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Physicochemical Stability of Mozobil® (Plerixafor) Solution for Injection in Glass Vials and Plastic Syringes over a Three-Month Storage Period

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Abstract

Background: The stability of ready-to-administer parenteral preparations is an important issue of drug safety. Profound knowledge about the physicochemical stability is necessary in order to determine the "beyond-use-dates" of solutions in injection vials after first opening and ready-to-administer preparations in syringes.

Object: The aim of this study was to determine the physicochemical stability of plerixafor solution marketed as Mozobil® solution for injection 20 mg/mL (1.2 mL). Therefore punctured vials and ready-to-administer syringes of Mozobil® solution for injection stored under refrigeration (2–8 °C) or at room temperature (25 °C) were analysed at predetermined intervals over a maximum storage period of three months.

Method: The stability of Mozobil® solution for injection was determined in the original glass vials stored under refrigeration (2–8 °C) and at room temperature (25 °C), both light protected. Plerixafor concentrations and pH values were determined on days 0, 14, 28, 56 and 84 after first puncture of the vial. Ready-to-administer syringes were aseptically prepared by withdrawing 0.2 mL injection concentrate via cannulas six times from the same Mozobil® vial into 1 mL 2-piece plastic syringes. Three syringes each were stored under refrigeration (2–8 °C) and at room temperature (25 °C), both light protected. Plerixafor concentrations and pH values were determined on days 0 and 84. Each sample was assayed three times by a validated stability-indicating reversed-phase high-performance liquid chromatography (RP-HPLC) assay with photodiode array detection (PDA) to analyze the concentration and purity of plerixafor. Whenever samples are taken the vials and syringes were visually checked for colour changes or particulate matter.

Results: No plerixafor degradation products were detected in the HPLC chromatograms over the period of 84 days, independent of the storage temperature. In vials and syringes plerixafor concentrations declined less than 5 % over the entire test period of 84 days. The pH values remained unchanged; the mean values varied between 6.79 and 6.60 for Mozobil® injection concentrate stored in vials and between 6.73 and 6.69 in the ready-to-administer syringes. No particulate matter and no colour changes were observed over the period of 84 days.

Conclusion: Plerixafor injection solution (Mozobil®) is stable in glass vials after first opening and in syringes for at least three months when stored light protected under refrigeration (2–8 °C) or at room temperature (25 °C). For microbiological reasons storage under refrigeration is recommended. The proven physicochemical stability of Mozobil® allows cost-saving pharmacy-based centralized preparation of ready-to-administer syringes.

Keywords: plerixafor, physicochemical stability, injection concentrate, ready-to-administer syringe, reversed-phase high-performance liquid chromatography (RP-HPLC)

Introduction

Mozobil® 20 mg/mL solution for injection containing plerixafor as active pharmaceutical ingredientis indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) [1]. Plerixafor (AMD3100) is a small bicyclamic molecule (Figure 1) that antagonizes the binding of the chemokine stromal cell-derived factor-1 (SDF-1), also known as CXCL12, to its cognate receptor CXCR4 [2]. Thereby plerixafor induces the mobilization of hematopoietic stem cells, which are characterized as CD34 + cells, from the bone marrow to the bloodstream [3]. In a phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus G-CSF for autologous

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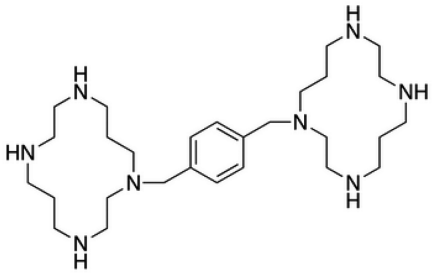

Figure 1: Chemical structure of plerixafor (AMD3100), 1,1′-[1,4-Phenylenebis(methylene)]bis[1,4,8,11-tetraazacyclotetradecane].

stem-cell mobilization in patients with non-Hodgkin's lymphoma was shown that plerixafor acts synergistic with G-CSF [4]. In another phase II clinical trial plerixafor in combination with G-CSF resulted in a significantly higher proportion of MM patients achieving the optimum CD34+ target range for transplantation in fewer apheresis days, compared with G-CSF alone [5]. Plerixafor is only used in patients expected to mobilize stem cells poorly, i. e. age over 60 and/or prior myelosuppressive chemotherapy and/or extensive prior chemotherapy and/or a peak circulating stem cell count of < 20 HSCs/μL [4]. Because the number of patients that need mobilization and collection of HSCs for transplantation is small, Mozobil® was classified as an orphan drug in October 2004 [6].

Each single-use vial of Mozobil® is filled to deliver 1.2 mL of 20 mg/mL plerixafor aqueous solution for injection containing 24 mg of plerixafor. The pH is adjusted in the range of 6.0–7.5 [1]. Plerixafor has eight basic amine functional groups, and is slightly soluble in water and saline, freely soluble in alcohols, glycol, and aqueous solutions of the pH < 10. Type I clear glass 2 mL vials are used as primary containers and closed with grey chlorobutyl rubber stoppers.

According to the Mozobil® label the product does not require any special storage conditions [1]. After opening the vial, the solution should be used immediately [1]. The content of each Mozobil® vial is appropriate to treat a patient with 100 kg body weight (0.24 mg/kg/d used on 2–4 (and up to 7) consecutive days) [1]. For patients with a lower body weight, the remaining solution must be discarded, resulting in a significant waste of this expensive drug (5,800 € per 1 mL).

According to the EPAR [6] stability of plerixafor active substance is given under a wide range of conditions (temperature, humidity, pH, light) and degradation is only observed under severe stress conditions. The results from photostability studies also show that plerixafor is not photosensitive and does not require special protection against light exposure [6]. Mozobil® solution for injection is terminally sterilized in an autoclave. The specification of the finished product includes sterility and freedom from bacterial endotoxins [6]. The commercial packaging is stable for at least three years when stored at 25 °C/60 % RH. No special precautions for storage are to be regarded [1]. In addition, the analysis and stability of repurposed plerixafor products over a period of six months at room temperature was published in abstract form [7].

Profound knowledge about the physicochemical stability is necessary in order to determine the in-use storage time of Mozobil® solution for injection in vials after first opening and the beyond-use-date of ready-to-administer Mozobil® containing preparations in 1 mL 2-piece plastic syringes. Decision-making is based on the physicochemical stability and concomitantly on the safe aseptic processing and is the responsibility of the pharmacist. Therefore, the purpose of this study is to determine the physicochemical stability of Mozobil® solution for injection in the original vials after first opening and in ready-to-administer syringes when stored under refrigeration (2–8 °C) or at room temperature (25 °C) both light protected over a period of 84 days. The storage conditions were chosen with an eye to clinical practice.

Chemical stability of plerixafor was planned to be determined with a stability-indicating reversed-phase high-performance liquid chromatography (RP-HPLC) assay which was previously published by M. Mathrusri Annapurna et al. [8]. Physicochemical stability was planned to be determined by visual inspection of clarity and colour as well as pH measurement.

Materials and methods

Preparation of test solutions

All tests were performed using commercially available Mozobil® 20 mg/mL solution for injection, 1.2 mL (lot-no.: J3001H103/J3001H76, received from Sanofi-Aventis, DE, GmbH). In order to determine the stability of Mozobil® solution for injection in the original glass vials, three Mozobil® vials were stored under refrigeration (2–8 °C) and additional three vials were stored at room temperature (25 °C), both light protected. Plerixafor concentrations were determined on days 0, 14, 28, 56 and 84 after first puncture of the vial. At each predetermined interval 0.2 mL aliquots were withdrawn from each vial using cannulas (BD Microlance™3) and syringes. The vial stopper was covered by a plastic film, consisting of paraffin wax and polyolefine (Parafilm M®, Bemis Company, Neenah, Wisconsin, US).

The cover was removed prior to the next sampling and the stopper was disinfected with alcohol before the aliquot was withdrawn.

Six Mozobil® ready-to-administer preparations were aseptically prepared by withdrawing 0.2 mL solution for injection from the same Mozobil® vial in 1 mL 2-piece syringes (Injekt®-F Tuberculin, 0.01 ml–1 ml, Luer Solo, lot-no.: 15G13C8, B. Braun Melsungen AG, DE) via cannulas. The barrel of the used syringe model is made of polypropylene (PP) and the plunger of polyethylene (PE). The syringe is free from latex, polyvinyl chloride (PVC) and silicone oil [9]. Three test syringes were stored under refrigeration (2–8 °C) and additional three syringes were stored at room temperature (25 °C), both light protected. Plerixafor concentrations were determined on days 0 and 84.

Sample preparation

Aliquots of the test solutions were twofold diluted in order to fit the calibration curve of the HPLC assay. In the first dilution step 25 µL aliquots of the test solutions were diluted with 975 µL mobile phase. Then 400 µL of the diluted solution were mixed with 600 µL mobile phase to achieve a concentration of 0.2 mg/mL plerixafor.

Determination of the chemical stability of plerixafor solution for injection

HPLC assay

The HPLC system consisted of a Waters Alliance 2695 with Waters photodiode array detector 996 (Waters, Eschborn, DE). The Waters Empower Pro, Empower Build 1154 Software, version 5.00.00.00 (Waters, Eschborn, DE) was used for data evaluation.

The separation was performed with a C18 column (Kromasil® 100, 250 mm × 4.6 mm, 5 µm particle size, lot-no.: 25131313, MZ-Analysentechnik GmbH, Mainz, DE), which was maintained at 25 °C. The mobile phase consisted of 88 % water HPLC grade (lot-no.: 4J011502/5E012225, AppliChem GmbH, Darmstadt, DE) and 12 % acetonitrile optigrade (lot-no.:1501861, LGC Standards GmbH, Wesel, DE). 1,000 mL of this solution were mixed with 1.18 mL trifluoroacetic acid (TFA) (lot–no.:S6406760/S6746460 031, Merck, Darmstadt, DE). The overall run time was 15 min, the flow rate 1.0 mL/min. 10 µL samples were injected by an autosampler in triplicate. The washing solution consisted of 95 % water HPLC grade (lot-no.: 4J011502/5E012225, AppliChem GmbH, Darmstadt, DE) and 5 % acetonitrile optigrade (details see above).

The absorption of plerixafor was measured at a wave length of 215 nm. The identity of the plerixafor peak was confirmed by concentration dependent peak area and PDA-chromatogram.

Validation of the RP-HPLC assay

The method was validated following the ICH Q2 (R1) Guidelines [10] for stability studies. A typical HPLC chromatogram is shown in Figure 2.

Suitability

Suitability of the HPLC method was proven by analyzing forced degraded samples of Mozobil® plerixafor injection concentrate. The injection concentrate (20 mg/mL) was either acidified with 10 µL of hydrochloric acid

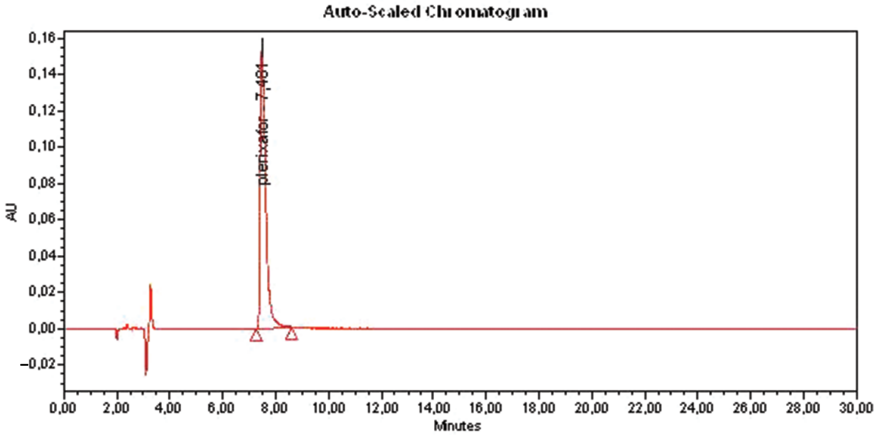

Figure 2: Representative HPLC-chromatogram of freshly prepared 0.2 mg/mL plerixafor solution (Mozobil®).

(Hydrochloric acid fuming 37% for analysis, lot-no.: K46428917510, Merck KGaA, Darmstadt, DE), alkalinized with 10 µL of sodium hydroxide solution (42% (m/v), prepared with sodium hydroxide pellets, lot-no.: 0000537465, AppliChem GmbH, Darmstadt, DE), or heated to 100 °C for 10 min.

Solutions were diluted with the mobile phase and assayed without prior neutralization.

Linearity

In order to study the linearity of the assay, standards ($n = 7$) were prepared by diluting Mozobil® injection solution with mobile phase to achieve the following concentrations: 0.3 mg/mL, 0.24 mg/mL, 0.22 mg/mL, 0.2 mg/mL, 0.18 mg/mL, 0.16 mg/mL, 0.1 mg/mL.

Aliquots of the calibration standards were injected in triplicate. The line of best fit was constructed by analyzing plots of peak area versus plerixafor concentrations.

Accuracy

Accuracy was evaluated with two different concentration levels (100%: 0.2 mg/mL and 80%: 0.16 mg/mL) and 10-fold injection.

Intra-day precision

The intra-day precision of the assay method was evaluated by carrying out 10 independent assays of plerixafor solution at two concentration levels (0.2 mg/mL and 0.16 mg/mL).

Inter-day precision

For inter-day precision at each concentration level (0.2 mg/mL and 0.16 mg/mL) a single injection of plerixafor solution was assayed daily on five consecutive days.

Determination of the physicochemical stability of plerixafor solution for injection

pH values were measured in triplicate in the undiluted aliquots taken from the test solutions at the predetermined intervals using a pH 210 Microprocessor pH-meter (Hanna Instruments, Kehl am Rhein, DE) with an InLab Ultra-Micro pH-glasselectrode (Mettler Toledo Inlab Ultra-micro pH, Gießen, DE). The instrument was calibrated with Hamilton DuraCal buffer pH 4.01 ± 0.01 and pH 7.01 ± 0.01.

Whenever samples were taken the vials were visually checked for colour changes and particulate matter.

Results

Validation of the RP-HPLC assay

Suitability

Under alkaline condition the peak of the degradation product (retention time 2.5 min) did not interfere with the plerixafor parent peak (retention time 7.5 min), see Figure 3.

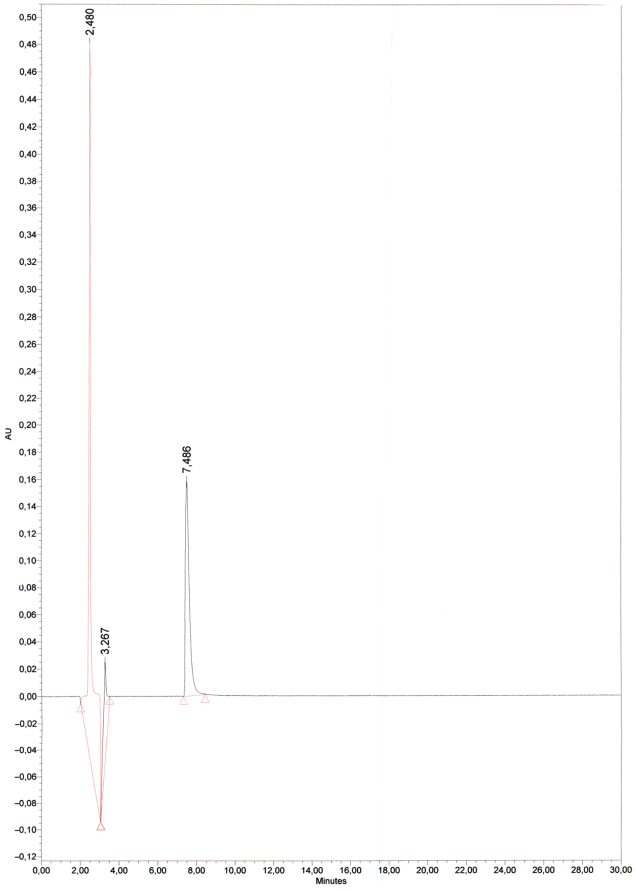

Figure 3: Representative HPLC-chromatogram of alkaline degraded plerixafor solution for injection (Mozobil®).

There were no changes induced by acidic degradation (Figure 4) and pure heating (Figure 5).

These results confirm the suitability of the HPLC method.

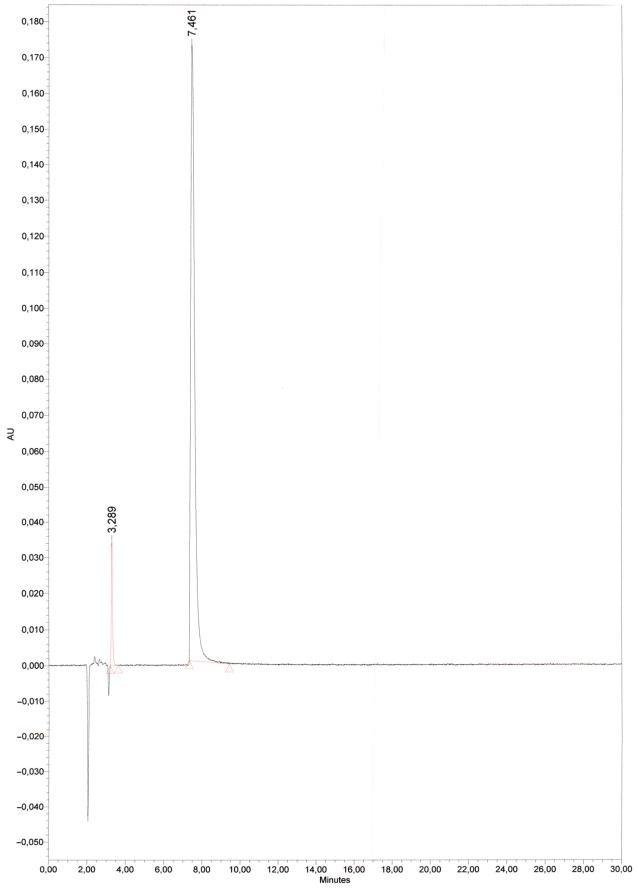

Figure 4: Representative HPLC-chromatogram of acid degraded plerixafor solution for injection (Mozobil®).

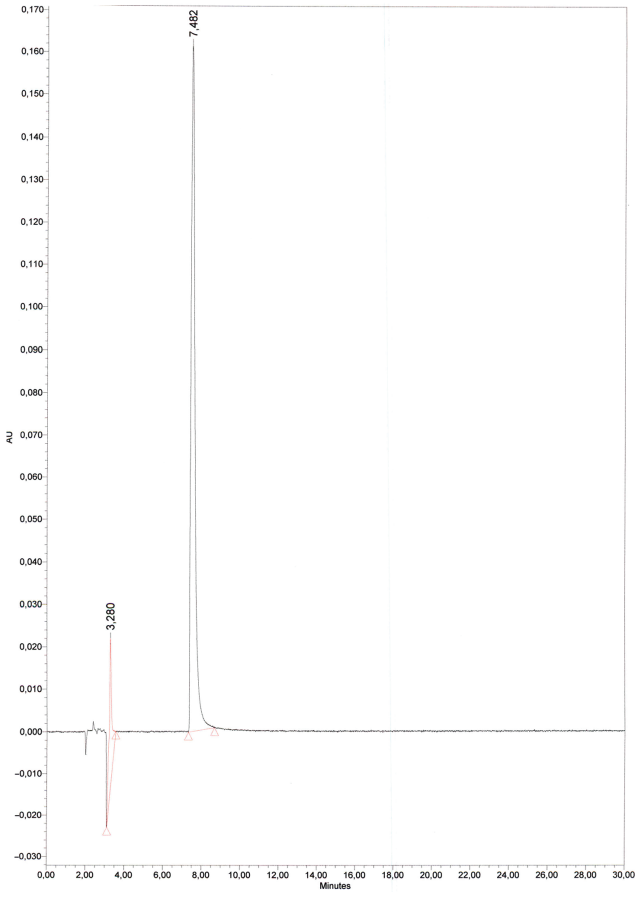

Figure 5: Representative HPLC-chromatogram of heat-degraded plerixafor solution for injection (Mozobil®).

Linearity

The correlation coefficient of $R^2 = 0.9994$ proved linearity over the concentration range. The equation of calibration curve was $y = 1.14e + 007x\text{-}1.02e + 005$.

Accuracy

The mean recovery was 103.4 % ± 0.1 % ($n = 10$). The accuracy was 102.6 % ± 0.1 % for 0.2 mg/mL and 104.1 % ± 0.1 % for 0.16 mg/mL plerixafor solution.

Intra-day precision

The % RSD (Relative Standard Deviation) was 0.97 % at the concentration 0.2 mg/mL and 0.74 % at 0.16 mg/mL.

Inter-day precision

The % RSD was 1.23 % at the concentration 0.2 mg/mL and 4.73 % at 0.16 mg/mL.

Chemical stability of plerixafor solution for injection

In the present study two known HPLC-methods [7, 8] for evaluating the stability of Mozobil® solution for injection were modified and validated. The overall run time amounted to 15 min, the flowrate to 1.0 mL/min, the injection volume to 10 µL. The mobile phase consisted of water, acetonitrile and trifluoroacetic acid (TFA). Samples were not filtered before measurement. Results of the degradation tests proved the suitability of the method. The validation parameters met the criteria of ICH Q2 (R1).

Neither in samples taken from the re-punctured Mozobil® glass vials nor taken from the aseptically prepared ready-to-administer syringes any plerixafor degradation products were detected in the HPLC chromatograms over the storage period of 84 days, independent of the temperature conditions. In addition no changes in the concentrations of plerixafor were registered. In vials and syringes plerixafor concentrations

Table 1: Stability of plerixafor solution for injection (Mozobil®) in re-punctured glass vials over a period of 84 days. Concentration expressed as mean ± relative standard deviation of triplicate assays of one test solution ($n = 3$).

Storage temperature	Test solution	Drug concentration in sample [mg/mL]		% Initial concentration remaining ± relative SD			
		Nominal	Actual Day 0	Day 14	Day 28	Day 56	Day 84
2–8 °C	1	0.2	0.204 ± 0.4	102.9 ± 0.7	102.9 ± 0.2	97.7 ± 0.4	102.4 ± 0.8
	2	0.2	0.211 ± 0.2	97.9 ± 0.2	97.9 ± 0.1	95.6 ± 0.1	100.4 ± 0.1
	3	0.2	0.216 ± 0.2	98.3 ± 0.2	98.3 ± 0.1	95.9 ± 0.3	99.4 ± 0.1
25 °C	1	0.2	0.215 ± 0.1	99.0 ± 0.2	99.0 ± 0.1	95.8 ± 0.2	99.9 ± 0.1
	2	0.2	0.218 ± 0.4	97.8 ± 0.1	97.8 ± 0.1	*93.6* ± 0.1	98.7 ± 0.1
	3	0.2	0.209 ± 0.6	102.1 ± 0.2	102.0 ± 0.6	98.7 ± 0.1	103.6 ± 0.1

Note: Drug concentrations in samples taken at time zero were designated as 100 %.

Table 2: Stability of plerixafor in ready-to-administer syringes over a period of 84 days. Concentration expressed as mean ± relative standard deviation of triplicate assays of one test solution ($n = 3$).

Syringe no.	Drug concentration in sample [mg/mL]		% Initial concentration remaining ± relative SD after 84 days of storage	
	Nominal	Actual Day 0	Storage temperature	
			2–8 °C	25 °C
1	0.2	0.200 ± 0.3	100.5 ± 0.1	101.2 ± 0.1
2	0.2	0.203 ± 0.2	98.7 ± 0.1	99.8 ± 0.1
3	0.2	0.206 ± 0.1	98.9 ± 0.1	98.5 ± 0.0

varied only within the accuracy limits of the assay over the entire test period of 84 days (see Tables 1 and 2).

Physicochemical stability of plerixafor solution for injection

No particulate matter and no colour changes were observed over the period of 84 days. The mean pH value varied from pH 6.71 at day 0 to pH 6.62 after three months in Mozobil® glass vials ($n = 18$) (Table 3). The pH value remained unchanged in the ready-to-administer preparations in plastic syringes as primary containers (Table 4).

Discussion

HPLC method

The used HPLC assay was adopted from published data [7, 8] and revalidated in order to achieve valid results. In the resulting chromatograms the sharp peak of plerixafor (retention time of about 8 min) was clearly separated from the peak of the sodium and/or chloride ion derived peak (retention time about 3 min). For that reason an overall runtime of 15 min was chosen. During the forced degradation experiments, the plerixafor parent peak and peaks of rarely observed degradation products were clearly separated. Also in previous degradation studies only minimal degradation was observed under most of the stress conditions applied [6]. According to the EPAR, increased levels of degradation have only been observed under severe stress conditions. No degradation products

Table 3: pH values of plerixafor injection solution in re-punctured vials stored under different storage conditions. pH values expressed as mean ± standard deviation of triplicate measurements of one test solution ($n = 3$).

Storage temperature	Test solution	pH values				
		Day 0	Day 14	Day 28	Day 56	Day 84
2–8 °C	1	6.70 ± 0.02	6.71 ± 0.01	6.63 ± 0.01	6.77 ± 0.01	6.62 ± 0.01
	2	6.73 ± 0.01	6.72 ± 0.01	6.60 ± 0.00	6.79 ± 0.00	6.66 ± 0.01
	3	6.73 ± 0.03	6.72 ± 0.01	6.65 ± 0.01	6.77 ± 0.01	6.60 ± 0.02
25 °C	1	6.72 ± 0.02	6.74 ± 0.01	6.66 ± 0.01	6.78 ± 0.01	6.63 ± 0.01
	2	6.69 ± 0.02	6.70 ± 0.01	6.63 ± 0.01	6.73 ± 0.01	6.60 ± 0.01
	3	6.69 ± 0.02	6.71 ± 0.01	6.62 ± 0.02	6.65 ± 0.01	6.61 ± 0.01

Table 4: pH values of plerixafor injection solution in ready-to-administer syringes stored under different storage conditions. pH values expressed as mean ± standard deviation of triplicate measurements of one test solution ($n = 3$).

Syringe no.	pH values			
	Day 0		Day 84	
	Storage temperature 2–8 °C	Storage temperature 25 °C	Storage temperature 2–8 °C	Storage temperature 25 °C
1	6.71 ± 0.01	6.72 ± 0.01	6.69 ± 0.01	6.73 ± 0.01
2	6.70 ± 0.01	6.70 ± 0.02	6.69 ± 0.01	6.71 ± 0.01
3	6.70 ± 0.02	6.70 ± 0.02	6.70 ± 0.01	6.69 ± 0.01

or significant trends were observed under the conditions specified in the SmPC [1].

Test solutions

Because of the body-weight adjusted dosage residual liquid will remain in the Mozobil® vials. When the withdrawal of the injection solution is performed under controlled conditions the residual liquid can be stored in the original glass vials and re-used. In order to simulate this scenario six Mozobil® vials were used for the stability tests. Re-puncturing of the vial stoppers was done more often than in daily practice thus representing an additional challenge. Storage of the test solutions at room temperature simulates worst conditions especially regarding microbiological stability.

The preparation of ready-to-administer syringes was simulated by withdrawal of 0.2 mL aliquots into six 1 mL 2-piece plastic syringes free from silicon oil. Thereby only one single Mozobil® vial had to be expended. A polyisoprene gasket is not necessary in 2-piece syringes and thereby the probability of leaching is reduced. The filling volume of the syringe is not expected to influence the degradation of plerixafor. On the contrary, the small filling volume (0.2 mL) represents a worse case condition because the disadvantageous ratio of volume and surface favours leaching. Plerixafor concentrations were determined only initially and at the end of the observation period because of the small available volumes.

Stability

No significant changes of plerixafor concentrations and pH values were found in the experimental tests of Mozobil® solution for injection in vials after first opening and ready-to-administer preparations in plastic syringes. Both products revealed to be physicochemically stable over a three-month period. On day 56, there was an outlier which is most probably caused by an imprecise dilution step (Table 1). Marginal variations in plerixafor concentrations can be explained by the dilution steps during sample preparation and by the standard deviations of the HPLC method. Because of the known stability of plerixafor, degradation reactions are not to be expected in the Mozobil® injection solution of neutral pH and storage at room temperature. However, contact with alkaline solutions should be avoided. As plerixafor is not photosensitive, light protection during storage is not mandatory, but light protected storage was chosen with an eye to daily practice. A temperature dependent difference in plerixafor stability (refrigerated or room temperature) gets most probably only obvious after longer storage periods.

Disposable plastic syringes used as primary containers represent a source of leachables which can diffuse under certain solvent and storage conditions [11]. Compounds leached into the product can affect the stability of the product and potentially increase the toxicological risk for the patient [12, 13]. However, determination of leachables was not in the scope of our study. With regard to the aspect of leaching the results cannot be assigned to 3-piece syringes [9, 14].

The present study has proven long-term physicochemical stability (84 days observation period) of ready-to-administer Mozobil® syringes and Mozobil® vials after first opening. Besides the physicochemical stability, microbiological stability is a crucial factor in assigning extended expiration dates to aseptically prepared unpreserved aqueous injection products. Therefore, storage under growth-inhibiting temperature conditions, i. e. refrigeration is recommended. Moreover, only if handling takes place under strict aseptic conditions the prolonged use of these solutions can be recommended. Thereby material and therefore treatment expenses can be

reduced. With regard to the price of Mozobil® in the German market for normal weight patients (70 kg body weight) savings of € 2.400 per injection, i. e. € 4.800 to 9.600 per course can be achieved.

Conclusion

Plerixafor injection solution (Mozobil®) is stable in glass vials after first opening and in syringes for at least three months when stored light protected under refrigeration (2–8 °C) or at room temperature (25 °C). For microbiological reasons storage under refrigeration is recommended. The proven physicochemical stability of Mozobil® allows cost-saving pharmacy-based centralized preparation of ready-to-administer syringes.

Conflict of interest: The authors state no conflict of interest. All authors have read the journal's Publication ethics and publication malpractice statement available at the journal's website and hereby confirm that they comply with all its parts applicable to the present scientific work.

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