Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Vegzelma

Active ingredient: Bevacizumab

Sponsor: Celltrion Healthcare Australia Pty Ltd

February 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- 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.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The 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. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACV	Advisory Committee on Vaccines
ARTG	Australian Register of Therapeutic Goods
CI	Confidence interval
CMI	Consumer Medicines Information
DLP	Data lock point
EMA	European Medicines Agency
NSCLC	Non-small cell lung cancer
nsNSCLC	Non-squamous non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PI	Product Information
PK	Pharmacokinetic(s)
PSUR	Periodic safety update report
RMP	Risk management plan
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration

Product submission

Submission details

Type of submission:	New biosimilar medicine
Product name:	Vegzelma
Active ingredient:	bevacizumab
	sponsor's code: CT-P16
Decision:	Approved
Date of decision:	30 August 2023
Date of entry onto ARTG:	5 September 2023
ARTG numbers:	398631 and 398632
, *Black Triangle Scheme*	No
Sponsor's name and address:	Celltrion Healthcare Australia Pty Ltd
	Suite 13-03, 31 Market Street
	Sydney NSW 2000
Dose form:	Solution for intravenous infusion
Strengths:	400 mg/16 mL and 100 mg/4 mL
Container:	Vials
Pack size:	One vial
Approved therapeutic uses:	***Metastatic Colorectal Cancer***
	Vegzelma (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.
	Locally recurrent or metastatic Breast Cancer
	Vegzelma (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 Clinical Trials).
	Advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer (NSCLC)
	Vegzelma (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
	Vegzelma (bevacizumab) in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer.

Grade IV Glioma

Vegzelma (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

Vegzelma (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

Vegzelma (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.*

Vegzelma (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

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

Route of administration:	Intravenous infusion
Dosage:	The recommended dosage is based on multiple factors, including the condition being treated, patient's body weight, line of treatment, and cycle of treatment. Vegzelma should be administered under the supervision of a physician experienced in the use of anti-neoplastic medicinal products. For information regarding dosage, including dose reduction, special populations, and preparation of infusion, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal

malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Celltrion Healthcare Australia Pty Ltd (the sponsor) to register Vegzelma (bevacizumab) 100 mg/4 mL and 400 mg/16 mL solution for intravenous infusion in vials for the following proposed indications:[1]

Metastatic Colorectal Cancer

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

Locally recurrent or metastatic Breast Cancer

Vegzelma (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 Clinical Trials).

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

Vegzelma (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

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

Grade IV Glioma

Vegzelma (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

Vegzelma (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

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

*Vegzelma (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.*

Vegzelma (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

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

Vegzelma (bevacizumab) is a recombinant humanised monoclonal antibody that binds specifically to all soluble forms of human vascular endothelial growth factor (VEGF), neutralising its biological activity and acting as an anti-neoplastic agent. Neutralising the biological activity of VEGF, the key driver of vasculogenesis and angiogenesis, regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

The proposed indications are the same as those approved for the innovator product, Avastin.[2]

With the expiry of the patent for bevacizumab there are now several biosimilar medicines of bevacizumab registered in the ARTG.

Regulatory status

Australian regulatory status

This product is considered a new biosimilar medicine for Australian regulatory purposes.

This submission was submitted through the TGA's Comparable Overseas Regulator B (COR-B) process, using evaluation reports from the European Medicines Agency (EMA).

For COR report-based applications indications must be equivalent, but not necessarily identical. Acceptable differences between the approved and proposed indication are limited to minor changes in the wording or minor differences in expression, as long as the text describes the same dosing range, patient population, and outcome. For a biosimilar product such as Vegzelma, the proposed indication must be identical to the indication approved for the originator in Australia.

In this case Vegzelma is not approved for use in Grade IV Glioma in the European Union but the innovator product Avastin is approved for this indication in Australia. Grade IV Glioma was proposed to be indicated for Vegzelma in Australia. The sponsor was asked to justify the omission in Europe. Additionally, there are minor dosing differences for the advanced,

[2] Bevacizumab, under the tradename Avastin, was first registered in the ARTG in February 2005 for the sponsor Roche Product Pty Ltd. In early 2021 Roche announced that Avastin was to be discontinued. Avastin was registered in the ARTG at the time that the Vegzelma application was submitted to the TGA. However, Avastin was cancelled from the ARTG by Roche on 3 August 2023. The 7 AusPARs published for Avastin for various extensions of indications continue to be available on the TGA website.

metastatic or recurrent non-squamous non-small cell lung cancer (nsNSCLC) indication: the recommended dose of Vegzelma is 7.5 mg/kg or 15 mg/kg every 3 weeks in the EU compared with 15 mg/kg every 3 weeks in Australia. Given these differences, the submission did not fully adhere to the administrative requirements of a COR submission, though it was evaluated according to those requirements.

Foreign regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status at the time of TGA approval

Region	Submission date	Status	Approved indications
European Union	20 January 2022	Approved on 18 August 2022	*Metastatic carcinoma of the colon or rectum* *Metastatic breast cancer* *Non-small cell lung cancer (NSCLC)* *Advanced and/or metastatic renal cell cancer* *Epithelial ovarian, fallopian tube and primary peritoneal cancer* *Cervical cancer*
United Kingdom	28 June 2022	Approved on 16 September 2022	*Metastatic carcinoma of the colon or rectum* *Metastatic breast cancer* *Non-small cell lung cancer (NSCLC)* *Advanced and/or metastatic renal cell cancer* *Epithelial ovarian, fallopian tube and primary peritoneal cancer* *Cervical cancer*
United States of America	30 September 2021	Approved on 27 September 2022	*Metastatic colorectal cancer* *First-line non-squamous non-small cell lung cancer* *Recurrent glioblastoma* *Metastatic renal cell carcinoma* *Persistent, recurrent, or metastatic cervical cancer* *Epithelial ovarian, fallopian tube and primary peritoneal cancer*

Region	Submission date	Status	Approved indications
Korea	29 September 2021	Approved on 28 September 2022	*Metastatic carcinoma of the colon or rectum* *Metastatic breast cancer* *Non-small cell lung cancer (NSCLC)* *Advanced and/or metastatic renal cell cancer* *Epithelial ovarian, fallopian tube and primary peritoneal cancer* *Grade IV Glioma* *Cervical cancer*
Canada	27 December 2021	Approved on 3 January 2023	*Metastatic colorectal cancer* *Locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC)* *Platinum-sensitive recurrent epithelial ovarian, fallopian tube and primary peritoneal cancer* *Platinum-resistant recurrent epithelial ovarian, fallopian tube and primary peritoneal cancer* *Malignant glioma (WHO Grade IV) - glioblastoma*
Brazil	20 January 2022	Under consideration	

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 2: Timeline for Submission PM-2022-04193-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	30 November 2022
First round evaluation completed	15 June 2023
Sponsor provides responses on questions raised in first round evaluation	14 July 2023
Second round evaluation completed	2 August 2023
Sponsor's notification to the TGA of errors/omissions in evaluation reports	9 August 2023

Description	Date
Delegate's[3] Overall benefit-risk assessment	15 August 2023
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	30 August 2023
Administrative activities and registration in the ARTG completed	5 September 2023
Number of working days from submission dossier acceptance to registration decision*	138

* The COR-B process has a 175 working day evaluation and decision timeframe.

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

There are no objections on quality grounds to the approval of Vegzelma.

The sponsor's code for the active ingredient is CT-P16. CT-P16 is a recombinant humanised monoclonal immunoglobulin G1 antibody. Like other immunoglobulins of the G1 subclass, CT-P16 is a glycoprotein with one N-linked glycosylation site in the CH2 domain of each heavy chain. The molecular weight is approximately 149 kDa.

Vegzelma and Avastin are identical with respect to pharmaceutical form, concentration and composition, and route of administration.

Comprehensive characterisation studies support biosimilarity between Vegzelma and EU-approved Avastin with respect to the structural, physicochemical, and biological properties. Proposed Vegzelma lots were shown to be highly comparable to EU-approved Avastin lots.

A bridging study demonstrated comparability between the reference medicinal product registered in Australia using EU-approved and Australia-registered Avastin. Two primary areas of comparability study for EU-approved and Australia-registered Avastin were estimated in the report: physicochemical characterisation including primary, higher order structure, heterogeneity, contents and purity/impurity studies; biological functionality of cell-based potency and binding affinity. Overall, the results demonstrated comparability between EU-approved and Australia-registered Avastin both in physicochemical attributes and biological activities. The characterisation studies supporting biosimilarity between Vegzelma and EU-approved Avastin can be viewed as biosimilarity between Vegzelma and Australia-approved Avastin.

[3] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who decided the submission under section 25 of the Act.

The drug product is a sterile colourless solution containing 400 mg or 100 mg of bevacizumab presented in 20 mL and 4 mL Type I borosilicate glass vials. The nominal concentration of the solution is 25.0 mg/mL. At the proposed storage condition of 2 to 8°C the shelf life is 48 months for the 400 mg drug product and 24 months for the 100 mg drug product.

The Quality evaluation recommended conditions of registration relating to laboratory testing, Certified Product Details, and compliance with Certified Product Details.

Nonclinical

The nonclinical dossier contained comparative analytical method validation studies and a repeat-dose toxicity study. The scope of the nonclinical program is adequate under the relevant EU guideline.[4] These studies were conducted using the EU-sourced Avastin as the reference product. No nonclinical data were provided to the TGA to verify the comparability of the EU-sourced and Australian-sourced Avastin. Comparative in vitro pharmacology studies were submitted as quality data and evaluated as part of the quality evaluation.

A comparative Good Laboratory Practice-compliant 4-week repeat-dose toxicity study was conducted in young cynomolgus monkeys. The toxicity profile of Vegzelma was compared with that of EU-Avastin (10 and 50 mg/kg/day twice weekly). The choice of species and duration of the study were acceptable as they allowed for a sufficient period of time for the development of treatment-related changes seen with the innovator. The intravenous route of administration was used for both test items. No unexpected toxicity findings were observed. No meaningful differences between Vegzelma and EU-Avastin were observed in the comparative toxicity study including toxicokinetics.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- two Phase I studies:
  - CT-P16 1.1, a randomised, double-blind, 3-arm, parallel group, single-dose study to compare the pharmacokinetics (PK) and safety of 3 formulations of bevacizumab (CT-P16, EU-Avastin and US-Avastin) in healthy male subjects. This study provided the pivotal PK outcomes to demonstrate bioequivalence between CT-P16, EU-Avastin, and US-Avastin.
  - CT-P16 1.2, a randomised, double-blind, parallel group, single-dose study to compare the PK and safety of CT-P16 and EU-Avastin in healthy Japanese male subjects.
- one Phase III study, CR-P16 3.1, the therapeutic similarity study. This was a double-blind, randomised, active-controlled, parallel group study to compare efficacy and safety of CT-P16 and EU-Avastin as first-line treatment for metastatic or recurrent nsNSCLC. This study provides comparative PK data (trough serum concentrations following repeated intravenous infusion) and long-term immunogenicity.

[4] Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. Effective in Australia from 17 August 2015. EMA/CHMP/BMWP/403543/2010.

There were no paediatric data. The clinical studies were stated to have been conducted in accordance with Good Clinical Practice Guidelines.

Bioequivalence to innovator product

Study CT-P16 1.1 was the pivotal PK study. Comparative PK results are shown below.

Figure 1: Study CT-P16 1.1 Statistical analysis of serum pharmacokinetic parameters for bevacizumab (ANCOVA) (pharmacokinetic population)

PK Parameters (unit)	Geometric LS Means						CT-P16 /EU-approved Avastin		CT-P16 /US-licensed Avastin		EU-approved Avastin /US-licensed Avastin	
	CT-P16 N = 46		EU-approved Avastin N = 47		US-licensed Avastin N = 48							
	n	Results	n	Results	n	Results	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
$AUC_{0\text{-}inf}$[1] (h·µg/mL)	45	41608.92	46	40054.33	46	42593.20	103.88	[99.04,108.96]	97.69	[93.14, 102.46]	94.04	[89.68, 98.61]
$AUC_{0\text{-}last}$[2] (h·µg/mL)	45	40746.44	47	39058.63	44	41400.01	104.32	[99.70, 109.15]	98.42	[93.99, 103.06]	94.34	[90.14, 98.74]
C_{max} (µg/mL)	46	116.01	47	112.65	48	111.53	102.98	[98.22, 107.97]	104.02	[99.24, 109.03]	101.01	[96.39, 105.85]

Abbreviations: ANCOVA = analysis of covariance; $AUC_{0\text{-}inf}$ = area under the concentration-time curve from time zero to infinity; $AUC_{0\text{-}last}$ = area under the concentration-time curve from time zero to the last quantifiable concentration; CI = confidence interval; C_{max} = maximum serum concentration; EMA = European Medicines Agency; EU = European Union; λz = Terminal elimination rate constant; LS = least squares; PK = pharmacokinetic; US = United States.

Note: Ratio of geometric means was calculated by backed transforming difference of LS means calculated using an ANCOVA model with treatment as a fixed effect and body weight (less than 70 kg versus 70 kg and over) assessed on Day −1 and study site as covariates.

[1] For 4 subjects (one in the CT-P16 treatment group; one in the EU-approved Avastin treatment group; 2 in the US licensed Avastin treatment group), $AUC_{0\text{-}inf}$ values were excluded from statistical analysis since the interval used to determine λz interval was less than 1.5-fold the estimated half-life.

[2] For 5 subjects (one in the CT-P16 treatment group; 4 in the US-licensed Avastin treatment group), $AUC_{0\text{-}last}$ values were excluded from statistical summary since they withdrew, and the last PK samples of these subjects were collected earlier than the planned time (Day 99) according to EMA guidance.

The primary PK parameters were comparable across the 3 treatment groups, with small inter-subject variability. The 90% confidence intervals (CI) for the geometric mean ratios of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max} were contained within the predefined bioequivalence margin of 80.00 to 125.00% (including 100.00%) for CT-P16/EU-Avastin and CT-P16/US-Avastin comparisons. For the comparison of AUCs of EU-Avastin and US-Avastin, the 90% CIs were within 80.00 to 125.00% however did not include 100.00%.

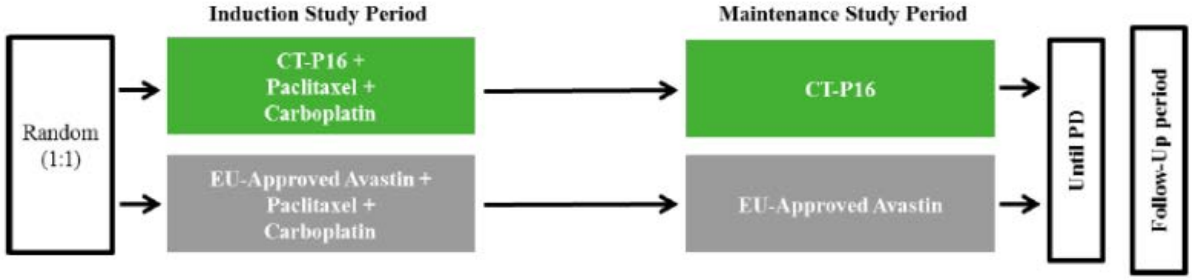
Study CT-P16 1.2 was a supportive PK study enrolling 46 Japanese men. Similarity of CT-P16 and EU-Avastin was demonstrated, with the 90% CIs for the geometric mean ratios of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max} within 80.00 to 125.00%.

Clinical comparison with innovator product

Study CT-P16 3.1 is an ongoing Phase III, randomised, double-blind, active-controlled, parallel-group, multinational, multicentre study comparing the efficacy, PK, and safety of CT-P16 and EU-Avastin when co-administered with paclitaxel and carboplatin as first-line treatment in subjects with metastatic or recurrent nsNSCLC. The study was conducted at 164 sites in 21 countries commencing 1 February 2019.

There were 689 subjects randomised in 1:1 ratio to receive CT-P16 or EU-Avastin 15 mg/kg intravenous every 3 weeks, with randomisation stratified by country, sex, disease status and ECOG Performance Status.[5] Study drug was administered concomitantly with intravenous paclitaxel and intravenous carboplatin during the Induction Study Period (at least 4 and up to 6 cycles, that is, up to 18 weeks).[6] Subjects with controlled disease then entered the Maintenance Study Period and received CT-P16 or EU-Avastin as monotherapy until disease progression or unacceptable toxicity. The study design is shown below.

Figure 2: Study CT-P16 3.1 Schematic of study design



- CT-P16 or EU-Approved Avastin: 15 mg/kg every 3 weeks IV
- Paclitaxel: 200 mg/m^2 every 3 weeks IV
- Carboplatin: Area under the curve 6 every 3 weeks IV
- Induction Study Period: maximum 6 cycles
- Maintenance Study Period: until disease progression, or intolerable toxicity, whichever occurs first
- Follow-Up Period: up to approximately 3 years from the last patient enrolled
- Randomization will be stratified by country, sex (female vs. male), disease status (recurrence vs. metastatic), and ECOG performance score (0 vs. 1).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PD, progressive disease.

The primary objective was to demonstrate that CT-P16 was similar to EU-Avastin in terms of efficacy as determined by objective response rate (ORR) during the Induction Study Period. The primary efficacy endpoint was ORR based on the best overall response during the Induction Study Period by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.[7] Secondary endpoints included response duration, progression-free survival (PFS) and overall survival (OS). A blinded independent tumour review committee was used to review the images for tumour responses. Images were also reviewed locally in a blinded manner for eligibility and treatment practice.

[5] Eastern Cooperative Oncology Group Performance Status: The ECOG has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the patient's daily living, and to determine appropriate treatment and prognosis. The ECOG Performance Status Scale is as follows: Grade 0 = Fully active, able to carry on all pre-disease performance without restriction; Grade 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work; Grade 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; Grade 3 = Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; Grade 4 = Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; Grade 5 = Dead.

[6] Paclitaxel is registered in the ARTG under multiple brand names and for multiple indications. Carboplatin is registered in the ARTG under multiple brand names and for multiple indications.

[7] The Response Evaluation Criteria In Solid Tumours (RECIST) is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in 2000 (and updated in 2009) by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), US National Cancer Institute (NCI) and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumours use RECIST.

The equivalence margin for ORR of −12.5% to 12.5% is similar to the margin previously applied for other bevacizumab biosimilars for demonstrating similar efficacy in first-line NSCLC indication. The margin was constructed using a meta-analysis of historical studies with the reference product and was agreed with EMA via Committee for Medicinal Products for Human Use (CHMP) Scientific Advice. According to the meta-analysis across 4 trials, randomised bevacizumab, added to chemotherapy, increases the probability of objective response by at least 12.89 percentage points (based on lower limit of 95% CIs). Thereby, the proposed margin is believed to preserve at least some positive fraction of the originator's efficacy.

The primary endpoint of the study was met. The risk difference (CT-P16 − EU-Avastin) for ORR at the end of the Induction Study Period was 0.40 (95% CI: −7.02, 7.83) for the intent-to-treat population and −1.90 (95% CI: −9.80, 6.00) for the per-protocol population, with the 95% CIs contained within the pre-specified equivalence margin (−12.5 to 12.5) for both analyses. Efficacy results are shown below.

Figure 3: Study CT-P16 3.1 Objective response rate and Best overall response during the Induction Study Period (central review) (Intent-To-Treat and Per-Protocol populations)

	ITT (Primary)		PP (Supportive)	
	CT-P16 (N=342)	EU-Avastin (N=347)	CT-P16 (N=318)	EU-Avastin (N=303)
Number of Responders (%)	145 (42.4%)	146 (42.1%)	144 (45.3%)	143 (47.2%)
Number of Non-Responders (%)	197 (57.6%)	201 (57.9%)	174 (54.7%)	160 (52.8%)
Objective Response Rate (%) (95% CI)	42.40 (37.16 - 47.64)	42.07 (36.88 - 47.27)	45.28 (39.81 - 50.75)	47.19 (41.57 – 52.82)
Risk Difference Estimate[1] (95% CI)	0.40 (-7.02, 7.83)		-1.90 (-9.80, 6.00)	
Best overall response, n (%)				
Complete response	2 (0.6%)	3 (0.9%)	2 (0.6%)	3 (1.0%)
Partial response	143 (41.8%)	143 (41.2%)	142 (44.7%)	140 (46.2%)
Stable disease	156 (45.6%)	140 (40.3%)	154 (48.4%)	138 (45.5%)
Progressive disease	17 (5.0%)	19 (5.5%)	17 (5.3%)	19 (6.3%)
Inevaluable	3 (0.9%)	3 (0.9%)	3 (0.9%)	3 (1.0%)
Missing	21 (6.1%)	39 (11.2%)	0	0

Note: Objective response rate was defined as the proportion of patients whose best overall response was CR or PR (considered as the 'Responder'). All other patients except responders were considered as non-responder including patients without postbaseline disease assessment.
[1] Logistic regression model included treatment groups (CT-P16 and EU-Avastin) as a fixed effect and region (EMEA vs. America vs. Asia), sex (female vs. male), disease status at baseline (recurrence vs. metastatic), and ECOG performance score at baseline (0 vs. 1) as covariates.
Abbreviations: CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PP, per-protocol; PR, partial response

Comparisons of the secondary efficacy measures of PFS and OS were consistent with the ORR results.

Safety

The Safety Population comprised 876 subjects: 689 nsNSCLC patients in Study CT-P16 3.1; 141 healthy male subjects in Study CT-P16 1.1; and 46 healthy male subjects in Study CT-P16 1.2. Comparative safety data, from Study CT-P16 3.1, was available from 345 nsNSCLC patients randomised to CT-P16 and 344 to Avastin. Of these, 246 patients received at least 6 months exposure (induction plus at least 3 maintenance cycles). A follow-up safety assessment included 148 (21.5%) patients who completed one year of treatment (at least 12 Maintenance Cycles).

Exposure to study drug was not balanced between the 2 treatment groups. After Cycle 1, a higher proportion of subjects were exposed to CT-P16 than EU-Avastin during the Induction Study Period (76.2% CT-P16 versus 69.8% Avastin), and during the Maintenance Study Period up to Cycle 9 when the difference was 34.2% CT-P16 versus 30.5% Avastin. The dose intensities of study drug and chemotherapy were comparable for CT-P16 and EU-Avastin groups.

Figure 4: Study CT-P16 3.1 Overview of adverse events (safety population)

	2nd CSR (Cut-off Date: 21 September 2021)					
	Induction Study Period		Maintenance Study Period		Whole Study Period[1]	
	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)
Total number of TEAEs	2284	2032	665	535	2957	2576
Number (%) of subjects with ≥ 1 TEAE	328 (95.1)	315 (91.6)	175 (50.7)	155 (45.1)	332 (96.2)	320 (93.0)
Related	144 (41.7)	147 (42.7)	82 (23.8)	76 (22.1)	178 (51.6)	174 (50.6)
Unrelated	313 (90.7)	300 (87.2)	147 (42.6)	126 (36.6)	318 (92.2)	307 (89.2)
Number (%) of subjects with ≥ 1 grade 3 or higher TEAE	121 (35.1)	119 (34.6)	49 (14.2)	34 (9.9)	151 (43.8)	144 (41.9)
Related	37 (10.7)	42 (12.2)	16 (4.6)	10 (2.9)	52 (15.1)	49 (14.2)
Unrelated	100 (29.0)	94 (27.3)	36 (10.4)	24 (7.0)	126 (36.5)	115 (33.4)
Number (%) of subjects with ≥ 1 TESAE	48 (13.9)	55 (16.0)	20 (5.8)	22 (6.4)	69 (20.0)	73 (21.2)
Related	14 (4.1)	19 (5.5)	4 (1.2)	4 (1.2)	18 (5.2)	23 (6.7)
Unrelated	38 (11.0)	38 (11.0)	16 (4.6)	18 (5.2)	55 (15.9)	54 (15.7)
Number (%) of subjects with ≥ 1 TEAE leading to study drug discontinuation	34 (9.9)	35 (10.2)	21 (6.1)	19 (5.5)	55 (15.9)	55 (16.0)
Related	12 (3.5)	15 (4.4)	10 (2.9)	6 (1.7)	22 (6.4)	21 (6.1)
Unrelated	22 (6.4)	20 (5.8)	11 (3.2)	13 (3.8)	33 (9.6)	34 (9.9)
Number (%) of subjects with ≥ 1 TEAE leading to death	16 (4.6)	16 (4.7)	6 (1.7)	8 (2.3)	23 (6.7)	24 (7.0)
Related	3 (0.9)	6 (1.7)	0	1 (0.3)	3 (0.9)	7 (2.0)
Unrelated	13 (3.8)	10 (2.9)	6 (1.7)	7 (2.0)	20 (5.8)	17 (4.9)

Abbreviations: CSR = clinical study report

[1] Whole Study Period includes data from Follow-up Period in addition to Induction Study Period and Maintenance Study Period.

At least one treatment-emergent adverse event (TEAE) was reported for a higher proportion of CT-P16 patients (96.2% versus 93.0%), both during the Induction (95.1% versus 91.6%) and Maintenance (50.7% versus 45.1%) Study Periods. The most commonly reported preferred terms (PT)[8] were alopecia (63.8% versus 63.4%), anaemia (31.6% versus 27.0%), neutropenia (21.7% versus 16.0%) and nausea (21.4% versus 18.9%).

There was a 5% or more higher incidence of TEAEs for the CT-P16 group versus EU-Avastin group for the following SOCs:[9] Blood and lymphatic disorders (50.4% versus 42.2%), General disorders and administration site conditions (41.2% versus 34.9%) and Nervous system disorders (52.5% versus 47.4%).

Treatment-emergent adverse events considered related to study drug were reported for a comparable proportion of patients in each group (51.6% versus 50.6%), with proteinuria the most frequent treatment-related PT (10.4% versus 9.3%). There were 43.8% CT-P16 and 41.9% EU-Avastin patients with Grade 3 or higher TEAEs,[10] most commonly neutropenia (10.4% versus 7.3%). The Grade 3 or higher events of dyspnoea (2.0% [n = 7] versus 0.0%) and pulmonary embolism (1.7% [n = 6] versus 0.9% [n = 3]) were higher in the CT-P16 group. There was no clear explanation for the imbalance of pulmonary embolism between the groups, though the incidences in both groups were within the range of other bevacizumab biosimilar studies in nsNSCLC patients and were not considered sufficient to preclude biosimilarity in terms of safety.

As noted in the PIs for other registered bevacizumab medicines, 'Grade 3-5 venous thromboembolic events have been reported in up to 10.6% of patients treated with chemotherapy plus bevacizumab compared with up to 5.4% in patients with chemotherapy alone'.

There were no between-group differences in the proportion of subjects with treatment-emergent serious AEs (20.0% versus 21.2%), treatment-related serious AEs (5.2% versus 6.7%) and deaths (6.7% versus 7.0%). Pneumonia was the most common treatment-emergent serious AE in both groups (2.3% versus 2.9%). Deaths considered related to study treatment by the investigator were lower in the CT-P16 group (0.9% versus 2.0%).

Immunogenicity assessment was considered insufficient by the EMA Assessor, and the adequacy of the assay in Study CT-P16 3.1 questionable, with the EMA Assessor noting the inability of the neutralising antibody assay to detect neutralising antibody at levels lower than 2000 ng/mL in any patients. As the prevalence of anti-drug antibody was low, neither of these issues were pursued further.

[8] The Medical Dictionary for Regulatory Activities (MedDRA) is an internationally used set of terms relating to medical conditions, medicines and medical devices. It was created to assist regulators with sharing information. It is also used by industry, academics, health professionals and other organisations that communicate medical information. In MedDRA, preferred terms (PT) are single concepts for symptoms, signs, disease diagnosis, therapeutic indications, investigations, procedures, and characteristics. There are over 20,000 preferred terms.

[9] In MedDRA, System Organ Class (SOC) is the highest level of the MedDRA terminology for classification of adverse events. There are 27 classes.

[10] The adverse event severity grading used US National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5 scale for assessing adverse event severity. In general: Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe or medically significant but not immediately life-threatening; Grade 4 = Life-threatening consequences; Grade 5 = Death related to AE.

Risk management plan

The sponsor is required to comply with product vigilance and risk minimisation requirements.

The TGA decided a risk management plan (RMP) was not required to be evaluated, as no additional pharmacovigilance activity or additional risk minimisation activity is currently conducted for the innovator, and the biosimilar will have the same indications, dosage form, strengths, and route of administration as the innovator product. See TGA's guidance on 'when an RMP is required'.

Risk-benefit analysis

Delegate's considerations

The sponsor submitted a comparability study between the reference medicinal product registered in Australia using EU-approved and Australia-registered Avastin. Physicochemical and biological comparability between Avastin registered in the EU and Australia has been satisfactorily demonstrated.

The primary objective of a comparative clinical study in a biosimilar development program is not to establish efficacy but to assess for clinically meaningful differences. The primary endpoint selected should be sufficiently sensitive to assess for clinically meaningful differences between the products. As such, it is not scientifically necessary for the primary endpoint in a comparative clinical study to be the same as the endpoint used to demonstrate efficacy of the reference product.[11] Of note the primary efficacy endpoint in the pivotal study to demonstrate efficacy of Avastin in NSCLC was OS with PFS and ORR as secondary endpoints. Additionally, the population selected was suitable for comparisons and the nsNSCLC population was chosen to demonstrate comparability in other biosimilar bevacizumab products. The ORR demonstrated similarity according to protocol-specified bounds, satisfying the requirement for efficacy comparable to that of the originator product.

There were no safety signals to suggest that the safety of Vegzelma would be clinically significantly different from that of the originator bevacizumab product.

The Delegate noted that the clinical evaluator considered that only those indications accepted by the EMA should be eligible for inclusion in the Product Information (PI) for Vegzelma. The Delegate disagreed and accepted the justification provided by the sponsor, which was based on extrapolation of clinical efficacy and safety based on the overall evidence of comparability. It was also noted that the TGA has previously accepted all Australian indications of bevacizumab (Avastin) for other biosimilar bevacizumab products. There is no evidence that bevacizumab has a unique mechanism of action in glioma.

Proposed action

The Delegate proposed to approve Vegzelma.

Advisory Committee considerations

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

[11] He K, Chen H, Gwise T, Casak S, Lemery S, Keegan P, et al. Statistical Considerations in Evaluating a Biosimilar Product in an Oncology Clinical Study. *Clin Cancer Res.* 2016;22(21):5167-5170. doi: 10.1158/1078-0432.CCR-16-1010.

Outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Vegzelma (bevacizumab) 100 mg/4 mL and 400 mg/16 mL solution for intravenous infusion in vials, indicated for:

Metastatic Colorectal Cancer

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

Locally recurrent or metastatic Breast Cancer

Vegzelma (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 Clinical Trials).

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

Vegzelma (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

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

Grade IV Glioma

Vegzelma (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

Vegzelma (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

Vegzelma (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.*

Vegzelma (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

Vegzelma (bevacizumab) in combination with paclitaxel and cisplatin is indicated for the treatment of persistent, recurrent or metastatic carcinoma of the cervix. Vegzelma (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

- Laboratory testing and compliance with Certified Product Details (CPD):
  - All batches of Vegzelma bevacizumab 100 mg/4 mL and 400 mg/16 mL concentrate solution for intravenous infusion, vial supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the CPD.
  - When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.
- 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-argpmguidance-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.

Attachment 1. Product Information

The Product Information (PI) approved with the submission for Vegzelma which is described in this AusPAR can be found as Attachment 1. It may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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Reference/Publication #