

## NON-INTERVENTIONAL STUDY A1501102 REPORT ABSTRACT

**Title:** Evaluation of the Effectiveness of Additional Risk Minimisation Measures (aRMMs) That Aim to Reduce the Risks of Phototoxicity, Squamous Cell Carcinoma (SCC) of the Skin and Hepatic Toxicity in Patients Receiving Voriconazole in the European Union (EU)

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**Rationale and background:** Pfizer Inc. conducted a survey of healthcare professionals (HCPs) to evaluate the effectiveness of the aRMMs implemented across Europe to mitigate the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin, and hepatic toxicity in patients prescribed voriconazole (VFEND<sup>®</sup>), a broad spectrum triazole antifungal agent used to treat or prevent a range of serious fungal infections in both in-patient and out-patient settings.

To ensure that these risks are adequately managed, routine and aRMMs in the EU were distributed beginning in April 2014. These include an updated voriconazole Summary of Product Characteristics (SmPC)<sup>2</sup> (routine) and a new comprehensive education programme (aRMMs) at the point of patient care that educated/reminded HCPs about the risks of phototoxicity, SCC of the skin, and hepatic toxicity and how to manage them.

The 3 components of the RM tools (which can be found in the protocol in [Appendix 2](#)) are the HCP Checklist, HCP Question & Answer (Q&A) Brochure, and Patient Alert Card. The key messages in the tools informing HCPs about the risks of phototoxicity, SCC of the skin, and hepatic toxicity with use of voriconazole and instructions on how to manage these risks were identified from the voriconazole SmPC<sup>2</sup> (version date 28 October 2013).

This non-interventional study was designated as a Post-Authorisation Safety Study (PASS) and was a commitment to the European Medicines Agency (EMA).

**Research question and objectives:** The overall objective was to evaluate the effectiveness of the aRMMs to mitigate the risks of phototoxicity, SCC of the skin, and hepatic toxicity in patients using voriconazole. The evaluation was conducted in 10 of the 33 countries in the EU where RM tools were implemented. Specifically, the goals of the study were to:

1. Assess HCPs' awareness of the RM tools (ie, HCP Checklist, HCP Q&A Brochure, and Patient Alert Card) by estimating the proportion of targeted HCPs who acknowledge receiving the tools.
2. Assess HCPs' utilization of the RM tools (ie, HCP Checklist, HCP Q&A Brochure, and Patient Alert Card) by estimating the proportion of targeted HCPs who acknowledge reading and utilizing the tools.
3. Assess HCPs' knowledge of the risks of phototoxicity, SCC of the skin, and hepatic toxicity with voriconazole by estimating the proportion of targeted HCPs with correct responses to risk knowledge questions.
4. Assess whether HCPs' self-reported behaviour/practices with respect to minimizing the risks of phototoxicity, SCC of the skin, and hepatic toxicity were in accordance with the voriconazole SmPC.<sup>2</sup> This was evaluated by estimating the proportion of targeted HCPs whose responses to the practice-related questions were consistent with the SmPC<sup>2</sup> prescribing information.
  - a) Assess the HCPs' knowledge of practice with respect to mitigating the risks by estimating the proportion of targeted HCPs with correct responses to knowledge of recommended practice questions.

**Study design:** The study objectives were accomplished by means of a cross-sectional survey of all targeted HCPs who were mailed the aRMMs and self-reported as prescribers of voriconazole in the following 10 countries: Austria, Denmark, France, Germany, Hungary, Ireland, Italy, Netherlands, Spain, and United Kingdom (UK). These countries were chosen based on practical considerations (eg, local regulations governing these types of studies) and because they represented the highest volume of voriconazole users across the EU and thereby were expected to provide representative findings in understanding the effectiveness of the aRMMs across the EU. The data from the HCPs were collected using a structured, self-administered questionnaire. The HCPs were invited to take the survey online using a secure uniform resource locator (URL) that required a unique identifier to access the survey.

**Setting:** Voriconazole is mainly prescribed by select specialty care physicians (ie, infectious disease physicians, haematologists, oncologists, and solid organ transplant physicians). These specialty care physicians across the study countries (in Austria, Denmark, France, Germany, Hungary, Ireland, Italy, Netherlands, Spain, and UK) constituted the study population for the survey.

**Subjects and study size, including dropouts:** This survey aimed to include responses from approximately 750 voriconazole prescribers across the 10 study countries. All HCPs in the 10 study countries that received the RM tools were invited to participate in the evaluation survey. Those HCPs who self-reported writing at least 1 prescription for voriconazole within 12 months of receiving the additional RM tools were eligible to complete the survey.

**Variables and data sources:** The variables for analyses were derived from the survey data to address the objectives outlined as follows:

- 1) Awareness of each of the RM tools among HCPs (Questions 9, 10, and 11)
- 2) Receipt and utilisation of the RM tools (Questions 9.1, 13, 15a, 20, and 21)
- 3) HCPs' knowledge/understanding of the risks of phototoxicity, SCC of the skin, and hepatic toxicity (Question 7)
- 4) HCPs' knowledge of recommended practices and self-reported practices with regard to strategies to mitigate the risks (Question 8, 15, 15a, 16, 17, 18, and 19)

Other survey questions included the following:

- 5) Screening items (Questions 1, 2, 3, and 4)
- 6) Demographic characteristics (Questions 5, 6, and 12)
- 7) Usefulness of RM tools in clinical practice (Question 14)

## **Results:**

### *Participants*

There were 27,396 prescribers invited to participate in the survey and of those, 661 invitations were returned as undeliverable; of the 26,735 delivered invitations 447 (1.7%) responded to the invitation (visited the survey website and provided their unique ID). Of the 447 respondents, 354 (79.2%) were eligible for participation of which 332 (93.8%) eligible respondents completed the survey.

### *RM tools receipt and utilization*

The proportions of HCPs who reported receiving the RM tools were low: 19.6% (n=65) for the HCP Q&A Brochure, 22.6% (n=75) for the HCP Checklist and 25.9% (n=86) for the Patient Alert Card.

Of those who reported receiving the HCP Q&A Brochure (n=65), 57 prescribers (87.7%) reported reading all (33.8%, n=22) or some of it (53.8%, n=35). With respect to utilization of the HCP Checklist, among the 75 prescribers who reported receiving it, 49 (65.3%) reported always (17.3%, n=13) or sometimes (48.0%, n=36) using the Checklist; 6 prescribers (8.0%) reported not remembering receiving the checklist. Of the 86 prescribers who reported receiving the Patient Alert Card, 58 (67.4%) reported always (25.6%, n=22) or sometimes (41.9%, n=36) distributing and filing in the Patient Alert Card.

### *Phototoxicity and SCC of the skin*

The rate of knowledge of the risk was 88.6% (n=294) for phototoxicity and 44.3% (n=147) for SCC of the skin. Respondents were in general very knowledgeable about practices recommended to mitigate the risks of phototoxicity and SCC of the skin. When asked which precautionary measures physicians should communicate to their patients for whom they have prescribed voriconazole, 89.5% (n=297) selected “avoiding exposure to direct sunlight”, 92.2% (n=306) selected “detecting signs and symptoms of phototoxicity”, and 81.6% (n=271) selected “use sufficient sunscreen with high sun protection factor (SPF)”. However, a smaller proportion, 62.0% (n=206), selected “covering sun-exposed” areas of the skin, a practice much related to the avoidance of exposure to direct sunlight aspect of risk mitigation.

A great majority (93.7%, n=311) correctly reported that long-term treatment (>6 months) with voriconazole should be considered only if the benefits outweigh the potential risks. When presented with the statement that if phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist, 86.4% (n=287) prescribers correctly responded “True”. Three quarters of respondents (75.6%, n=251) knew that voriconazole should be discontinued if premalignant skin lesions or SCC of the skin are identified. More than three quarters of prescribers (76.5%, n=254) correctly answered that voriconazole should be discontinued in a patient in case of any of the 3 events: phototoxicity, SCC of the skin, or premalignant lesions.

The area of knowledge that received a small proportion of correct responses pertained to the frequency of dermatologic evaluations to be performed when voriconazole is continuously used despite the occurrence of phototoxicity-related lesions. Almost half (48.2%, n=160) of prescribers responded correctly that those dermatologic evaluations should be performed on a systematic and regular basis. Importantly, an additional 12.7% (n=42) reported that they think dermatologic evaluations should be done “weekly”, 14.5% (n=48) reported that they think they should be performed “monthly”. With regard to self-reported practice aimed at risk mitigation, 92.4% (n=307) of respondents reported always (69.3%, n=230) or sometimes (23.2%, n=77) advising patients to avoid exposure to direct sunlight and/or to use measures such as protective clothing and sunscreen.

#### *Hepatic toxicity*

The rate of knowledge by prescribers of the risk of hepatic toxicity with voriconazole was 96.4% (n=320). The results indicate that respondents are very well informed about the practices to mitigate the risk of hepatic toxicity as 95.5% (n=317) correctly responded that laboratory evaluations of hepatic function (specifically AST and ALT) should be performed at initiation and during the first month of treatment with voriconazole and 94.3% (n=313) of respondents correctly answered that if the liver function tests become markedly elevated, voriconazole should be discontinued, unless the medical judgment of the risk-benefit balance of the treatment for the patient justified continued use. A great majority (91.6%, n=304) correctly answered that physicians should communicate to their patients clinical signs of liver damage such as jaundice that warrant contacting the doctor immediately. The 2 questions that received <80% correct responses pertained to the recommended frequency of the liver function tests to be performed on patients prescribed voriconazole. There were 72.0%

(n=239) who correctly answered that liver function tests (specifically AST and ALT) should be performed at voriconazole treatment initiation and weekly thereafter for 1 month. When asked about a scenario where there are no changes in liver function tests after 1 month of initiation of voriconazole, how often should they monitor liver function during the voriconazole treatment maintenance, 78.3% (n=260) correctly answered that this should be done on a monthly basis.

#### *All risks in general*

Respondents demonstrated a high level of self-reported practice to mitigate voriconazole risk in general. Specifically, 90.4% (n=300) reported always (68.1%, n=226) or sometimes (22.3%, n=74) advising patients of the importance of monitoring risks of voriconazole use and signs and symptoms of serious risks that warrant contacting a doctor immediately. A small proportion reported always (12.3%, n=41) or sometimes (28.3%, n=94) discussing the contents of the Patient Alert Card with patients when initiating treatment with voriconazole.

#### *Knowledge of risks, practices, and self-reported behaviour according to reading of the HCP Q&A Brochure*

The data indicate that there are numeric trends of slightly greater knowledge of risks and practice as well as self-reported behaviour among those who read the voriconazole HCP Q&A Brochure compared to those who did not receive it or read it; however, one of the subgroups was small (ie, number of HCPs reporting reading the Brochure, n=57), CIs were wide, and thus, meaningful evaluation of differences was not possible with a reasonable degree of precision.

#### *Other subgroup analyses*

The sample sizes of many of the subgroups were too small to make meaningful comparisons. The results of the subgroup analyses can be found in [Section 15](#).

### **Discussion**

The objective of the study was to evaluate the effectiveness of the additional risk minimization measures (aRMMs) being implemented across the EU to mitigate the risks of phototoxicity, SCC of the skin, and hepatic toxicity in patients using voriconazole.

The survey results indicated that generally, despite the low rate of undeliverable mail of the RM tools (1.7%), it appears that HCPs either did not actually receive the RM tools or did not recall receiving them. Reliance on the respondent's recall for whether or not the additional RM tools were received is an inherent limitation of the study methodology. If the respondent says she/he did not receive a particular tool, the risk minimisation programme is evaluated as not optimally disseminating material. It is also a possibility that the length of time that passed between dissemination of voriconazole RM tools and the evaluation survey (>12 months for some countries) may be a potential factor in low recall of RM tools. Some

variability in reported receipt may also have been related to familiarity of the information and wording of the question.

The study results do indicate that despite low reported receipt or recall of receipt of RM tools, reported knowledge of the risks of phototoxicity and hepatotoxicity and the appropriate practices for safe use of the product is high among voriconazole prescribers, although knowledge of the risk of SCC of the skin itself is low. This lower knowledge rate for SCC of the skin may be due to the relative rarity and latency of SCC of the skin compared to hepatotoxicity and phototoxicity, especially for the typical voriconazole prescriber (eg, prescribed for acutely ill patients with invasive fungal infections).

Practices recommended to mitigate the risks were overall high (many met or exceeded the 80% threshold for success, and most others were  $\geq 70\%$ ) with the exception of information regarding regular dermatological evaluation if voriconazole continues despite occurrence of phototoxicity.

With regard to the reported tool utilization, data indicate that among those who received the tools, 32.3% to 45.3% found the tools very useful and 1.3% to 9.2% found the tools extremely useful. Further, 18.7% to 24.6% had no opinion/not sure about tool usefulness. Thus, a modest portion found the tools useful; however, this finding is limited by the small number of those who recalled receiving the tools.

Numerical trends toward greater knowledge or desired behaviour with respect to risk mitigation among those who reported reading the HCP Q&A Brochure were observed. However, the study was not powered to test the difference, and the sample sizes of the subgroups were too small to make definitive conclusions whether reading the HCP Q&A Brochure has any impact. The sample size gives adequate precision ( $< \pm 5.4\%$ ) around the estimate for the overall results ( $n=332$ ), but given the small subgroup sample sizes (eg,  $n=2$ ,  $n=57$ ), results are indeterminate given the low precision around the estimates (many  $> \pm 10\%$ ).

Although an a priori threshold of 80% correct per risk question was used to define the success of the program, the selection of this threshold for success is subjective and not based on a prior knowledge, experience, or established scientific criteria in the education or risk communication literature (as acknowledged by EMA: 7 May 2015 PRAC Rapporteur PASS Protocol Assessment Report; Procedure no.: EMEA/H/C/000387/MEA 087.2). It was expected that the knowledge may differ by key risk message, clinical practice, HCP specialties, and countries. Although the MAH could not confirm the difference in knowledge according to HCP specialties or countries, given the sample size, knowledge did vary by risk message.

It must be emphasized that the MAH has taken all possible measures to enhance HCP participation. The steps included inviting most of the HCPs who were mailed the RM tools (27,396), sending multiple reminder letters, and supplementing outreach with email invitations and reminders where it was an option.

### *Limitations*

Some limitations should be considered, including the low response rate. It has been noted in literature that participation rates have been decreasing over the past 30 years with more decline in recent years<sup>3</sup> and that for surveys evaluating program effectiveness it was not uncommon for the response rate to be below 10%.<sup>4</sup>

The potential reasons for low study participation (1.7%) were evaluated and are described below:

- **Challenge in identifying voriconazole prescribers.** Although one of the survey inclusion criteria is that the HCP must have prescribed voriconazole within the past 12 months preceding the survey, per protocol, the survey invitations were sent to all potential prescribers of voriconazole in the 10 EU countries who were mailed the aRMM educational materials. Due to local privacy restrictions, the MAH was unable to obtain a list of confirmed voriconazole prescribers. Therefore, the target eligible survey population (ie, self-reported prescribers of voriconazole in the past 12 months) is smaller than the entire population of voriconazole prescribers.
- **Low interest in responding.** Physicians may have competing priorities; lack of interest in participating in studies, particularly with low or no remuneration for their time or studies regarding older drugs with well-established safety profiles.
- **Logistical challenges.** The postal mail invitations may not have reached or been opened by the intended recipient. For example, based on available addresses, it may have been delivered only to the central hospital mail hub; or the office staff may have reviewed and discarded the invitation; and/or it was discarded without opening by the intended recipient. Other potential modes of outreach considered are discussed below.

Further, the statistical interpretability of the subgroup analyses is limited by the small sizes of some subgroups, resulting in wide CIs for results. As noted previously, the sample sizes of many of the subgroups were too small to make meaningful comparisons. Additionally, participants were self-selected and most analyses were based on self-reported characteristics that were subjective and/or could not be confirmed. Some members of the population had no chance of being sampled (as HCPs in 10 of 33 countries were invited to participate); therefore, the extent to which this sample represented the entire population of physicians who prescribe voriconazole cannot be known. Reliance on respondents' recall is another inherent limitation of survey research.

#### *Generalisability*

Because participation in the survey was voluntary and a relatively small proportion of those invited responded and completed the survey in some countries despite efforts to maximize the response rate (overall survey response rate=1.7%), there is a possibility that the participants may differ in terms of characteristics, motivations, awareness of the aRMM, and knowledge of voriconazole risks from those who did not respond to the survey.

When respondents were compared with all invited HCPs in terms of country of practice and medical specialty, the results showed that the distribution of these 2 HCP characteristics was different between the 2 groups. Further, the majority of respondents who completed the survey were from Spain and in the medical specialties of haematology and oncology. Thus, a potential selection bias cannot be ruled out and the generalizability of the study results to all prescribers of voriconazole is unknown.

### *Conclusions*

- Prescribers demonstrated a high level of knowledge and awareness of phototoxicity and hepatic toxicity risks (above 80%). The knowledge of SCC of the skin was low (44.3%).
- The overall knowledge of risk mitigation practices was high (many met or exceeded the 80% threshold for success, and most others were  $\geq 70\%$ ) except for the frequency of dermatologic evaluations recommended if voriconazole is continuously used despite the occurrence of phototoxicity-related lesions (48.2%).
- The source for this knowledge is not clearly linked to the educational material based on the responses received.
- Although a few questions scored below 80%, this threshold was subjective and not based on objective considerations or prior knowledge.
- Due to relatively low reported use of the educational materials, the level of value added and the contribution of the aRMM program is not clear.
- In UBC's experience, there is variability across programs in risk awareness, RM tools receipt, and knowledge of appropriate practices among HCPs; thus, the results are not uncommon/unexpected.
- This evaluation of the education programme provided an opportunity to gain insights into the level of understanding of voriconazole risks and risk mitigation practices.

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