Physicochemical stability study of Cabazitaxel Zentiva® in vials after "opening" and in diluted solutions in infusion bags of 3 types.

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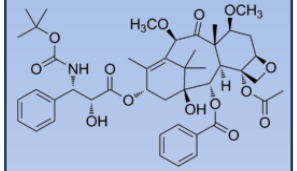
Introduction

Cabazitaxel is an antineoplastic agent, indicated, in combination with prednisone or prednisolone, for the treatment of adult patients with metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen.
To our knowledge, few studies have been published on the stability of cabazitaxel in infusion bags. The Stabilis® database has selected a study demonstrating the stability of this molecule at 0.15 mg/mL for 28 days at 4°C and 25°C in polyolefin bags[1].

[1] Lazzarini R *et al.* Physicochemical stability of cabazitaxel and docetaxel solutions. EJHP 2014 ;22:150-15.



Objectives

Physicochemical stability study of **Cabazitaxel Zentiva®** solutions :

1		**20 mg/mL** vials after opening with a SPIKE device	∅	25°C	Day 0, 14 and 28
2		**0.1 and 0.26 mg/mL** in three types of infusion bags[2,3,4]	NaCl 0.9% D5W	2-8°C[2] 25°C[3,4]	

[2] **Freeflex®** : polypropylene multilayers
[3] **Viaflo®** : multilayer high density polyethylene, polyamide, polypropylene
[4] **Easyflex®** : polyolefin

D5W : dextrose 5% in water

Materials and methods

Chemical stability

1. Method : RP-HPLC with DAD detector at 232 nm[1]
- C18 LiCrospher® 12.5 cm, particule size= 3.5 µm
- **Mobile phase** : isocratic mode : 42% of water for chromatography, 32% of methanol and 26% of acetonitrile
- **Flow rate** : 1.2 mL/min **Injection volume**: 25 µL

Validation of analytical method as recommended by ICH Q2(R1)
- **Forced degradation** to evaluate **stability indicating capability**

ACIDIC DEGRADATION	ALKALINE DEGRADATION	PHOTOLYTIC DEGRADATION
HCl – 1.69 M 10 min	NaOH – 0.05 M 1 min	24 h

- **Linearity** : standard curve with 5 points : 50 – 400 µg/mL
- **Repeatability and intermediate precision** : 3-point measurement (100, 200 and 300 µg/mL)
- **Specificity**

2. pH measurements (Crison pH25 pHmeter) : for each infusion bags

Physical stability

1. Visual examination : change of colour, precipitation, gaz formation

Study design

NaCl 0.9% - D5W
0.1 and 0.26 mg/mL

3 x Freeflex® 2-8°C
3x Viaflo® and 3x Easyflex® at 25°C

Two different batches at 25°C

Day 0,14 and 28

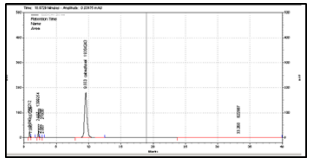
- **Analysis by RP-HPLC** : concentrations and degradations products (n=1/bag ; n=3/vial)
- **pH measurements** for infusion bags
- **Visual examination** for each condition

Acceptance criteria

± 10% of initial concentration and **no visual or significative pH value modification**

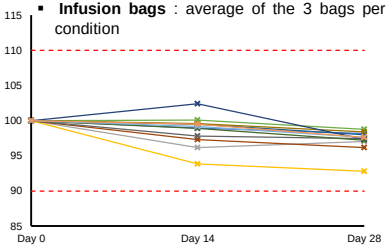
Results

1. Validation of the method
- **Linearity** : $R^2 > 0.9997$
- **Repeatability** : [0.43-1.15%]
- **Intermediate precision** : [0.82-1.65%]
- **Retention time** : 9.5 min
- **Stability indicating capability :**

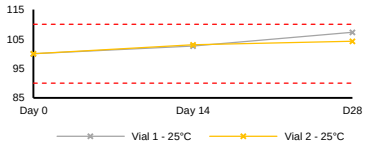


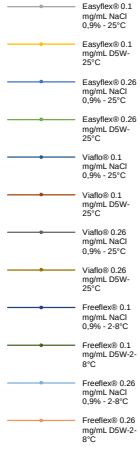
Chromatogram of cabazitaxel solution at 200 µg/mL after alkaline degradation (NaOH 0.05 M, 1 min)

2. A. Chemical stability - HPLC analysis
- **Infusion bags** : average of the 3 bags per condition



- **Vials** :





2. B. Chemical stability in infusion bags pH values
- No modification : maximum variation at D14 : 0.39 pH unit and 0.24 at D28

3. Physical stability
- No visual modification

Conclusion

Cabazitaxel Zentiva® 20 mg/mL vials with a SPIKE were physically and chemically **stable for 28 days at 25°C**, allowing the remainder of the vial to be used over several days.

Cabazitaxel Zentiva® solutions diluted at 0.1 and 0.26 mg/mL in NaCl 0.9% or in D5W were physically and chemically **stable for 28 days at 2-8°C** in Freeflex® infusion bags **or 25°C** in Viaflo® and Easyflex® infusion bags, allowing preparations in advance.

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