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

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

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

Single samples withdrawn immediately after preparation and at day 1, 3, 5, 7, 14

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

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

Concldusion

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


Funding

The study was funded by Esteve Pharmaceuticals GmbH