Physicochemical stability of subcutaneous daratumumab (DARZALEX® 1800 mg injection solution) in plastic syringes over a period of 28 days stored refrigerated or at room temperature

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Background and Importance

In multiple myeloma patients, the subcutaneous (SC) formulation of daratumumab (DARZALEX® 1800 mg injection solution) is increasingly used instead of the intravenous (IV) form due to practicability issues (fixed dose, short application time), safety, and efficacy. Only recently, the manufacturer (Janssen-Cilag International NV) specified the physicochemical stability of Daratumumab SC withdrawn into plastic syringes for 24 hours at 2-8°C protected from light and another 12 hours at room temperature (15-25°C) at ambient light for the prepared syringe [1].

Aim and Objectives

The aim of the study was to determine the long term **physicochemical stability** of ready-to-administer DARZALEX® 1800 mg injection solution in different types of syringes at different temperatures (2-8°C, 22±2°C) over a 28-day period.

Materials and Methods

Preparation of test solutions: Daratumumab (DARZALEX® 1800 mg injection solution, 16 mL) withdrawn into plastic 3-piece luer-lock syringes capped with combi-stoppers (B.Braun)

Storage: 2-8°C (light protected)

B.Braun Original-Perfusor® 50 mL (Polypropylene)

BD Plastipak Luer-Lock-syringes 20 mL (Polypropylene)

Single samples withdrawn immediately (0) and at day 2, 7, 14, 21, 28

Storage: 22±2°C (light protected)

B.Braun Original-Perfusor® 50 mL (Polypropylene)

BD Plastipak Luer-Lock-syringes 20 mL (Polypropylene)

Size-exclusion HPLC (SEC) with UV detection

- **Validated**: according to ICH Q2 (R1) Guideline
- **Detector**: DAD at 280 nm
- **Column**: Tosoh Bioscience TSKgel G3000SWXL, 5 µm, 7.8 x 300 mm
- **Mobile phase**: 150 mM Phosphate-buffered saline (PBS)
- **Flow-Rate**: 1.0 mL/min
- **Injection volume**: 1 µL (in triplicate)

Ion-exchange HPLC (IEC) with UV detection

- **Validated**: according to ICH Q2 (R1) Guideline
- **Detector**: DAD at 280 nm
- **Guard column**: Thermo Scientific Propac WCX-10, 5 µm, 4 x 50 mm
- **Column**: Thermo Scientific ProPac WCX-10, 5 µm, 4 x 250 mm
- **Mobile phase**: A: 20 mM 2-(N-morpholino)ethanesulfonic acid (MES) + 60 mM NaCl
  B: 20 mM MES + 180 mM NaCl
- **Flow-Rate**: 0.8 mL/min
- **Injection volume**: 25 µL (in triplicate)

pH measurement

Visual inspection for visible particles or colour changes

Results

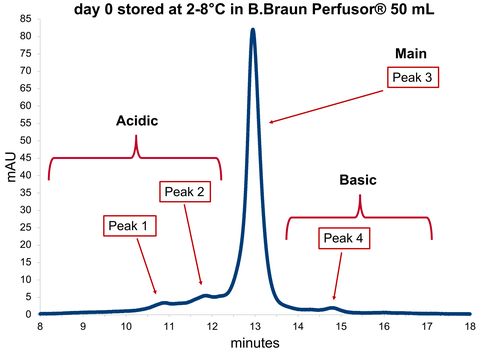
Tab. 1: Physicochemical stability of daratumumab (DARZALEX® 1800 mg injection solution) in B.Braun 50 mL and BD 20 mL syringes **stored at 2-8°C** over 28 days. SEC results expressed as % remaining daratumumab concentration ±SD (n=9), initial concentration day 0 set as 100%. IEC results expressed as % peak area of the total peak areas (100%) (n=9).

Time point [day]	Syringe type	SEC	IEC			
		Intact monomer Area [%]	Peak 1 Area [%]	Peak 2 Area [%]	Peak 3 Area [%]	Peak 4 Area [%]
0	B.Braun 50 mL	100.0 (±0.0)	0.9 (±0.06)	1.0 (±0.07)	97.0 (±0.15)	1.1 (±0.04)
2		100.6 (±1.0)	0.9 (±0.06)	1.1 (±0.04)	96.9 (±0.15)	1.1 (±0.09)
7		98.2 (±0.8)	0.9 (±0.04)	1.0 (±0.06)	97.0 (±0.10)	1.1 (±0.07)
14		98.1 (±0.6)	1.0 (±0.03)	1.2 (±0.06)	96.7 (±0.10)	1.1 (±0.08)
21		99.1 (±1.0)	1.0 (±0.07)	1.2 (±0.06)	96.7 (±0.08)	1.1 (±0.03)
28		99.7 (±0.7)	0.9 (±0.06)	1.0 (±0.07)	96.9 (±0.12)	1.1 (±0.05)
0	BD 20 mL	100.0 (±0.0)	0.9 (±0.06)	1.1 (±0.06)	96.9 (±0.12)	1.1 (±0.08)
2		99.9 (±0.5)	0.9 (±0.07)	1.2 (±0.05)	96.8 (±0.13)	1.1 (±0.06)
7		98.4 (±0.5)	0.9 (±0.07)	1.1 (±0.06)	97.0 (±0.11)	1.0 (±0.09)
14		98.2 (±0.4)	0.9 (±0.04)	1.3 (±0.06)	96.7 (±0.12)	1.1 (±0.08)
21		99.0 (±0.5)	0.9 (±0.03)	1.2 (±0.07)	96.8 (±0.12)	1.1 (±0.08)
28		100.2 (±0.7)	0.9 (±0.08)	1.0 (±0.03)	96.9 (±0.08)	1.1 (±0.05)

Tab. 2: Physicochemical stability of daratumumab (DARZALEX® 1800 mg injection solution) in B.Braun 50 mL and BD 20 mL syringes **stored at 22±2°C** over 28 days. SEC results expressed as % remaining daratumumab concentration ±SD (n=9), initial concentration day 0 set as 100%. IEC results expressed as % peak area of the total peak areas (100%) (n=9).

Time point [day]	Syringe type	SEC	IEC			
		Intact monomer Area [%]	Peak 1 Area [%]	Peak 2 Area [%]	Peak 3 Area [%]	Peak 4 Area [%]
0	B.Braun 50 mL	100.0 (±0.0)	0.9 (±0.06)	1.1 (±0.07)	96.8 (±0.13)	1.1 (±0.03)
2		99.5 (±0.7)	0.9 (±0.07)	1.2 (±0.08)	96.7 (±0.11)	1.2 (±0.09)
7		98.1 (±0.6)	0.9 (±0.05)	1.0 (±0.03)	96.9 (±0.10)	1.1 (±0.07)
14		97.7 (±0.4)	1.1 (±0.05)	1.1 (±0.04)	96.6 (±0.11)	1.2 (±0.07)
21		98.2 (±0.6)	1.1 (±0.05)	1.0 (±0.05)	96.7 (±0.07)	1.2 (±0.06)
28		99.6 (±0.3)	1.3 (±0.03)	0.9 (±0.05)	96.6 (±0.07)	1.2 (±0.06)
0	BD 20 mL	100.0 (±0.0)	0.9 (±0.08)	1.2 (±0.05)	96.7 (±0.15)	1.2 (±0.08)
2		99.2 (±0.8)	1.0 (±0.08)	1.2 (±0.08)	96.8 (±0.17)	1.1 (±0.09)
7		97.9 (±0.6)	1.0 (±0.08)	1.0 (±0.04)	96.9 (±0.11)	1.1 (±0.07)
14		97.9 (±1.8)	1.1 (±0.06)	1.1 (±0.08)	96.6 (±0.15)	1.2 (±0.08)
21		98.1 (±0.8)	1.1 (±0.05)	1.0 (±0.07)	96.7 (±0.08)	1.2 (±0.04)
28		99.6 (±0.7)	1.3 (±0.06)	0.9 (±0.06)	96.6 (±0.05)	1.3 (±0.05)

Ion-exchange chromatogram of Darzalex 1800 mg day 0 stored at 2-8°C in B.Braun Perfusor® 50 mL



Independent of syringe type or storage temperature:

- **SEC:** neither the formation of aggregates nor of fragments was detected. Daratumumab concentrations declined less than 5% over 28 days.
- **IEC:** peak pattern and peak areas of acid and basic daratumumab charge variants showed no significant changes over 28 days.
- **pH:** values of all samples varied between pH 5.64-5.72 over 28 days.
- **Visual inspection:** solutions remained clear, without colour changes or visible particles over 28 days.

Conclusion

Ready-to-administer Daratumumab SC preparations (DARZALEX® 1800 mg injection solution) are physicochemically stable in capped **plastic syringes** (BD Plastipak 20 mL, B.Braun Perfusor® 50 mL) for at least **28 days when stored refrigerated (2-8°C) or at room temperature (22±2°C)** protected from light. For microbiological reasons storage under refrigeration is recommended.

References

[1] Darzalex Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf