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1 **Voriconazole topical cream formulation: evidence for stability and antifungal activity**

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16

17 **Abstract**

18 Voriconazole systemic use might be restricted by adverse events such as hepatotoxicity and  
19 neurotoxicity or drug-drug interactions. Topical application on skin could help to better treat  
20 local infection and limit unwanted whole-body exposure. Topical cream voriconazole was  
21 stable for 90 days under refrigerated condition. After oral voriconazole treatment failure, the  
22 patient was successfully treated with the topical 1% voriconazole cream.

23

24 **Keywords**

25 voriconazole; stability; topical; skin infection; fungi; *Fusarium solani*

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## 28 **1. Introduction**

29 Voriconazole (VCZ) is a broad-spectrum triazole antifungal agent which is widely used in the  
30 treatment of invasive fungal infections.<sup>1-4</sup> Its potential serious adverse effects could limit its  
31 use.<sup>5</sup> In case of intolerance to systemic administration (oral or parenteral), serious adverse  
32 events or contraindications, topical skin VCZ treatment could be proposed to patients with  
33 fungal skin infections.<sup>6,7</sup> In this study, we investigated the stability of 1% VCZ cream and its  
34 activity in a 30-year old patient with skin fusariosis, with a background of Hyper-IgE syndrome  
35 (HIES) due to STAT3 deficiency (i.e., a rare autosomal dominant primary immunodeficiency).  
36 The patient was admitted to our hospital for pretibial skin lesions with crusted areas. He had a  
37 history of eczematous dermatitis, lymphoma, recurrent respiratory tract infections, and  
38 onychomycosis. Skin biopsies were positive to *Fusarium* sp, and an MRI of the leg showed  
39 cutaneous and subcutaneous involvement of the anterolateral proximal part of the left leg. The  
40 patient was treated with oral VCZ, but during follow-up, the skin fusariosis worsened. Topical  
41 treatment with VCZ 1% was started as an adjunct to oral VCZ, and after four months of this  
42 treatment, the patient was considered cured.

## 43 **2. Materials and methods**

### 44 **2.1. Preparation of voriconazole cream**

45 VCZ cream was prepared by mixing 1 g of VCZ for injection containing  
46 hydroxypropylbetacyclodextrin and lactose (Accord Healthcare, France) into 100 g of a topical  
47 vehicle (Excipial Hydrocrème, Galderna, La Defense, France), and transferred in empty  
48 ointment tube (COOPER, Melun, France). The topical vehicle contains aqua, paraffin oil,  
49 isopropyl myristate, cetearyl alcohol, glyceryl stearate, pentylene glycol, and polysorbate 20.  
50 The tubes were kept sealed until the day of analysis, stored either under refrigeration (at 4-8°C;  
51 n = 27) or at room temperature (22-25°C; n = 27). To minimize the risk of microbial  
52 contamination, the 1% VCZ topical cream was prepared under a laminar flow. Moreover, the

53 topical base used in the study was microbiologically controlled according to the European  
54 Standard ISO 17516:2014 (<https://www.iso.org/obp/ui/#iso:std:iso:17516:ed-1:v1:en>) which  
55 specified absence in 1 g of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida*  
56 *albicans*, and total coliforms and fecal coliforms. The Excipial certificate of compliance gave  
57 some specifications such as pH around 5.4, total aerobic microbial count <100 cfu/g, total  
58 combined yeast count <10 cfu/g, absence of *P. aeruginosa* and *S. aureus*. The shelf life of the  
59 vehicle was 36 months.

## 60 **2.2 Sample analysis**

61 On days 0, 3, 7, 14, 21, 30, 45, 60 and 90, one gram of cream of each tube was diluted with  
62 water to obtain a theoretical final concentration of 200 µg/mL. The contents of the volumetric  
63 flask were mixed for 30 min to enable complete dissolution of VCZ. The mixture was  
64 centrifuged at 15,000 rpm and 20 µL of the supernatant were injected into a high-performance  
65 liquid chromatograph (HPLC). Three tubes were analyzed in triplicate for each condition at the  
66 designed time points. The HPLC method of Gu et al. was adapted.<sup>8</sup> A liquid chromatography  
67 (LC) system (Dionex Ultimate 3000, ThermoScientific, Villebon-sur-Yvette, France)  
68 comprised a RS-3000 degasser, a HPG-3000 pump, a WPS-3000 autosampler, a column oven,  
69 and a RS-3000 diode array detector. Data acquisition (e.g. peak time, area) was carried out  
70 using in line Chromeleon® software (Thermo Scientific, V6.80 SR15b build 4981). A  
71 Lichrospher 100 C<sub>8</sub> column (dimensions, 250 by 4.0 mm; and particle size, 5 µm; Merck,  
72 Fontenay-sous-Bois, France) was used. The column temperature was 25°C, and the flow rate  
73 was 1.0 mL/min. Isocratic elution was performed using purified water and acetonitrile (50:50,  
74 v/v) as the mobile phase. The UV absorbance detector wavelength was set at 254 nm.  
75 Calibration standard and quality control (QC) stock solutions of VCZ (1 mg/ml) were prepared  
76 in water independently. Working solutions of VCZ were prepared daily by serial dilution of

77 stock solutions with mobile phase to prepare calibration standards (0.05, 0.1, 0.15, 0.2, 0.25,  
78 and 0.3 mg/mL) and QC samples (0.05 and 0.3 mg/mL).

79 Forced degradation studies were performed to demonstrate the stability-indicating capability of  
80 the HPLC method in cream. To generate photodegradation products, samples were exposed to  
81 artificial weathering light, using a xenon test chamber Q-SUN Xe-1 operating in window mode  
82 (Q-Lab Corporation, Saarbrücken, Germany). The light beam, presenting a characteristic  
83 spectrum ranging from 300 to 800 nm, was delivered at an intensity of 1.50 W/m<sup>2</sup> at 420 nm  
84 (UV irradiance from 300 to 400 nm: 66.5 W/m<sup>2</sup>; illuminance: 119.6 klx). Samples were  
85 monitored for pH by using a SevenEasy S20 pH meter (Mettler-Toledo, Viroflay, France) with  
86 a calibrated InLab® Expert Pro-ISM pH sensor (Mettler-Toledo, France).

### 87 **3. Results**

#### 88 **3.1. Analysis**

89 Good linearity over range of concentrations from 0.05 to 0.3 mg/mL was observed  
90 ( $y=0.3928\pm 0.0025x - 2.0434\pm 0.5294$ ,  $r^2 = 0.9995$ ). The intraday (n = 5) and interday (n = 3)  
91 accuracies (percent bias) were within  $\pm 1.1\%$ , and precisions (coefficients of variation) were  
92 within 3%. The lower limits of detection and quantification were 0.001 and 0.004 mg/mL,  
93 respectively. Slight degradation of VCZ was observed upon exposure to acidic conditions  
94 without the appearance of degradation products. With photolytic stress condition, the  
95 degradation of VCZ was less than 10% with the appearance of degradation peaks. VCZ was  
96 more decomposed in alkaline, oxidative, and thermal stress conditions. The peaks of  
97 degradation products were well separated from the intact drug, with VCZ concentrations  
98 reduced by 3.7 to 36.4% compared to the initial concentration, indicating the suitability of the  
99 assay to determine the stability of VCZ. Typical HPLC chromatograms of the standard VCZ  
100 and VCZ extracted from cream are represented in Fig. 1. HPLC chromatograms of degraded  
101 voriconazole are shown in Fig. 2.

### 102 **3.2. Physical Stability of voriconazole**

103 Under refrigerated conditions (4-8°C), 1% VCZ cream was stable for 90 days, with a dosage of  
104  $0.97 \pm 0.02\%$  on day 90 (Fig. 3); the minimum requirement of the Food and Drug  
105 Administration (<https://www.fda.gov/media/69957/download>) is  $\geq 90\%$  of initial dosage. The  
106 cream under refrigerated condition was smooth, thick, and odorless throughout the study period.  
107 Instead, at room temperature (22-25°C), the cream dissociated into two phases at day 21 to turn  
108 liquid. Negligible changes in pH were observed for refrigerated condition (mean  $\pm$  SD,  $5.19 \pm$   
109  $0.08$ ) and room temperature (mean  $\pm$  SD,  $5.20 \pm 0.07$ ). The stability of individual excipients  
110 used in formulation was not performed.

### 111 **3.3. Case report**

112 The clinical activity of topical VCZ was preliminarily investigated in a 30-year-old man with a  
113 cutaneous *F. solani* infection on his right forearm. The fungal infection was focused on  
114 histological examination with periodic acid Schiff and Grocott's stains, and was confirmed by  
115 polymerase chain reaction (PCR) assay. For which, he received oral VCZ treatment at 200 mg  
116 twice daily. The plasma sample analysis of the drug revealed plasma VCZ concentrations  
117 fluctuating and often below 1 mg/L, despite the increase in doses. One hypothesis to explain  
118 the treatment failure was the variability of systemic VCZ exposures based on genetic  
119 polymorphisms in CYP2C19. The CYP2C19 poor metabolizers have demonstrated higher VCZ  
120 systemic levels.<sup>9</sup> The genetic polymorphism in the CYP2C19 gene of the patient was normal.  
121 Thus, the other hypothesis was the poor compliance to therapy. The unsuccessful oral treatment  
122 of VCZ resulted in the introduction of an additional topical application with the 1% VCZ cream  
123 once daily with an occlusive patch. Within three months of local application and the  
124 discontinuation of oral treatment, the healing of the *Fusarium* skin lesion was complete. Related  
125 to the skin infection, the patient revealed a pulmonary infection to *Pseudomonas aeruginosa*  
126 treated with ceftazidime and ciprofloxacin.

127 **4. Discussion and Conclusions**

128 The most effective drugs against *Fusarium* are considered to be amphotericin B and VCZ.<sup>10-12</sup>  
129 The MIC ranges of VCZ for the clinical *Fusarium* strains were 1 to 16 µg/mL.<sup>13</sup> Thus, the 1%  
130 VCZ cream was justified for skin infections caused by *Fusarium* species. To our knowledge,  
131 this is the first report showing the stability of VCZ cream and its clinical efficacy in a patient  
132 with *F. solani* skin infection. Our preliminary results support the need for a pilot study to further  
133 investigate the efficacy and safety of VCZ cream for the management of cutaneous and  
134 subcutaneous fungal infections due to susceptible pathogens.

135

136 **Declarations**

137 **Funding:** No funding

138 **Competing Interests:** None

139 **Ethical Approval:** Written informed consent was obtained from the patient for publication of  
140 this case report.

141

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188

189 **Figure captions**

190 Figure 1. Typical HPLC chromatograms of the standard voriconazole (A) and voriconazole  
191 extracted from cream (B)

192 Figure 2. HPLC chromatograms degraded voriconazole

193 Figure 3. Stability of 1% voriconazole at refrigerated and room temperatures





