KEY MESSAGE

In-use stability of Vegzelma™ was sustained in all tested dilution factors and in both PP/PE infusion bags after refrigerated storage for 60 days at 5±3°C followed by 7 days exposure at 30±2°C/75±5% RH.[4,*]

*To reduce microbiological hazard, the product should be used as soon as practicable after preparation. If storage is necessary, in-use storage times and conditions are the responsibility of the user and would not be longer than 24 hours at 2–8°C.[13]

PE, polyethylene; **PP,** polypropylene; **RH,** relative humidity.

Additional Data Sheets and Consumer Medicine Information can be obtained from the Medsafe website at https://www.medsafe.govt.nz/medicines/infosearch.asp

HEALTHCARE CELLTRION

In-Use Stability Data of **Vegzelma™**

HEALTHCARE CELLTRION

Vegzelma™ bevacizumab

Why is in-use stability important?

In-use stability is an important tool to assess the quality of drug substances which may vary with time under the influence of a variety of factors.

Vegzelma™ was tested to demonstrate its in-use stability through a lot of evaluation factors under different dilution conditions required for IV infusion.[4]

- Regulatory agencies define the purpose and importance of in-use stability as follows:

European Medicines Agency

The purpose of in-use stability testing is to establish – where applicable – a period of time during which a medicinal product can be used whilst retaining quality within an accepted specification once the container is opened.[1]

World Health Organization

The purpose of in-use stability testing is to provide information for the labelling on the preparation, storage conditions and utilization period of a medicinal product after opening, reconstitution or dilution of a solution.[2]

Ministry of Food and Drug Safety

The purpose of in-use stability testing is to provide information for the labeling on the preparation, storage conditions and duration of quality within accepted specifications after opening.[3]

In-use stability evaluation factors[4]

General	Purity/Impurity	Content	Potency
• Clarity • Color • Visible particles • pH • Osmolality • Sub-visible particles	• CE-SDS (Non-reduced) • CE-SDS (Reduced) • IEC-HPLC • SEC-HPLC (Diluted)	• Protein concentration (UV_{280}) (Before/After)	• HUVEC assay • VEGF binding ELISA

The results of dilution for infusion stability study demonstrate that there was no significant change in the quality of Vegzelma™ under the various conditions. (storage temperature, infusion bags)[4]

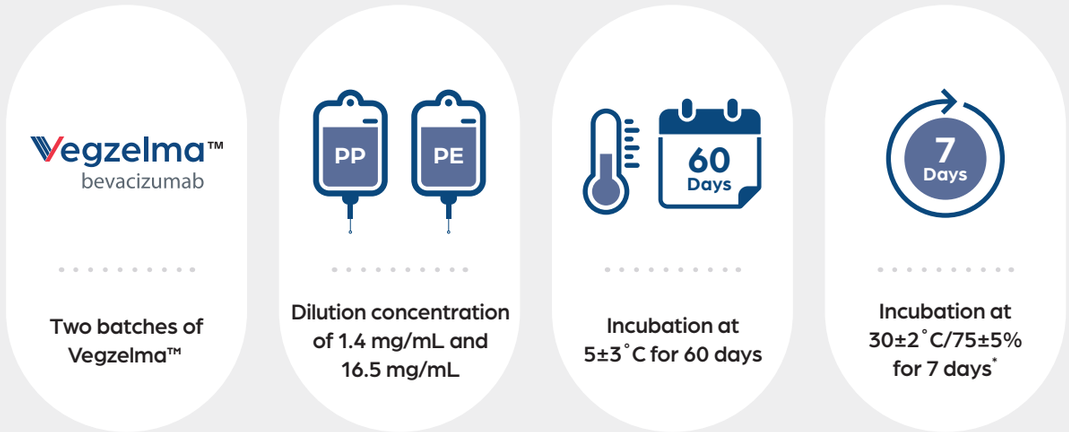
CE-SDS, capillary electrophoresis sodium dodecyl sulfate; **ELISA,** enzyme-linked immunosorbent assay; **HPLC,** high performance liquid chromatography; **HUVEC,** human umbilical vein endothelial cells; **IEC,** ion exchange chromatography; **IV,** intravenous; **SEC,** size exclusion chromatography; **UV,** ultraviolet; **VEGF,** vascular endothelial growth factor.

In-use stability testing:

How was the in-use stability of Vegzelma™ tested?

Study Design[4]

- ✓ Two batches of Vegzelma™ 400 mg were used for in-use stability testing.
- ✓ Diluted Vegzelma™ solutions of 1.4 mg/mL and 16.5 mg/mL were prepared in 0.9% sodium chloride solution in either PP or PE infusion bags.
- ✓ Samples were incubated for 60 days at 5±3˚C and subsequently for 7 days at 30±2˚C/75±5% RH.



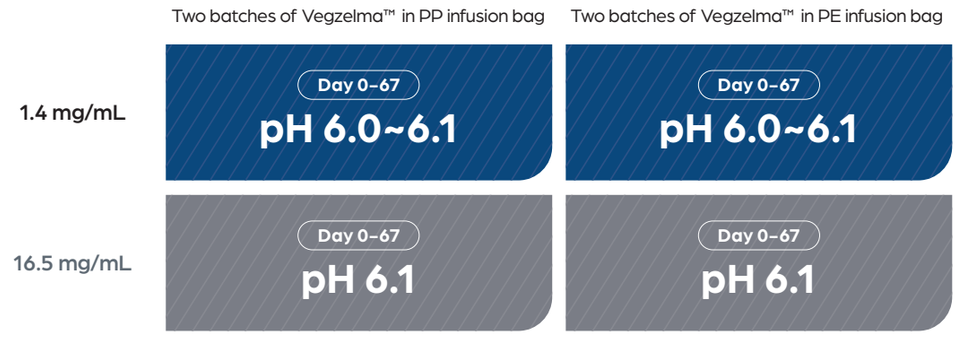
*In consideration such as equipment temperature, it is reflected a period of up to 7 days at temperatures as not exceeding 30˚C in EU SmPC.

EU, European Union; **PE,** polyethylene; **PP,** polypropylene; **RH,** relative humidity; **SmPC,** summary of product characteristics.

1 The results of physicochemical analysis showed that in-use stability of Vegzelma™ for IV infusion was not affected under the following conditions.[4–12]

pH[4–12]

- ✓ The pH of Vegzelma™ in both infusion bags ranged between 6.0–6.1 and was stable for up to 67 days.



Sub-visible particles[4–12]

- ✓ There was no significant trend of sub-visible particles during the dilution for infusion storage period.

Presence of sub-visible particles (number of particles/mL) following preparation of Vegzelma™ for IV infusion

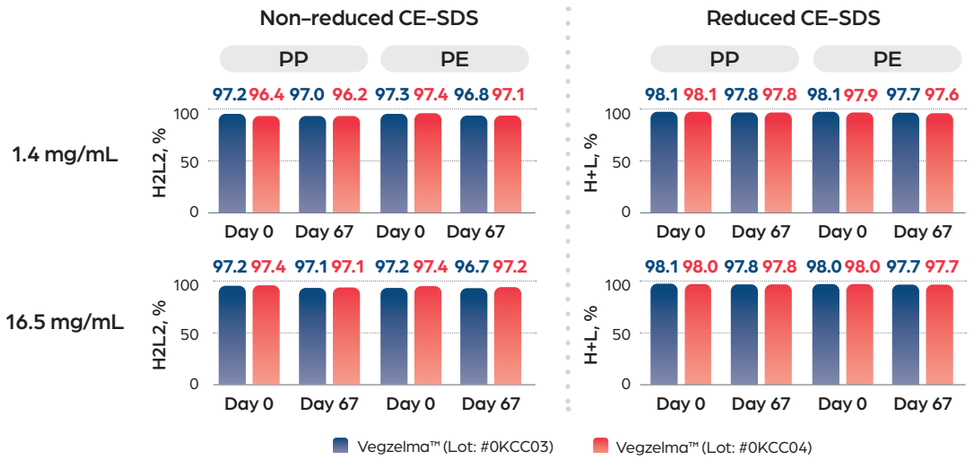
Test results (number of particles/mL)		≥10 µm				≥25 µm			
		Vegzelma™ (Lot: #0KCC03)		Vegzelma™ (Lot: #0KCC04)		Vegzelma™ (Lot: #0KCC03)		Vegzelma™ (Lot: #0KCC04)	
Target dilution concentration. (mg/mL)	Infusion bag	Day 0	Day 67	Day 0	Day 67	Day 0	Day 67	Day 0	Day 67
1.4	PP	5	1	6	1	0	0	0	0
	PE	2	2	4	4	0	0	0	0
16.5	PP	1	5	28	6	0	0	2	1
	PE	3	4	4	14	0	0	0	0

IV, intravenous; **PE,** polyethylene; **PP,** polypropylene; **RH,** relative humidity.

2 The proportions of molecular weight variants of Vegzelma™ remained stable under the below tested in-use conditions.[4–12]

CE-SDS[4–12]

✓ CE-SDS test results were stable in both types of infusion bag for 67 days.



SEC-HPLC (Diluted)[4–12]

✓ As a result of SEC-HPLC analyses, it was confirmed that the recovery result of the monomer was stable at ≥97.6%.

	Two batches of Vegzelma™ in PP infusion bag	Two batches of Vegzelma™ in PE infusion bag
1.4 mg/mL	Day 0–67 **97.6~98.1%**	Day 0–67 **97.7~98.2%**
16.5 mg/mL	Day 0–67 **98.0~98.2%**	Day 0–67 **98.0~98.2%**

CE-SDS, capillary electrophoresis sodium dodecyl sulfate; **PE,** polyethylene; **PP,** polypropylene; **SEC-HPLC,** size exclusion chromatography-high performance liquid chromatography.

3 The results of potency analysis showed that Vegzelma™ remained stable under in-use conditions.[4–12]

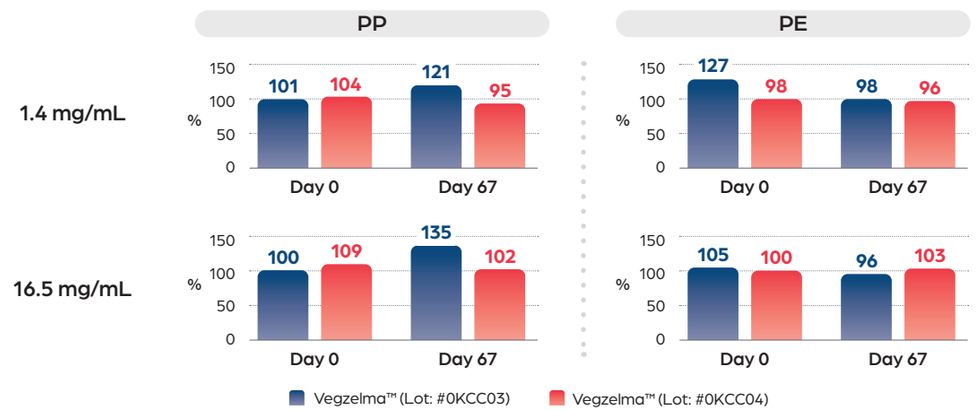
HUVEC assay[4–12]

✓ The results of HUVEC assay showed that binding rate was stable regardless of infusion bag type and dilution concentration.

	Two batches of Vegzelma™ in PP infusion bag	Two batches of Vegzelma™ in PE infusion bag
1.4 mg/mL	Day 0–67 **84~109%**	Day 0–67 **89~110%**
16.5 mg/mL	Day 0–67 **78~108%**	Day 0–67 **85~105%**

VEGF binding ELISA[4–12]

✓ Although there was fluctuation in VEGF binding ELISA results, there was no significant trend during the dilution for infusion storage period.



ELISA, enzyme-linked immunosorbent assay; **HUVEC,** human umbilical vein endothelial cells; **PE,** polyethylene; **PP,** polypropylene; **VEGF,** vascular endothelial growth factor.

IMPORTANT INFORMATION ABOUT VEGZELMA (BEVACIZUMAB)

From 1 March 2025, Vegzelma will be funded under special authority criteria for: recurrent respiratory papillomatosis, ocular conditions, unresectable hepatocellular carcinoma (liver cancer) and advanced ovarian cancer. By 1 August 2025, all people with recurrent respiratory papillomatosis will need to have transitioned to the Vegzelma brand of bevacizumab. For people with ocular conditions, 'any brand' of bevacizumab will continue to be funded in Health New Zealand | Te Whatu Ora hospitals.

Before prescribing, please refer to the data sheet available on the Medsafe website at www.medsafe.govt.nz

Vegzelma (bevacizumab) is a Prescription Medicine containing 100mg or 400mg bevacizumab concentrate for solution for infusion.*

INDICATIONS: Treatment of Metastatic Colorectal Cancer in combination with fluoropyrimidine-based chemotherapy; Treatment of Advanced and/or metastatic Renal Cell Cancer in combination with interferon alfa-2a; Treatment of Advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer (NSCLC) in combination with carboplatin and paclitaxel for first-line treatment; Treatment of Metastatic Breast Cancer in combination with paclitaxel for first-line treatment in patients in whom an anthracycline-based therapy is contraindicated; Treatment of Relapsed high grade malignant Glioma as a single agent; Treatment of Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer in combination with carboplatin and paclitaxel for first-line treatment of advanced (FIGO stages IIIB, IIIC and IV) disease, in combination with carboplatin and paclitaxel for recurrent, platinum-sensitive disease, in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin for recurrent, platinum-resistant disease in patients who have received no more than two prior chemotherapy regimens and have not received any prior anti-angiogenic therapy including bevacizumab; Treatment of Cervical Cancer in combination with paclitaxel and cisplatin or paclitaxel and topotecan. **CONTRAINDICATIONS:** Vegzelma is contraindicated in patients with: known hypersensitivity to any components of the product; Chinese hamster ovary cell products or other recombinant human or humanised antibodies and NSCLC patients with recent pulmonary haemoptysis. **PRECAUTIONS:** Not for IV push, bolus administration; Vegzelma solutions should not be administered or mixed with dextrose or glucose solutions; gastrointestinal (GI) perforations and fistulae and non-GI fistulae: Discontinue for GI perforations, tracheo-esophageal fistula or any Grade 4 fistula. Consider discontinuation for internal fistula not arising in the GI tract; hypertension: Adequately control pre-existing hypertension before starting Vegzelma. Monitor and treat and discontinue if medically significant hypertension cannot be adequately controlled with antihypertensive therapy or if patient develops hypertensive crisis or hypertensive encephalopathy; wound healing complications: Do not initiate for at least 28 days following major surgery or until surgical wound is fully healed. Withhold treatment in patients who experience wound healing complications or are undergoing elective surgery; thromboembolism: Discontinue Vegzelma in patients who develop Arterial Thromboembolic Events (ATE). Exercise caution when treating patients receiving bevacizumab plus chemotherapy with a history of ATE, diabetes or ≥ 65 years. Discontinue Vegzelma in patients with Grade 4 Venous Thromboembolic Events (VTE) including pulmonary embolism. Monitor for ≤ Grade 3 VTE; haemorrhage: Discontinue in patients with Grade 3 or 4 bleeding during bevacizumab therapy. Monitor for signs and symptoms of CNS bleeding and discontinue in case of intracranial bleeding. Exercise caution before initiating Vegzelma therapy in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism; pulmonary heamorrhage: Patients with recent pulmonary haemorrhage/haemoptysis should not be treated with bevacizumab; aneurysms and artery dissections: Before initiating bevacizumab carefully consider this risk in patients with risk factors such as hypertension or history of aneurysm; posterior reversible encephalopathy syndrome (PRES): Discontinue if patient develops PRES and treat specific symptoms including control of hypertension; proteinuria: Test for proteinuria prior to starting bevacizumab. Withhold until < 2 g/24h urine protein; congestive heart failure (CHF): Exercise caution when treating patients with significant cardiovascular disease or pre-existing CHF; neutropenia: Increased rates of severe neutropenia, febrile neutropenia or infection with severe neutropenia (including some fatalities) have been observed in patients treated with myeolotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone; hypersensitivity reactions and infusion reactions: Close observation of patient during and following administration of bevacizumab is recommended. Discontinue for anaphylactic reaction or Grade ≥3 infusion-related reaction; ovarian failure: New cases of ovarian failure were reported more frequently in patients receiving bevacizumab. After discontinuation of bevacizumab treatment, ovarian function recovered in a majority of women; Fertility, pregnancy and lactation: Women of childbearing potential should consider adequate contraception to prevent pregnancy and continue use for ≥ 6 months after last dose. Not recommended for use during pregnancy and lactation. Breastfeeding should be discontinued for ≥ 6 months following from last dose. Long term effects of treatment with bevacizumab on fertility are unknown. **INTERACTIONS:** In two clinical studies of metastatic renal cell carcinoma, microangiopathic haemolytic anaemia was reported in 7/19 patients treated with bevacizumab (10 mg/kg every two weeks) and sunitinib malate (50 mg daily) combination. All these findings were reversible upon discontinuation of bevacizumab and sunitinib malate. **ADVERSE EFFECTS:** Most common: febrile neutropenia, leucopenia, neutropenia, thrombocytopenia, anorexia, hypomagnesaemia, hyponatraemia, peripheral sensory neuropathy, dysgeusia, headache, dysarthria, eye disorder, lacrimation increased, hypertension, dyspnoea, epistaxis, rhinitis, cough, diarrhoea, nausea, vomiting, abdominal pain, constipation, stomatitis, rectal haemorhage, ovarian failure, exfoliative dermatitis, dry skin, skin discolouration, arthralgia, proteinuria, asthenia, fatigue, pyrexia, asthenia, pain, mucosal inflammation, weight decreased; Common: sepsis, abscess, cellulitis, infection, anaemia, lymphopenia, hypersensitivity, anaphylactic reactions, infusion-related reactions, dehydration, hyponatraemia, cerebrovascular accident, syncope, somnolence, headache, cardiac failure (congestive), supraventricular tachycardia, thromboembolism (arterial), deep vein thrombosis, haemorrhage, pulmonary embolism, dyspnoea, hypoxia, epistaxis, intestinal perforation (Ileus), intestinal obstruction, recto-vaginal fistulae, gastrointestinal disorder, stomatitis, proctalgia, palmar-plantar erythrodysaesthesia syndrome, muscular weakness, myalgia, arthralgia, back pain, proteinuria, urinary tract infection, pain, lethargy, mucosal inflammation, pelvic pain. **DOSAGE AND ADMINISTRATION:** Withdraw the necessary amount of Vegzelma and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final Vegzelma solution should be kept within the range of 1.4-16.5 mg/mL. The initial Vegzelma dose should be delivered over 90 minutes as an IV infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. Dose reduction of Vegzelma for adverse reactions is not recommended. Metastatic Colorectal Cancer*:* First-line treatment: 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks; Second-line treatment: 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks until disease progression. Advanced and/or Metastatic Renal Cell Cancer: 10 m/kg every 2 weeks until disease progression. Vegzelma should be given in combination with IFN alfa-2a (Roferon-A ®). Advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer (NSCLC)*:* 15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles of treatment followed by Vegzelma as a single agent until disease progression. Metastatic Breast Cancer: 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks until disease progression. Relapsed high grade malignant Glioma: 10 mg/kg every 2 weeks until disease progression. Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer*:* Front-line treatment: 15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Vegzelma as a single agent for a total of 15 months therapy or until disease progression, whichever occurs earlier; Treatment of recurrent, platinum-sensitive disease: 15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel for 6 cycles (up to 8 cycles) followed by continued use of Vegzelma as a single agent until disease progression; Treatment of recurrent, platinum-resistant disease: 10 mg/kg every 2 weeks in combination with one of the following agents - paclitaxel, topotecan (weekly) or pegylated liposomal doxorubicin. Alternatively, 15 mg/kg every 3 weeks in combination with topotecan given on days 1-5, every 3 weeks until disease progression. Cervical Cancer*:* 15 mg/kg every 3 weeks, in combination with paclitaxel and cisplatin or paclitaxel and toptecan until disease progression.
*not all dosage forms might be available at the same time.

Date of preparation: Jan-2025 (based on Data Sheet last updated 3-Oct-2024). Material last updated 10-Feb-2025, TAPS BG4652, February 2025

References: 1. The European Agency for the Evaluation of Medicinal Products. Note for Guidance on In-use Stability Testing of Human Medicinal Products. **2.** WHO guidelines on stability testing of active pharmaceutical ingredients and finished pharmaceutical products. Annex 10, WHO Technical Report Series 1010, 2018. **3.** National Institute of Food and Drug Safety Evaluation. Guidelines for setting the period of use after opening the drug product. **4.** Data on file I. Celltrion Healthcare. **5.** Data on file II. Celltrion Healthcare. **6.** Data on file III. Celltrion Healthcare. **7.** Data on file IV. Celltrion Healthcare. **8.** Data on file V. Celltrion Healthcare. **9.** Data on file VI. Celltrion Healthcare. **10.** Data on file VII. Celltrion Healthcare. **11.** Data on file VIII. Celltrion Healthcare. **12.** Data on file IX. Celltrion Healthcare. **13.** Medsafe - Vegzelma New Zealand Data Sheet v04-0624

To allow for quick identification of new safety information, kindly report any side effects you may observe at the following contact channels.
Phone: 0800 838 899 or Email: medinfo-nz@celltrionhc.com

Celltrion Healthcare New Zealand Ltd. NZBN: 9429047096424
Floor 1, 103 Carlton Gore Road, Newmarket,
Auckland, 1023, New Zealand
www.celltrionhealthcare.com