Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Bevacizumab

Proprietary Product Name: Zirabev

Sponsor: Pfizer Australia Pty Ltd

February 2020

TGA Health Safety Regulation

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.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- 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; it provides 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.

Contents

Common abbreviations

Abbreviation	Meaning
%CV	Percent coefficient of variation
ACM	Advisory Committee on Medicines
ADA	Antidrug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific Annex
AU	Australian
AUC_t	Area under the concentration time curve from time zero to time t
BMI	Body mass index
CDC	Complement dependent cytotoxicity
CHMP	Committee for Medicinal Products for Human Use (EU)
CI	Confidence intervals
C_{max}	Maximum plasma concentration
CPD	Certified Product Details
CR	Complete response
DLP	Data lock point
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency (EU)
EU	European Union
EU-RMP	European Union-risk management plan
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practice (USA)
ITT	Intent to treat

Abbreviation	Meaning
IV	Intravenous
mAb	Monoclonal antibody
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
PBS	Pharmaceutical Benefits Scheme
PF-06439535	Bevacizumab (drug development name)
PFS	Progression free survival
PI	Product Information
PK	Pharmacokinetic(s)
PP	Per protocol
PR	Partial response
PSUR	Periodic safety update reports
RD	Risk difference
RMP	Risk management plan
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
US(A)	United States (of America)
VEGF-A	Vascular endothelial growth factor-A

I. Introduction to product submission

Submission details

Type of submission:	New biosimilar medicine
Decision:	Approved
Date of decision:	28 October 2019
Date of entry onto ARTG:	21 November 2019
ARTG numbers:	309320 and 309321
▼ *Black Triangle Scheme*	No
Active ingredient:	Bevacizumab
Product name:	Zirabev
Sponsor's name and address:	Pfizer Australia Pty Ltd Level 17, 151 Clarence Street Sydney NSW 2000
Dose form:	Concentrated solution for injection
Strengths:	100 mg/4 mL and 400 mg/16 mL
Container:	Vial
Pack size:	One
Approved therapeutic use:	***Metastatic colorectal cancer*** *Zirabev (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.* ***Locally recurrent or metastatic breast cancer*** *Zirabev (bevacizumab) in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer in patients in whom an anthracycline-based therapy is contraindicated. (see Section 5.1 Pharmacodynamic properties – Clinical trials).* ***Advanced, metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC)*** *Zirabev (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent, non-squamous, non-small cell lung cancer.* ***Advanced and/or metastatic renal cell cancer*** *Zirabev (bevacizumab) in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or*

metastatic renal cell cancer.

Grade IV glioma

Zirabev (bevacizumab) as a single agent, is indicated for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy.

Epithelial ovarian, fallopian tube or primary peritoneal cancer

Zirabev (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer

Zirabev (bevacizumab), in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, is indicated for the treatment of patients with first recurrence of platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior bevacizumab or other VEGF-targeted angiogenesis inhibitors.

Zirabev (bevacizumab) in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens, and have not received any prior anti-angiogenic therapy including bevacizumab.

Cervical Cancer

Zirabev (bevacizumab) in combination with paclitaxel and cisplatin is indicated for the treatment of persistent, recurrent or metastatic carcinoma of the cervix. Zirabev (bevacizumab) in combination with paclitaxel and topotecan is an acceptable alternative where cisplatin is not tolerated or not indicated.

Route of administration: Intravenous (IV) infusion

Dosage:

Metastatic colorectal cancer

The recommended dose of Zirabev, administered as an IV infusion, is as follows;

First-line treatment

5 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg of body weight given once every 3 weeks.

Second-line treatment

10 mg/kg of body weight given every 2 weeks or 15 mg/kg of body weight given once every 3 weeks.

It is recommended that Zirabev treatment be continued until progression of the underlying disease.

Locally recurrent or metastatic breast cancer

The recommended dose of Zirabev is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

It is recommended that Zirabev treatment be continued until progression of the underlying disease.

Advanced, metastatic or recurrent non-squamous non-small cell lung cancer

The recommended dose of Zirabev in combination with carboplatin and paclitaxel is 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

Zirabev is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by Zirabev as a single agent until disease progression.

Advanced and/or metastatic renal cell cancer

The recommended dose of is Zirabev 10 mg/kg given once every 2 weeks as an IV infusion. It is recommended that Zirabev treatment be continued until progression of the underlying disease.

Zirabev should be given in combination with IFN alfa-2a (Roferon-A). The recommended IFN alfa-2a dose is 9 MIU three times a week, however, if 9 MIU is not tolerated, the dosage may be reduced to 6 MIU and further to 3 MIU three times a week (see Section 5.1 Pharmacodynamic properties; Clinical trials). Please also refer to the Roferon-A Product Information.

Grade IV glioma

The recommended dose of Zirabev is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

It is recommended that Zirabev treatment be continued until progression of the underlying disease.

Epithelial ovarian, fallopian tube or primary peritoneal cancer

The recommended dose of Zirabev administered as an IV infusion is as follows:

First line treatment

15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles of treatment, followed by continued use of Zirabev as single agent.

It is recommended that Zirabev treatment be continued for a total of 15 months therapy or until disease progression, whichever occurs earlier.

Treatment of recurrent disease

- Platinum sensitive: 15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and paclitaxel for 6 cycles (up to 8 cycles) followed by

continued use of Zirabev as a single agent until disease progression. Alternatively, 15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and gemcitabine for 6 cycles (up to 10 cycles), followed by continued use of Zirabev as single agent until disease progression.

- Platinum resistant: 10 mg/kg body weight given once every 2 weeks when administered in combination with one of the following agents – paclitaxel or topotecan (given weekly) or pegylated liposomal doxorubicin. Alternatively, 15 mg/kg every 3 weeks when administered in combination with topotecan given on days 1-5, every 3 weeks. (See Section 5.1 Pharmacodynamic properties – Clinical trials Study MO22224 for descriptions of the chemotherapy regimens).

It is recommended that treatment be continued until disease progression.

Cervical cancer

Zirabev is administered in combination with paclitaxel and cisplatin or, if cisplatin is not tolerated or not indicated, paclitaxel and topotecan (see Section 5.1 Pharmacodynamic properties – Clinical trials, study GOG-0240 for further details on the chemotherapy regimens).

The recommended dose of Zirabev is 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

It is recommended that Zirabev treatment be continued until progression of the underlying disease.

For further information refer to the Product Information.

Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd (the sponsor) to register Zirabev (bevacizumab) 100 mg/4 mL and 400 mg/16 mL concentrated solution for injection for infusion for the following proposed indications:

Metastatic Colorectal Cancer

Zirabev (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.

Locally recurrent or metastatic Breast Cancer

Zirabev (bevacizumab) in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer in patients in whom an anthracycline-based therapy is contraindicated.

Advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer (NSCLC)

Zirabev (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent, non-squamous, non-small cell lung cancer.

Advanced and/or metastatic Renal Cell Cancer

Zirabev (bevacizumab) in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer.

Grade IV Glioma

Zirabev (bevacizumab) as a single agent, is indicated for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Zirabev (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Zirabev (bevacizumab), in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, is indicated for the treatment of patients with first recurrence of platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior bevacizumab or other VEGF-targeted angiogenesis inhibitors.

Zirabev (bevacizumab) in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens, and have not received any prior anti-angiogenic therapy including bevacizumab.

Cervical Cancer

Zirabev (bevacizumab) in combination with paclitaxel and cisplatin is indicated for the treatment of persistent, recurrent or metastatic carcinoma of the cervix. Zirabev (bevacizumab) in combination with paclitaxel and topotecan is an acceptable alternative where cisplatin is not tolerated or not indicated.

Zirabev has been developed as a biosimilar medicine to the reference product Avastin (bevacizumab). Avastin (bevacizumab) was first approved in Australia in 2005 for the treatment of metastatic colon cancer. Bevacizumab is a recombinant humanised monoclonal antibody that binds to and neutralises the activity of vascular endothelial growth factor-A (VEGF-A), preventing angiogenesis, which in turn prevents tumour growth.

The sponsor requested extrapolation to all the currently approved indications of Avastin in Australia at the time of submission, as listed above.

Regulatory status

Zirabev (bevacizumab) is a new biosimilar medicine for Australian regulatory purposes. The reference product Avastin (bevacizumab) received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 24 February 2005.

At the time the TGA considered this application, a similar application had been approved in the European Union (EU), United States of America (USA) and Canada, and was under consideration in Switzerland (Table 1).

Table 1: International regulatory status of Zirabev as of September 2019

Region	Status	Summary of approved indications
EU	Approved with marketing authorisation valid in the EU from 14 February 2019	• Metastatic cancer of colon/rectum • Metastatic breast cancer • Advanced, metastatic or recurrent non-small cell lung cancer • Advanced/metastatic renal cell cancer • Persistent, recurrent or metastatic carcinoma of the cervix
USA	Approved 27 June 2019	• Metastatic colorectal cancer (not adjuvant) • Locally advanced or metastatic non-small cell lung cancer • Recurrent glioblastoma • Metastatic renal cell carcinoma • Persistent, recurrent or metastatic carcinoma of the cervix
Canada	Approved 14 June 2019	• Metastatic colorectal cancer • Locally advanced, metastatic or recurrent non-small cell lung cancer • Platinum-resistant recurrent epithelial ovarian, fallopian tube and primary peritoneal cancer • Glioblastoma after relapse or disease progression
Switzerland	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 2 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2018-03842-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	31 October 2018
First round evaluation completed	5 April 2019
Sponsor provides responses on questions raised in first round evaluation	31 May 2019
Second round evaluation completed	22 July 2019
Delegate's Overall benefit-risk assessment	11 September 2019
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	28 October 2019
Completion of administrative activities and registration on the ARTG	21 November 2019
Number of working days from submission dossier acceptance to registration decision*	211

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

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

Quality

The quality evaluator discusses biosimilarity in their summary of evaluation, which included the following points:

- During the development of Zirabev bevacizumab, EU and US batches of Avastin bevacizumab were used as the main reference product to demonstrate biosimilarity in terms of quality and nonclinical comparability exercise. An additional bridging comparability study was performed between the EU/US and Australian (AU) Avastin to present EU/US Avastin as representative of the Australian registered innovator product.
- Extensive characterisation studies involving comparison of primary, secondary and tertiary structures, physicochemical properties and biological activities showed that Zirabev and EU/US Avastin are generally similar. However, several differences have been noted as highlighted below:

  - Elevated levels of H chain C-terminal lysine; the C-terminal region of a monoclonal antibody (mAb) is not involved in target antigen binding, therefore no impact on biological activity.
  - Minor differences in the abundance of some low-level N-linked glycoforms; bevacizumab complement dependent cytotoxicity (CDC)/ antibody-dependent cell-mediated cytotoxicity (ADCC) activity is not relevant and therefore these differences are not expected to be clinically relevant.
  - Elevated basic species levels (charge isoforms) due to C-terminal lysine (see above).
  - Lower levels of fragments; this is clinically desirable and therefore, this quantitative difference is not meaningful.
- Overall, the sponsor has demonstrated that Zirabev is comparable to Avastin in terms of structure, species, function and degradation profile (that is, physicochemically and biologically).

To summarise, the quality evaluator has no objections on quality grounds to the approval of Zirabev. In their summary, the quality evaluator states:

- There are no objections on quality grounds to the approval of Zirabev (bevacizumab) 100 mg/4 mL and 400 mg/16 mL concentrated solution for injection for infusion.
- The active substance of Zirabev (bevacizumab) has been developed as a similar biological medicinal product (biosimilar) to that of the currently registered reference product Avastin (bevacizumab).

Nonclinical

The scope of the nonclinical data was pharmacokinetic and repeat-dose toxicity studies with Zirabev and Avastin. Comparative *in vitro* pharmacology studies were contained in quality dossier and evaluated in the quality evaluation report.

The summary, conclusions and recommendation by the nonclinical evaluator included the following information:

- No meaningful differences between Zirabev bevacizumab and Avastin bevacizumab were observed in the comparative pharmacokinetic (PK) and the toxicity study.
- There are no nonclinical objections to the approval of Zirabev provided that the quality evaluator finds that EU-sourced Avastin used in the nonclinical investigations to be comparable to the Australian product, and *in vitro* pharmacology studies demonstrated comparability between Zirabev and Avastin.
- Statements in the draft PI Zirabev that pertain to nonclinical data are consistent with those for the approved Australian PI for Avastin and are therefore acceptable from a nonclinical perspective.

Clinical

There are 3 clinical studies included in the Australian dossier to consider which are summarised briefly below in Table 3.

Table 3: Clinical studies included in the Australian dossier

Study number and design	Study population	Primary objective	Secondary objectives
B7391002 Phase I single dose, single arm, open label study	21 healthy male volunteers	• To assess inter subject variability in single dose PK of bevacizumab-EU	• Assess single dose safety and tolerability of bevacizumab-EU. • Assess PK of bevacizumab-EU after a single dose
B7391001 Phase I double blinded, randomised, 3 arm parallel comparative study	102 healthy male volunteers	• Compare the PK between Zirabev to bevacizumab-EU. • Compare the PK between Zirabev to bevacizumab-US	• Compare the PK of bevacizumab-EU to bevacizumab-US. • Evaluate the single dose safety, tolerability and immunogenicity of Zirabev.
B7391003 Phase III double blind, randomised, parallel group clinical study	719 adult patients with advanced non-squamous non-small cell lung cancer	• Compare overall response rate (ORR) following treatment with Zirabev plus paclitaxel and carboplatin to bevacizumab-EU plus paclitaxel and carboplatin	• Evaluate the safety of Zirabev plus paclitaxel and carboplatin • Evaluate secondary measures of tumour control • Evaluate the population PK of Zirabev and bevacizumab-EU • Evaluate the immunogenicity of Zirabev and bevacizumab-EU

Pharmacokinetics

There are 2 studies in the PK program for Zirabev.

Study B7391002

Study B7391002 was a Phase I, single dose, single arm open label PK variability study conducted at 1 centre in Belgium from 8 April 2013 to 1 August 2013. 21 healthy male volunteers received a single dose (5 mg/kg) of bevacizumab-EU as a 90 minute IV infusion.

In Study B7391002, the mean maximum plasma concentration (C_{max}) was 117 µg/mL. The mean area under the concentration time curve from time zero to time t (AUC_t) was 43020 µg*hour/mL.

The PK of bevacizumab-EU following a single IV dose of 5 mg/kg showed relatively low variability, and appeared to be generally safe and well tolerated in healthy male subjects.

Study B7391001

Study B7391001 was a Phase I, double blinded, randomised, 3 armed parallel comparative study conducted at 1 centre in the US from 24 January 2014 to 5 August 2014. 102 healthy male volunteers (aged 21 to 55 years old) were randomised to receive a single dose (5 mg/kg) of Avastin bevacizumab-EU, Avastin bevacizumab-US or Zirabev bevacizumab as a 90 minute IV infusion.

Table 4 below summarises the PK data.

Table 4: Pharmacokinetic data from Study B7391001

	Zirabev	Avastin bevacizumab-EU	Avastin bevacizumab-US	90% confidence interval for ratio between Zirabev and Avastin bevacizumab-EU
Mean C_{max}	143 µg/mL	137 µg/mL	130 µg/mL	98.36, 110.84
Mean AUC_{inf}	43080 µg*hour/mL	43830 µg*hour/mL	41450 µg*hour/mL	92.16, 105.44

The mean concentration-time profiles, the mean C_{max} and AUC_{inf} were consistent across the three drugs. In addition, the inter-subject variability for each of the PK parameters was similar across the three study drugs, with percent coefficient of variation (%CV) values of 14 to 15%, 12 to 16% and 13 to 19% for C_{max}, AUC_T and AUC_{inf} respectively.

The PK similarity comparisons of Zirabev to bevacizumab-EU and bevacizumab-US demonstrated bioequivalent results; the 90% confidence intervals (CIs) for the test to reference ratios of PK parameters were within the bioequivalence window of 80 to 125%. These results are consistent with Zirabev being pharmacokinetically equivalent to both reference products.

Efficacy

Clinical comparability study

Design

The design of Study B7391003 is outlined in Table 5.

Table 5: Design of Study B7391003

Study B7391003	This was a randomised, double blind, phase 3 study to assess the efficacy, safety, PK and immunogenicity of Zirabev plus paclitaxel-carboplatin compared to bevacizumab-EU plus paclitaxel-carboplatin for first line treatment of patients with advanced non-squamous non-small cell lung cancer. The primary endpoint was to compare the confirmed objective response rate (ORR) by week 19 following the treatment detailed above. The secondary endpoint was to evaluate secondary measures of tumour control, to evaluate the population PK, safety and immunogenicity of Zirabev and bevacizumab-EU.
Patients n=719	719 subjects with advanced non-squamous non-small cell lung cancer were randomised in this study (the ITT population). Subjects were randomised (1:1) to receive at least 4 cycles and no more than 6 cycles of either Zirabev plus paclitaxel-carboplatin or bevacizumab-EU plus paclitaxel-carboplatin. Randomisation was stratified by: • Region • Sex • Smoking history (never/ever) The study was conducted at 216 centres in Australia, Brazil, Bulgaria, Chile, Croatia, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, India, Italy, Japan, Korea, Malaysia, Netherlands, Philippines, Poland, Romania, Russian Federation, South Africa, Spain, Taiwan, Turkey, Ukraine and United States. The study began on 20 April 2015 and the last subject last visit was 22 December 2017.
Zirabev group n= 358	Paclitaxel was administered as the first drug when chemotherapy was administered - 200mg/m^2 by IV infusion over 3 hours on Day 1 in 21 day cycles. Carboplatin was administered as the second drug when chemotherapy was administered. IV infusion dosing based on the use of mathematical formulae. Zirabev was administered at 15mg/kg by IV infusion on Day 1 on each of the 21 day cycles.
Bevacizumab-EU group n= 361	Paclitaxel was administered as the first drug when chemotherapy was administered - 200mg/m^2 by IV infusion over 3 hours on Day 1 in 21 day cycles. Carboplatin was administered as the second drug when chemotherapy was administered. IV infusion dosing based on the use of mathematical formulae. Bevacizumab-EU was administered at 15mg/kg by IV infusion on Day 1 on each of the 21 day cycles.
Endpoints	Primary efficacy endpoint • Objective response rate (ORR), defined as the percent of patients within each treatment group who achieved a best overall response (BOR – including complete response [CR] or partial response [PR]) by Week 19, in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and subsequently confirmed on a follow-up tumour assessment by Week 25, based on the Sponsor's derived BOR using tumour measurements reported by the investigator. Secondary efficacy endpoint • Duration of response (DOR): defined as the time from the date of the first documentation of objective tumour response (CR or PR) to the first documentation of progressive disease (PD) or to death due to any cause in the absence of documented PD. Note: DOR was only evaluated in the primary endpoint population in the patients who achieved a CR or PR by week 19 which was confirmed by week 25. • One-year progression free survival (PFS) rate: defined as the time from date of randomisation to first progression of disease or death due to any cause, whichever occurred first • One year survival rate from randomisation: defined as the time from date of randomisation to death due to any causes.

Equivalence margin

The equivalence margin chosen for the study was based on prior advice received from the EU Committee for Medicinal Products for Human Use (CHMP) regarding trial design and efficacy. The CHMP indicated 'it is considered feasible to plan the trial based on operating characteristics foreseeing a margin of ± 12 to 13% points on the risk difference (RD) scale. Conduct of the trial based on such operating characteristics would be supported.'

Inclusion and exclusion criteria

The inclusion and exclusion criteria used in this study were in line with those according to the Avastin labelling, and considered adequate.

Disposition

Of the 719 patients randomised, 358 patients were randomised to the Zirabev group and 361 patients to the Avastin bevacizumab-EU group. Table 6 below summarises the patient disposition.

Table 6: Study B7391003 patient disposition

Number (%) of Patients	PF-06439535	Bevacizumab-EU	Total
Randomized[a]	358	361	719
Treated	356 (99.4)	358 (99.2)	714 (99.3)
Study			
Discontinued	356 (99.4)	358 (99.2)	714 (99.3)
Randomized not treated	2 (0.6)	3 (0.8)	5 (0.7)
Treatment			
Discontinued[b]	356 (99.4)	358 (99.2)	714 (99.3)
Analyzed for efficacy			
ITT population	358 (100.0)	361 (100.0)	719 (100.0)
PP population[c]	351 (98.0)	355 (98.3)	706 (98.2)
PK population	351 (98.0)	354 (98.1)	705 (98.1)
Analyzed for safety			
Safety population[d]	356 (99.4)	358 (99.2)	714 (99.3)
AEs	356 (100.0)	358 (100.0)	714 (100.0)
Laboratory data	342 (96.1)	348 (97.2)	690 (96.6)

PF-06439535 = Zirabev/sponsor's investigational bevacizumab

Baseline characteristics

The demographic and baseline characteristics were approximately balanced across the two arms, including age, race, ethnicity, body mass index (BMI) and fertility potential. There were more men (n = 467) than women (n = 252) in both arms, likely reflecting the higher burden of disease experienced by men with respect to NSCLC.

Primary endpoint results

Overall response rate

Using the intent to treat (ITT) population, the ORR was similar between both groups; 45.3% in the Zirabev group and 44.6% in the Avastin bevacizumab-EU group, and met the pre-specified equivalence margin of (-13% to 13%). The analysis of ORR provided an unstratified risk ratio of 1.0146 (Zirabev versus bevacizumab-EU) with a 95% CI of 0.8628 to 1.1933 and an unstratified risk difference of 0.6531 (Zirabev versus bevacizumab-EU) with a 95% CI of -6.6% to 7.9%.

Complete responses (CR) were uncommon, but occurred in small numbers in both treatment arms: 9 in the Zirabev group, and 4 in the bevacizumab-EU group. Partial responses (PR) and disease progression were well balanced between the two treatment arms. Responses were assessed radiologically at Week 19 of the study and subsequently confirmed by Week 25.

Secondary endpoint results

Duration of response

As detailed above in the ORR section, the percentage of all patients who achieved objective response (CR or PR) in the ITT population was comparable between the two treatment groups. Using a Cox proportional hazards model with region, gender and smoking history as stratification factors, the hazard ratio when comparing duration of response (DOR) between the Zirabev and Avastin bevacizumab-EU groups was 0.790, with a 95% CI of 0.6-1.039. The stratified log-rank test resulted in a 2 sided p value of 0.0906, indicating no statistically significant difference with respect to DOR between the two treatment groups.

Progression free survival rate

The progression free survival (PFS) in the ITT population was comparable between the two treatment groups; there were 63.7% and 70.6% of patients who had objective progression or had died without objective progression in the Zirabev group and Avastin bevacizumab-EU group respectively at one year. The probability of being progression free at Week 55 was 32.3% (95% CI 26.9 to 37.8%) in the Zirabev group and 30.5% (95% CI 25.3 to 35.8%) in the bevacizumab-EU group. Using a Cox proportional hazards model with region, gender and smoking history as strata, the hazard ratio when comparing PFS between Zirabev and bevacizumab-EU groups was 0.930, with a 95% CI of 0.776 to 1.114. The stratified log-rank test resulted in a 2 sided p-value of 0.4388, indicating no statistically significant difference between the two treatment groups.

1 year survival rate

The percentage of patients who died due to all causes in the ITT population was comparable between the two groups. There were 40.2% and 41.3% of patients who died at 1 year in the Zirabev and Avastin bevacizumab-EU groups respectively. Using a Cox proportional hazards model with region, gender and smoking history as strata, the hazard ratio when comparing OS between the Zirabev and bevacizumab-EU groups was 0.918, with a 95% CI of 0.729 to 1.157. The stratified log-rank test resulted in a 2 sided p-value of 0.4726, indicating no statistically significant difference between the two treatment groups.

Note that all secondary endpoint analyses were also performed in the per protocol (PP) population, and all analyses were consistent with results in the ITT population.

Subgroup analysis

Subgroup analysis revealed no marked differences in ORR between the two treatment arms when the PP population was stratified by variables including smoking history, gender, geographical location, race, prior cancer treatments and Eastern Cooperative Oncology Group (ECOG) performance status. However, results from subgroup analysis are not statistically significant.

Summary of clinical efficacy data

The results of the 2 PK studies and the Phase III clinical comparability study support biosimilarity between Zirabev and Avastin bevacizumab-EU.

Safety

Comparative safety data of Zirabev was derived from two studies; Study B7391001 and Study B7391003.

The safety population consists of a total of 815 subjects:

- 101 subjects from Study B739100;
- 714 subjects from Study B7391003.

Patient exposure

Study B7391001

102 subjects were randomised to one of three arms to receive a single IV dose of 5 mg/kg of either Zirabev (n = 33), Avastin bevacizumab-EU (n = 36) or Avastin bevacizumab-US (n = 33). 1 subject did not receive a dose.

Study B7391003

719 patients were randomised in a 1:1 ratio to receive an IV dose of 15 mg/kg of Zirabev plus paclitaxel and carboplatin (n = 358) or bevacizumab-EU plus paclitaxel and carboplatin (n = 361) for at least four and no more than 6 cycles, followed by the assigned blinded bevacizumab monotherapy.

Adverse events

Study B7391001

Of 101 healthy volunteers that received the study drug, 55 subjects (54.5%) experienced an adverse event (AE); the majority being Grade 1 or 2. The most common treatment-emergent adverse events (TEAEs) were upper respiratory tract infection, headache, dyspepsia, myalgia and diarrhoea. There was only 1 Grade 3 or 4 AE and no Grade 5 events.

Twenty subjects (19.8%) experienced 31 treatment-related AEs; the majority being Grade 1 or Grade 2. The most common treatment related AEs were dyspepsia and macular rash.

Study B7391003

355 subjects received Zirabev, with 344 subjects (97%) experiencing an AE.

358 subjects received Avastin Bevacizumab-EU, with 347 subjects (97%) experiencing an AE.

Table 7, below, further characterises some of these AEs.

Table 7: Study B7391003 adverse events

	Zirabev group (n = 355)	Bevacizumab group (n = 358)
Subjects with adverse events	344 (97%)	347 (97%)
Subjects with serious adverse events	81 (22.8%)	80 (22.3%)
Subjects with Grade 3 or 4 adverse events	159 (44.8%)	159 (44.4%)
Subjects with Grade 5 adverse events	21 (5.9%)	24 (6.7%)

	Zirabev group (n = 355)	Bevacizumab group (n = 358)
Subjects who discontinued ANY treatment due to adverse events	85 (23.9%)	86 (24%)
Subjects who discontinued bevacizumab ONLY due to adverse events	37 (10.4%)	29 (8.1%)
Subjects who discontinued bevacizumab and chemotherapy due to adverse events	30 (8.4%)	28 (7.8%)
Subjects with dose reduction of bevacizumab ONLY due to adverse events	0	0

As expected, the incidence of AEs was high, and comparable between both groups. Serious adverse events (SAEs) were similar in both groups at 22.8% and 22.3% in the Zirabev and Avastin bevacizumab-EU arms respectively. Treatment discontinuation due to adverse events was similar in both groups, at 23.9% and 24% in the Zirabev and bevacizumab-EU arms respectively.

The most commonly reported adverse events were alopecia, anaemia, fatigue, nausea, neutropaenia, thrombocytopaenia and hypertension, with the majority of these being Grade 1 or Grade 2 events.

A total of 343 (48%) of subjects experienced a Grade 3 or higher TEAE; both the Zirabev and bevacizumab-EU arms had an incidence of 48%. The most frequently reported were hypertension (9.3% and 8.7% in the Zirabev and bevacizumab-EU arms respectively), neutropaenia (7.3% and 8.9% in the Zirabev and bevacizumab-EU arms respectively) and anaemia (5.3% and 5.0% in the Zirabev and bevacizumab-EU arms respectively).

Bevacizumab related TEAEs were AEs considered to be related to bevacizumab with or without causal relationship to chemotherapy in accordance with the investigator's assessment. The most frequently reported bevacizumab-related TEAE was hypertension, with 45 (12.6%) of patients in the Zirabev group and 40 (11.2%) of patients in the bevacizumab-EU group experiencing this.

Treatment-emergent adverse event of special interest in Study B7391003

TEAEs of special interest were selected based on the established safety profile of bevacizumab as reported in the Avastin PI.

TEAEs of special interest in Study B7391003 are shown in Table 8.

Table 8: Treatment emergent adverse events of special interest in Study B7391003

	Zirabev (n = 356)	Avastin Bevacizumab-EU (n = 358)	Risk difference	95% Confidence Interval
Arterial thromboembolism	8	7	0.292	-2.009 to 2.640
Bleeding/haemorrhage	83	69	4.041	-1.985 to 10.082

	Zirabev (n = 356)	Avastin Bevacizumab-EU (n = 358)	Risk difference	95% Confidence Interval
Cardiac disorders	29	29	0.046	-4.053 to 4.152
Hypertension (Grade 3 or higher)	34	32	0.612	-3.711 to 4.949
Venous thromboembolism	13	11	0.579	-2.195 to 3.424
Gastrointestinal perforations	0	3	Not reported	Not reported
Wound healing complications	1	0	Not reported	Not reported
Posterior reversible encephalopathy syndrome	0	0	Not reported	Not reported
Proteinuria/nephrotic syndrome	28	34	-1.632	-5.862 to 2.566

Serious adverse events in Study B7391003

The most common SAEs were very similar in both treatment arms in this study (Table 9).

Table 9: Serious adverse events in Study B7391003

	Zirabev (n = 356)	Avastin bevacizumab-EU (n = 358)
Pneumonia	8 (2.2%)	6 (1.7%)
Febrile neutropaenia	5 (1.4%)	7 (2%)
Neutropaenia	4 (1.1%)	6 (1.7%)
Disease progression	4 (1.1%)	5 (1.4%)
Pulmonary embolism	7 (2%)	2 (0.6%)
Anaemia	2 (0.6%)	5 (1.4%)

Grade 5 adverse events (deaths)

There were a similar proportion of deaths occurring in the safety reporting period (during treatment and up to 28 days after the last dose) in the Zirabev and Avastin bevacizumab-EU groups, 5.9% and 6.7% respectively. The majority of deaths were due to disease progression, but there were 6 deaths (acute myocardial infarction, pneumonia, haemoptysis, pulmonary haemorrhage, haemorrhage and death) in the Zirabev group and 1 death (pulmonary haemorrhage) in the bevacizumab-EU group from study treatment

toxicity, which was defined as deaths related to blinded bevacizumab therapy with or without causal relationship to chemotherapy.

Immunogenicity

In Study B7391003, antidrug antibodies (ADAs) were assessed prior to any treatment, as well as post treatment. Comparable results were demonstrated between both treatment groups.

At Baseline, in the safety population, both the Zirabev and bevacizumab-EU groups had a low level of ADAs; both less than 1%. This increased slightly to 1.4% and 1.5% in the bevacizumab-EU and Zirabev groups respectively, post treatment.

Laboratory findings

Haematology

Grade 3 thrombocytopaenia (with respect to shift from Baseline) occurred in 2.9% of subjects in the Zirabev and Avastin bevacizumab-EU arms respectively. Grade 4 thrombocytopaenia occurred in 2.1% and 4% of subjects in the Zirabev and bevacizumab-EU arms respectively.

5% of subjects in the Zirabev arm experienced Grade 3 neutropaenia, compared to 5.5% of subjects in the bevacizumab-EU arm. Grade 4 neutropaenia was experienced by 3.5% of patients in the Zirabev arm, and 6.6% of patients in the bevacizumab-EU arm.

No subjects experienced Grade 4 anaemia, but 5.6% and 5.7% of subjects in the Zirabev and bevacizumab-EU arms respectively experienced Grade 3 anaemia.

Chemistry

The only biochemical finding of note was derangements in sodium level. 29.5% and 21.4% of subjects in the Zirabev and Avastin bevacizumab-EU groups respectively experienced Grade 3 hyponatraemia, with 1% in the Zirabev group and 1.9% of subjects in the bevacizumab-EU group experiencing Grade 4 hyponatraemia.

Summary of clinical safety data

No new safety signals were identified after treatment with Zirabev. The submitted safety data is considered acceptable to support biosimilarity of Zirabev and Avastin bevacizumab.

Risk management plan

The sponsor has submitted European Union-Risk Management Plan (EU-RMP) version 0.11 (date 23 May 2018; data lock point (DLP) 8 May 2017) and Australian Specific Annex (ASA; dated August 2018) in support of this application. In their response to TGA questions, the sponsor has provided EU RMP version 0.3 (date 8 November 2018; DLP 17 January 2018) and ASA version 1.1 (date 31 May 2019).

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 10.[1]

[1] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

Table 10: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Bleeding/haemorrhage	✓	–	✓	–
	Pulmonary haemorrhage	✓	–	✓	–
	Proteinuria	✓	–	✓	–
	Arterial thromboembolic events	✓[1]	–	✓	–
	Hypertension	✓	–	✓	–
	Congestive heart failure	✓[1]	–	✓	–
	Wound healing complications	✓	–	✓	–
	Gastrointestinal perforations	✓	–	✓	–
	Reversible posterior leukoencephalopathy syndrome	✓	–	✓	–
	Neutropenia	✓	–	✓	–
	Venous thromboembolic events	✓	–	✓	–
	Fistula (other than gastrointestinal)	✓	–	✓	–
	Thrombotic microangiopathy	✓	–	✓	–
	Pulmonary hypertension	✓	–	✓	–
	Ovarian failure	✓	–	✓	–
	Hypersensitivity reactions/infusion reactions	✓	–	✓	–
	Gall bladder perforation	✓	–	✓	–
	Peripheral sensory neuropathy	✓	–	✓	–

- All suspected adverse reactions that are reported to the personnel of the company are collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Cardiac disorders (excluding congestive heart failure and arterial thromboembolic events)	✓	–	✓	–
	Osteonecrosis of the jaw	✓[1]	–	✓	–
	Necrotizing fasciitis	✓	–	✓	–
	Adverse events following off-label intravitreal use	✓	–	✓	–
	Embryo-fetal development disturbance	✓	–	✓	–
	Osteonecrosis in children	✓	–	✓	–
Important potential risks	None	–	–	–	–
Missing information	Safety profile of the different treatment combinations in patients with non-squamous non-small cell lung cancer	✓	–	✓	–
	Long-term effects of bevacizumab when used in the pediatric population	✓	–	✓	–
	Safety and efficacy in patients with renal impairment	✓	–	✓	–
	Safety and efficacy in patients with hepatic impairment	✓	–	✓	–
	Use in lactating women	✓	–	✓	–

1 Targeted follow-up questionnaire to align with innovator.

Routine pharmacovigilance activities have been agreed on to address all safety concerns. At this point in time, the summary of safety concerns in the risk management plan (RMP) is satisfactory.

Risk-benefit analysis

Delegate's considerations

Extrapolation of indications

Avastin is currently registered for 9 indications. The clinical comparability study (Study B7391003) was performed in patients with NSCLC. Avastin is licensed for this indication in Australia (although not funded via the Pharmaceutical Benefits Scheme (PBS)).

Guidelines from the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) allow for the possibility that a biosimilar could be approved for one or more of the indications for the reference biological medicine, given sufficient scientific justification, using a 'totality-of-evidence' approach'. The guidelines discuss:

- mechanism of action;
- PK and distribution;
- dose, route-of-administration;
- immunogenicity; and
- toxicity.

A list of EMA guidelines for biosimilars is available online on the EMA website.[2]

With respect to Zirabev:

- The mechanism of action of bevacizumab is the same in all the indications:
  - It is a monoclonal antibody that inhibits the binding of vascular endothelial growth factor to cell receptors on endothelial cells.
- Studies on the reference biological medicine (Avastin) show that the PK is the same for all indications.
- It is administered by the same route (IV) in all indications.
- Data for the reference biological medicine (Avastin) show that bevacizumab has low immunogenicity across all indications.
- The available safety information for the reference biological medicine (Avastin) does not indicate that there are any significant differences in expected toxicities for each condition of use and patient population.

Given this information, extrapolation of indications for Zirabev to all the indications of Avastin in Australia is appropriate.

Proposed action

There are no major barriers to approving Zirabev in Australia foreseen at this present stage.

Advisory Committee Considerations[3]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

[2] European Medicines Agency/European Commission: Guidelines on biosimilars; available on the EMA website under Multidisciplinary: biosimilar.

[3] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Zirabev (bevacizumab) 100 mg/4 mL and 400 mg/16 mL concentrated solution for injection for infusion, indicated for:

Metastatic colorectal cancer

Zirabev (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.

Locally recurrent or metastatic breast cancer

Zirabev (bevacizumab) in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer in patients in whom an anthracycline-based therapy is contraindicated. (see Section 5.1 Pharmacodynamic properties – Clinical trials).

Advanced, metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC)

Zirabev (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent, non-squamous, non-small cell lung cancer.

Advanced and/or metastatic renal cell cancer

Zirabev (bevacizumab) in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer.

Grade IV glioma

Zirabev (bevacizumab) as a single agent, is indicated for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy.

Epithelial ovarian, fallopian tube or primary peritoneal cancer

Zirabev (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer

Zirabev (bevacizumab), in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, is indicated for the treatment of patients with first recurrence of platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior bevacizumab or other VEGF-targeted angiogenesis inhibitors.

Zirabev (bevacizumab) in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens, and have not received any prior anti-angiogenic therapy including bevacizumab.

Cervical Cancer

Zirabev (bevacizumab) in combination with paclitaxel and cisplatin is indicated for the treatment of persistent, recurrent or metastatic carcinoma of the cervix. Zirabev (bevacizumab) in combination with paclitaxel and topotecan is an acceptable alternative where cisplatin is not tolerated or not indicated.

Specific conditions of registration applying to these goods

- The bevacizumab (Zirabev) EU-RMP (version 0.3, date 8 November 2018; data lock point 17 January 2018), with Australian Specific Annex (version 1.1; date 31 May 2019), included with submission PM-2018-03842-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of theapproval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- Batch testing conditions
  - It is a condition of registration that all batches of Zirabev (bevacizumab) imported into Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - It is a condition of registration that up to 5 initial batches of Zirabev (bevacizumab) imported into Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Resultshttp://www.tga.gov.au/ws-labs-index.
  - The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at https://www.tga.gov.au/publication/testing-biological-medicines.
  - This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

- Certified Product Details

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

  The CPD should be emailed to Biochemistry.Testing@health.gov.au as a single PDF document.

- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Zirabev approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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