciptin) compared to EU-Avastin	Phase III Double blind, randomised, comparator	<u>Treatment cycle 1-6</u> 15 mg/kg MB02 or EU-Avastin administered by i.v. infusion with concomitant paclitaxel (200 mg/m ²) and carboplatin (to achieve an area under the plasma concentration time curve of 6 mg/mL × min [AUC ₆]). All treatments administered on Day 1	Subjects with Stage IIIB/IV non-squamous NSCLC Randomised: 627 subjects BEVZ92: 315 EU-Avastin: 312

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			<p>of a 21-day treatment cycle</p> <p>Treatment cycle >7 15 mg/kg MB02 or EU-Avastin administered by i.v. infusion as monotherapy on Day 1 of 21-day cycle</p> <p>Treatment was administered until disease progression, unacceptable toxicity or withdrawal of consent</p> <p>52 weeks maximum duration</p>	
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Source: Bevaciptin (bevacizumab) Category 3 submission, page 10

Abbreviations: CRC: Colorectal cancer; EU: European Union; i.v.: intravenous; MAA; Marketing authorization application; N/A; Not applicable; NSCLC; Non-small cell lung cancer; ORR; Objective response rate; OS; Overall survival; PFS; Progression-free survival; PK: pharmacokinetics; UK; United Kingdom; US: United States

* The drug product in study BEVZ92-A-01-13 was made at a different manufacturing site to the to-be-marketed product. However, it is included here as a relevant reference to the safety data.

5.4 As a Category 3 submission, no evaluation of the clinical evidence was undertaken.

Clinical claim

5.5 The submission claimed that there are five clinical studies supporting the claim of biosimilarity of Bevaciptin to the innovator product Avastin (see Table 1).

5.6 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

5.7 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

5.8 An economic analysis was not provided in this submission.

5.9 The requested price was based on the approved ex-manufacturer price (AEMP) of bevacizumab (Mvasi) solution for I.V. infusion 100 mg in 4 mL and solution for I.V. infusion 400 mg in 16 mL; \$122.00 and \$488.00 respectively.

5.10 The DPMA of bevacizumab as of February 2022 was:

- \$2,282.28 for PBS code 12479T (private hospital use of bevacizumab solution for I.V. infusion 100 mg in 4 mL and solution for I.V. infusion 400 mg in 16 mL); and
- \$2,354.05 for PBS code 12508H (public hospital use of bevacizumab solution for I.V. infusion 100 mg in 4 mL and solution for I.V. infusion 400 mg in 16 mL).

5.11 Equi-effective doses were not presented in this submission. Based on the Product Information for Bevaciptin and Mvasi, the equi-effective doses of Bevaciptin and Mvasi should be: 100 mg of Bevaciptin = 100 mg of Mvasi, and 400 mg of Bevaciptin = 400 mg of Mvasi.

Estimated PBS utilisation and financial implications

5.12 The submission stated that as Bevaciptin would replace bevacizumab treatments currently listed on the PBS at an equivalent cost, the financial impact of the listing would be cost neutral to the PBS. Listing Bevaciptin on the PBS is not expected to increase the overall use of bevacizumab on the PBS as it is expected that Bevaciptin would substitute for Mvasi.

5.13 The market was assumed to be relatively static in terms of change in bevacizumab usage. The submission found that the market had been increasing by 3.47% per year since 2016 which formed the basis for the estimated trajectory of the market.

5.14 The sponsor used their own general commercial experience to estimate the rate of displacement with Bevaciptin over six years (Table 2). As bevacizumab products are all at an equivalent cost, an increased uptake of Bevaciptin will not affect the expected cost neutrality.

5.15 As a Category 3 submission, neither the economic analysis nor the financial estimates analysis has been independently evaluated.

Table 2. Estimated rate of displacement with Bevaciptin over six years

	2022	2023	2024	2025	2026	2027
Rate of displacement of bevacizumab units	10%	12.5%	12.5%	15%	15%	15%

Source: Bevaciptin (Bevacizumab) Category 3 Submission, page 23

For more detail on PBAC’s view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy) listing of bevacizumab (Becaviptin) in the form of solution for I.V. infusion 100 mg in 4 mL and solution for I.V infusion 400 mg in 16 mL, as an additional biosimilar brand under the same conditions as Mvasi. The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of Bevaciptin would be acceptable if it were cost-minimised to Mvasi.

6.2 The PBAC accepted the TGA determination that Bevaciptin is biosimilar to Avastin.

6.3 The PBAC recommended listing Bevaciptin under the same conditions as the PBS-listed bevacizumab biosimilar Mvasi on the basis that both brands are biosimilar to the reference brand of bevacizumab, Avastin.

6.4 The PBAC considered the equi-effective doses of Bevaciptin and Mvasi to be: 100 mg of Bevaciptin = 100 mg of Mvasi and 400 mg of Bevaciptin = 400 mg of Mvasi.

- 6.5 The PBAC noted that EFC medicines are governed by the *National Health (Efficient Funding of Chemotherapy) Special Arrangement 2011*, and that subsection 33(2) allows substitution of brands under the same item code. Therefore, the Bevaciptin and Mvasi brands of bevacizumab should be treated as equivalent to each other.
- 6.6 The PBAC noted that the listing of Bevaciptin on the PBS is expected to be cost neutral and its listing is not expected to increase the overall use of bevacizumab on the PBS.
- 6.7 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Bevaciptin is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over Mvasi, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 6.8 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

- 7.1 Add new item:

Name and form of drug	Proprietary Name, Manufacturer
BEVACIZUMAB bevacizumab solution for I.V. infusion 100 mg in 4 mL bevacizumab solution for I.V. infusion 400 mg in 16 mL	Bevaciptin Cipla Australia Pty Ltd

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

8 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.

9 Sponsor's Comment

The sponsor had no comment.