20-21-22 MARCH 2024 Bordeaux
Sustainable healthcare - Opportunities & strategies

Poster No.: 3PC-014
ATC code: L01- ANTINEOPLASTIC AGENTS

# PHYSICOCHEMICAL STABILITY OF BEVACIZUMAB 25 MG/ML CONCENTRATE (VEGZELMA®) IN ORIGINAL GLASS VIALS AFTER FIRST OPENING

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## Background and Importance

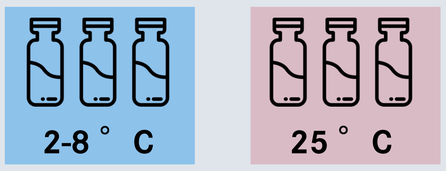
Various EMA-approved bevacizumab biosimilars are marketed. Stability data beyond those given in the SmPCs are required to promote efficient centralized preparation of ready-to-administer bevacizumab infusion solutions and to avoid wastage. Of note, stability data of bevacizumab originator and biosimilar products are product-specific and not generalizable. So far, information regarding prolonged stability of the bevacizumab biosimilar product Vegzelma® (Celltrion) after first opening in punctured vials is missing.

## Aim and Objectives

The aim of the study was to investigate the physicochemical stability of bevacizumab 25 mg/mL concentrate (Vegzelma®) punctured and stored in the original glass vial at two different storage temperatures over a 28-day period.

## Materials and Methods

**Vegzelma® 25 mg/mL concentrate in original glass vials punctured at day 0**




- **Sampling time points immediately (day 0), day 1, 7, 14, 21, 28**
- **Orthogonal analysis**

**Stored light-protected for 28 days**

### Size exclusion chromatography (SEC) assay

- Validation based on ICH Q2 (R1)
- Column: TSKgel G3000SWXL 7.8 mm x 300 mm, 5 µm, Tosoh Bioscience
- Injection volume: 15 µL
- Flow rate: 1.0 mL/min
- Detection wavelength: 280 nm
- Mobile phase: PBS buffer (150 mM)
- Run time: 20 min
- Elution mode: isocratic

### Ion exchange chromatography (IEC) assay

- Validation based on ICH Q2 (R1)
- Column: Propac WCX-10 BioLC Analytical 4 mm x 250 mm, 10 µm, Thermo Fisher Scientific
- Injection volume: 20 µL
- Flow rate: 0.8 mL/min
- Detection wavelength: 280 nm
- Mobile phase: A: 20 mM 2-(N-Morpholino)ethanesulfonic acid (MES) + 60 mM NaCl pH 6.0
  B: 20 mM MES + 180 mM NaCl pH 6.0
- Run time: 51 min
- Elution mode: gradient

### Dynamic light scattering (DLS) particle analysis

- System: Zetasizer Nano – ZS (Malvern Instruments Ltd.)
- Cuvettes: UV cuvette mikro, 12.5 x 12.5 x 45 mm
- Refractive index: 1.342
- Viscosity: 1.0178 mPa·s

- **pH measurement**
- **Visual inspection**

**Funding:** The study was funded in part by Celltrion.

## Results

Tab. 1: Physicochemical stability of **Vegzelma® 25 mg/mL concentrate stored at 2-8 ° C** over 28 days.
DLS: mean hydrodynamic diameter (mHD), (n=3); SEC: mean % rate of remaining bevacizumab monomer (initial concentration on day 0 = 100%) ± RSD (n=9); IEC: mean % peak area of the total peak areas (100%) ± RSD (n=9)

| Time point | DLS | SEC | IEC | | | | |
|---|---|---|---|---|---|---|---|
| | mHD | Intact monomer | Acidic Peak (1) | Acidic Peak (2) | Main Peak (3) | Basic Peak (4) | Basic Peak (5) |
| [day] | [nm] | [%] | Peak area [%] | Peak area [%] | Peak area [%] | Peak area [%] | Peak area [%] |
| 0 | 14.02 | 100.00 (± 0.3) | 3.44 (± 1.78) | 8.76 (± 0.92) | 80.41 (± 0.21) | 4.12 (± 7.03) | 3.27 (± 3.82) |
| 1 | 13.47 | 99.72 (± 0.3) | - | - | - | - | - |
| 7 | 14.04 | 99.88 (± 0.3) | 3.94 (± 9.33) | 8.54 (± 3.02) | 79.35 (± 0.61) | 4.38 (± 4.96) | 3.80 (± 5.20) |
| 14 | 14.24 | 100.00 (± 0.4) | 3.68 (± 1.91) | 8.66 (± 0.67) | 79.97 (± 0.38) | 4.37 (± 5.85) | 3.31 (± 0.89) |
| 21 | 13.84 | 99.68 (± 0.7) | 3.52 (± 3.53) | 8.62 (± 1.84) | 79.73 (± 0.67) | 4.83 (± 8.92) | 3.30 (± 7.00) |
| 28 | 14.74 | 98.56 (± 1.0) | 3.66 (± 1.61) | 8.20 (± 2.86) | 80.15 (± 0.33) | 4.56 (± 7.18) | 3.43 (± 1.30) |

Tab. 2: Physicochemical stability of **Vegzelma® 25 mg/mL concentrate stored at 25 ° C** over 28 days.
DLS: mean hydrodynamic diameter (mHD), (n=3), SEC mean % rate of remaining bevacizumab monomer (initial concentration on day 0 = 100%) ± RSD (n=9), IEC: mean % peak area of the total peak areas (100%) ± RSD (n=9)

| Time point | DLS | SEC | IEC | | | | |
|---|---|---|---|---|---|---|---|
| | mHD | Intact monomer | Acidic Peak (1) | Acidic Peak (2) | Main Peak (3) | Basic Peak (4) | Basic Peak (5) |
| [day] | [nm] | [%] | Peak area [%] | Peak area [%] | Peak area [%] | Peak area [%] | Peak area [%] |
| 0 | 13.60 | 100.00 (± 0.2) | 3.60 (± 5.63) | 9.32 (± 4.27) | 79.76 (± 0.62) | 4.04 (± 6.00) | 3.27 (± 6.24) |
| 1 | 13.43 | 98.96 (± 0.3) | - | - | - | - | - |
| 7 | 13.81 | 99.04 (± 0.3) | 4.29 (± 3.79) | 8.87 (± 1.01) | 79.08 (± 0.59) | 4.29 (± 5.57) | 3.46 (± 7.46) |
| 14 | 13.78 | 98.84 (± 0.2) | 4.96 (± 3.70) | 9.72 (± 1.36) | 77.96 (± 0.33) | 4.03 (± 2.40) | 3.33 (± 2.42) |
| 21 | 13.61 | 98.80 (± 0.2) | 5.01 (± 0.94) | 9.55 (± 0.37) | 77.23 (± 0.42) | 4.57 (± 5.27) | 3.63 (± 4.21) |
| 28 | 13.88 | 97.80 (± 1.0) | 5.60 (± 0.23) | 9.63 (± 0.61) | 77.07 (± 0.28) | 4.24 (± 5.28) | 3.46 (± 1.30) |

Results irrespective of storage temperature:

- DLS: Hydrodynamic diameters remained constant, no small sized aggregates
- SEC: Bevacizumab concentrations decreased slightly but remained within the specification (± 5% of the initial concentration)
  The peak area of the oligomer peak detected on day 0 remained unchanged over the 28-day period (see Fig. 1)
- IEC: No significant changes in the peak pattern were detected
- pH: pH values varied between 6.07 and 6.15 over the 28-day period
- **Visual appearance:** No visible particles or colour changes during 28 days

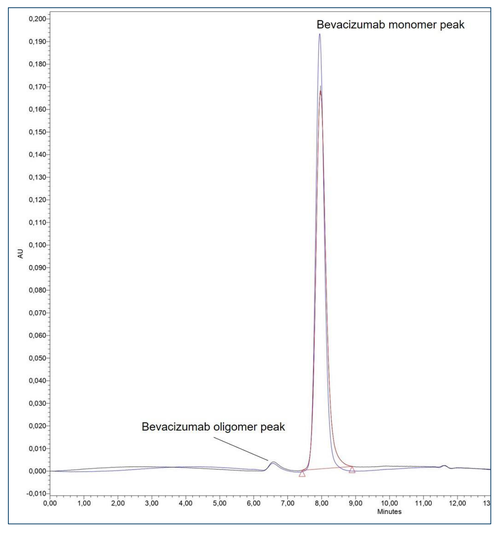



Fig. 1: Overlay of SEC chromatograms of Vegzelma® 25 mg/mL solutions on day 0 (blue) and day 28 (red) stored at 25 ° C.

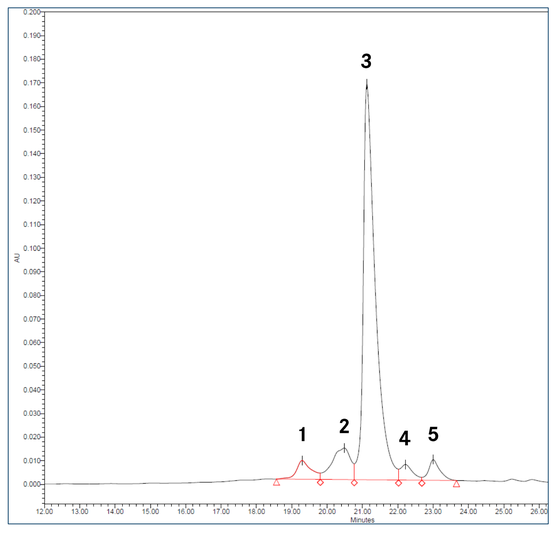



Fig. 2: IEC chromatogram of a freshly prepared Vegzelma® 25 mg/mL solution. Peak 1 and 2 correspond to the acidic variants, peak 4 and 5 to the basic variants of the bevacizumab main peak 3.

## Conclusion and Relevance

Bevacizumab 25 mg/mL concentrate (Vegzelma®) revealed to be physicochemically stable for at least 28 days stored light protected at 2-8 ° C or at 25 ° C after first opening. Vegzelma® residues in punctured original glass vials can be used cost-effectively for up to 28 days.