PP-029

STABILITY OF FROZEN 1% VORICONAZOLE EYE DROPS IN GLASS AND IN INNOVATIVE CONTAINERS

M.ROCHE[1], D.LANNOY[1], F.BOURDON[1], C.DHORNE[1], C.BERNERON[1], C.DANEL[2], M.J.GARCIA FERNANDEZ[2],N.SIMON[1,2], P.ODOU[1,2]

[1] Centre Hospitalier Régional Universitaire, Pharmacie, Lille, France

[2] Université Lille 2, EA 7365-GRITA-Groupe de Recherche sur les formes injectables et les Technologies Associées, Lille, France

Background

Voriconazole is effective on most keratitis causative fungi with an excellent transcorneal penetration.
Voriconazole eye drops (VED) specialities being unavailable in Europe, they are usually compounded in hospital pharmacies.

New eyedrops containers emerged on hospital market, e.g; High-Density-PolyEthylene bottles available in trays (CAT®), for which few stability data are available[1], or Novelia® bottles which innovative insert maintains sterility after opening (no stability data available).

Purpose

To collect data on VED stability in 3 different containers in order to switch if necessary: Amber glass, HDPE bottles and Novelia® bottles stored frozen (-20°C) and refrigerated once thawed.

Material and Methods

Voriconazole concentration was assessed using a stability-indicating HPLC-UV Diode-Array-Detector method (Ultimate 3000® Thermo Scientific, France).

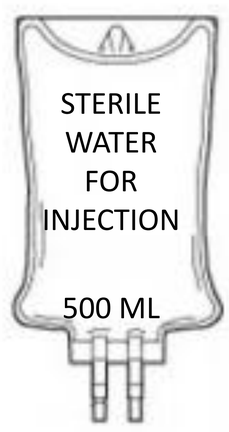
Racemization (impurity D-(2S,3R)-voriconazole) was detected by chiral HPLC (Waters 600®, Guyancourt, France)

European Pharmacopoeia 2.9.19 apparatus (light obscuration particle count test (APSS-2000, Particle measuring systems, Boulder, USA) was used for non visible particle count.

Containers were statistically compared using appropriate non parametric tests (α<5%).

Compounding of Voriconazole eye drops at 10mg/mL (1%)

Three batches of VED (10mL) were aseptically compounded and **stored at -20°C** in 3 different containers:
Amber glass (N = 32, Gravis®), HDPE bottles (N = 32, CAT®) and Novelia® bottles (N = 31,Nemera®)



Sterile water for injection (BAXTER®)

Vfend® (PFIZER®)

Stability study led according to the GERPAC-SFPC stability studies guidelines

D0 D1 D3 D7 D14 D21 D52 D85 D100

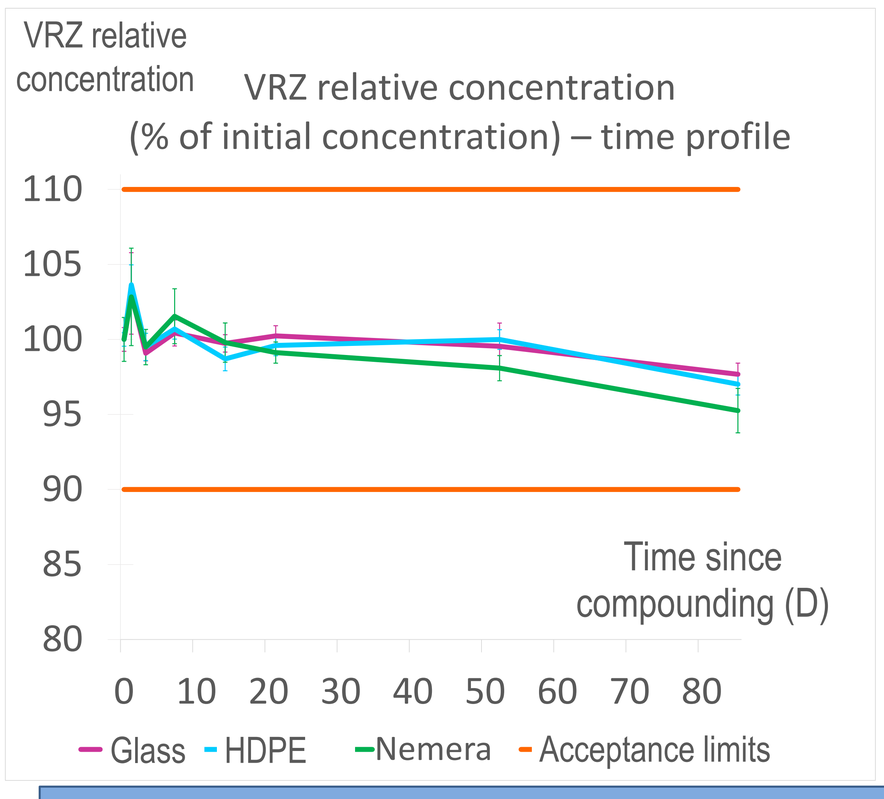
Frozen (-20°C) → 2-8°C

At each time point: Analyses performed in triplicates after thawing
- Visual aspect
- Voriconazole relative concentration (% of initial concentration)
- pH
- Osmolality

At D0 and D85:
- Signs of racemization (quantification of impurity D),
- Non-visible particles count for particle size ≥10µm and ≥25µm
- Sterility assay (performed in duplicate)

Parameters were measured :
- when stored for three months at -20°C,
- then thawed, after 15 days at +2-+8°C, comparing two thawing methods (2-8°C for 6 hours or 25°C for 2 hours)

Results



	D0 Amber glass	D85 Amber glass	D0 HDPE bottles	D85 HDPE bottles	D0 Nemera	D85 Nemera
Osmolality (mOsm/kg)	533.3	533.2	530.4	522.2	532.5	517.5
pH	6.31	6.38	6.32	6.34	6.33	6.33
Particles >10µm (particle/mL)	8.93	70.27	25.33	11.73	34.13	24.73
Particles>25µm (particle/mL)	1	3.13	5.27	0.93	5.33	1.53

Discussion

pH and osmolality remained stable (NS).
Sterility was preserved with no change in visual aspect.
Counts of ≥ 10µm particles remained inferior to 80 particles /mL.
About Voriconazole degradation products (unknown toxicity), areas increased by maximum 1.45 , remaining unquantifiable.
Impact of thawing method on stability was not evidenced.
Impurity D was not detected (LOD=0.3µg/mL) : no racemization was shown.

During storage at -20°C:
- Concentration was between 95.2 ± 1.4% and 103.6 ± 1.3% of initial concentration (Co) (Non significant (NS))

Fifteen days after thawing:
- Concentration was between 97.1 ± 1.6% and 98.6 ± 0.8% of Co (NS)

Conclusion

Voriconazole eye drops remained stable up to three months at -20°C and fifteen days after thawing (stored at 2-8°C).
No notable difference was evidenced between the three containers, allowing to chose the most suitable.

[1] Amoros-Reboredo P. *et al*. Stability of frozen 1% voriconazole ophthalmic solution. Am J Health Syst Pharm (2015);72(6):479-82

marine.roche@etu.univ-lille2.fr.