

3PC-031

# PHYSICOCHEMICAL STABILITY OF DILUTED 'THIOTEPA RIEMSER' INFUSION SOLUTIONS IN PREFILLED 5% GLUCOSE INFUSION BAGS

## Background and Importance

Newly formulated Thiotepa Riemser was approved in 2021 for conditioning treatment prior to haematopoietic progenitor cell transplantation.

According to the SmPC, the ready-to-administer (RTA) infusion solutions are physicochemically stable for 24 hours stored at 2-8 °C or 4 hours stored at room temperature. Stability of thiotepa containing RTA infusion solutions is known to be concentration dependent [1].

## Aim and Objectives

**Extended stability data** are missing for thiotepa RTA infusion solutions prepared with the newly formulated Thiotepa Riemser lyophilisate and **Glucose 5%** (G5) solution as vehicle.

The aim of the study was to investigate the **physicochemical in-use stability** of diluted Thiotepa Riemser RTA infusion solutions of three different concentrations (1 mg/mL, 2 mg/mL, 3 mg/mL) in prefilled G5 infusion bags.

## Materials and Methods

### Preparation of test solutions

- Thiotepa Riemser 100 mg
- 100 ml Glucose 5% Freeflex® polyolefin bags
- Three test solutions for each concentration and storage condition

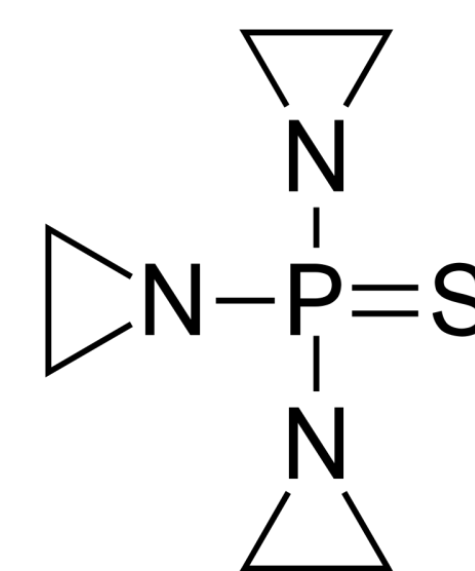


**Storage**  
2-8 °C  
(light protected)  
or  
25 °C  
(daylight)

**Single samples withdrawn**  
immediately after preparation and  
at day 1, 3, 5, 7, 14

### HPLC assay

- Adapted from the Thiotepa USP, BP monography
- Validated according to ICH Q2 (R1) guideline
- RP-HPLC with DAD detector at 215 nm
- Column: Nucleodur 100 C18, particle size 5 µm, 150 x 4.6 mm
- Mobile phase: 15% Acetonitrile in 0.1 M Phosphate buffer pH 7
- Flow rate: 1 mL/min
- Injection volume: 10 µL in triplicate

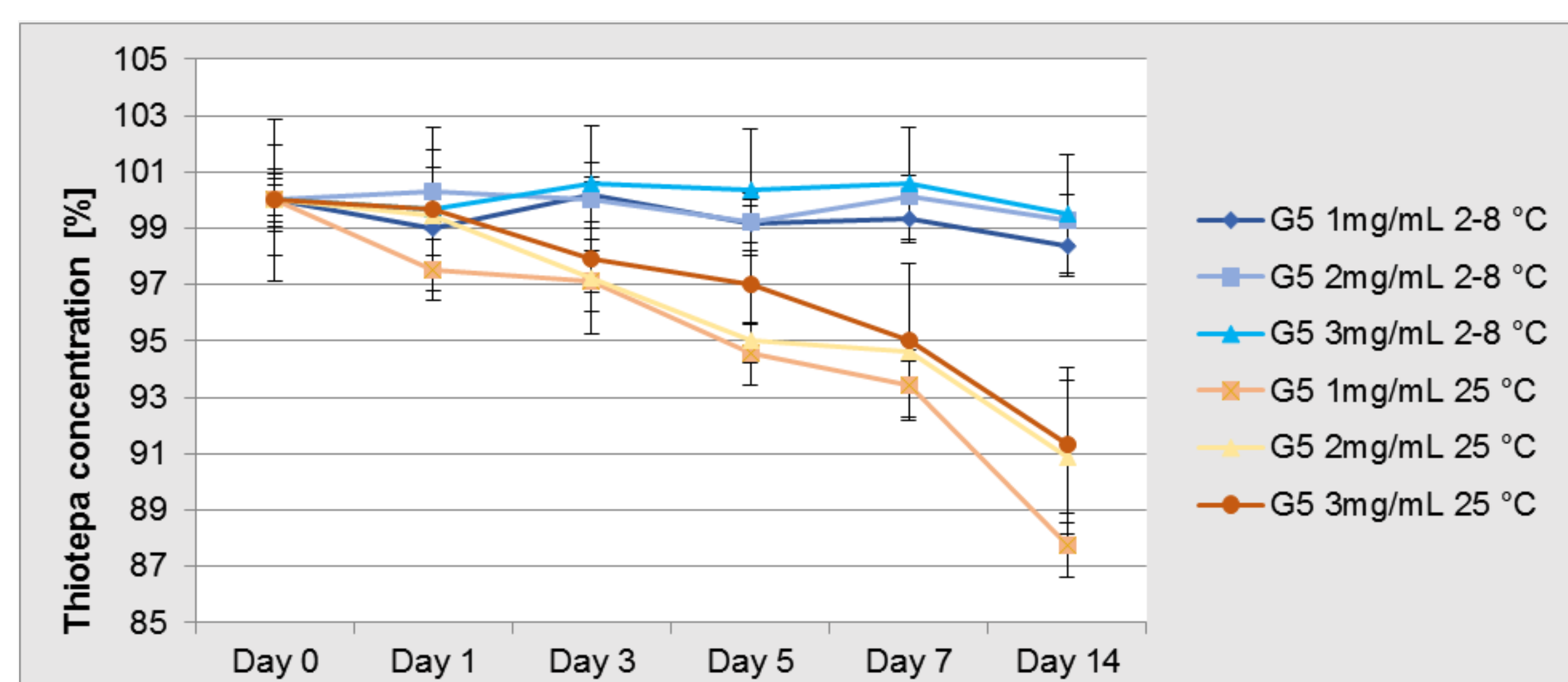


- **HPLC analysis** of thiotepa concentrations and related compounds
- **pH** measurement
- **Osmolality** measurement
- **Visual inspection** for colour changes and visible particles
- **Non-visible particles** counted on day 0 and day 14

## Results

### Thiotepa concentration determined by HPLC

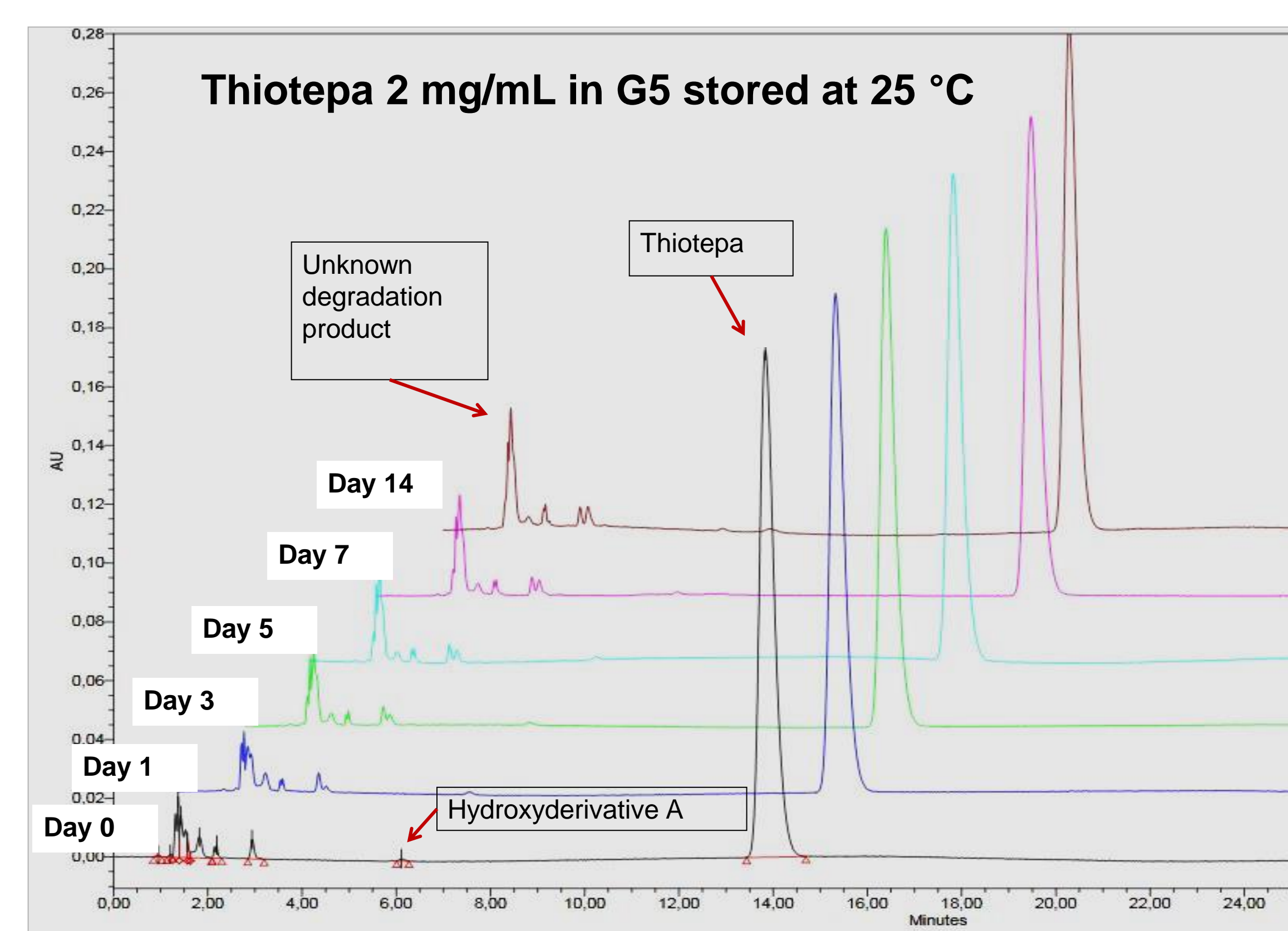
- In diluted thiotepa 1, 2, 3 mg/mL infusion solutions stored at 2-8 °C, thiotepa concentrations remained above 98% of the initial concentration over the 14 day observation period
- In diluted thiotepa 1, 2, 3 mg/mL infusion solutions stored at 25 °C, thiotepa concentrations fell below 95% of the initial concentration on day ≥ 3



- **pH**: between 6.2 and 7.6, slight increase over time
- **Osmolality**: no significant changes over time
- **Visual inspection**: no colour change, no visible particles
- **Non-visible particles**: no increase of particles over time

### Related compounds

- Chromatograms revealed several peaks with relative retention times (RRT) < 0.8 of hydrophilic degradation products, partly increasing over time
- Peaks with RRT 0.44 refer to the known impurity **Hydroxyderivative A**
- Peaks with retention time 1 to 3.5 min are partly derived from **G5**



## Conclusion

Thiotepa 1 mg/mL, 2 mg/mL and 3 mg/mL infusion solutions in G5 are physicochemically stable for **14 days when stored at 2-8 °C**. When stored at 25 °C, thiotepa infusion solutions are stable for **3 days (1 mg/mL) or 5 days (2 mg/mL, 3 mg/mL)**. Degradation is highly **temperature-dependent**, therefore infusion solutions should be stored at 2-8 °C. Specifications of related compounds (e.g. Hydroxyderivative A) were neglected because the **hydroxylated thiotepa derivatives** are associated with a loss of efficacy but not higher toxicity than thiotepa itself. The formation of chloro derivatives was excluded by using chloride-free G5 vehicle solution.

## References

[1] Q.A. Xu, L.A. Trissel, Y.Zhang, J.F. Martinez, D.L. Gilbert, Stability of thiotepa (lyophilized) in 5% dextrose injection at 4 and 23 °C; Am J Health-Syt Pharm Vol. 53, 1996

## Funding

The study was funded by Esteve Pharmaceuticals GmbH