NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

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)
Protocol number	A1501102
Version identifier of the final study report	2.0
Date of last version of the final study report	17 May 2016
EU Post Authorisation Study (PAS) register number	NCEPP/SDPP/10428
Active substance	Voriconazole (a broad spectrum triazole antifungal agent)
Medicinal product	Voriconazole (VFEND®)
Product reference	EU/1/02/212/001-027
Procedure number	EMEA/H/C/000387
Marketing Authorisation Holder (MAH)	Pfizer Limited
Joint Post Authorisation Safety Study (PASS)	No
Research question and objectives	The objective of the study is to evaluate the effectiveness of the aRMMs implemented across the European Union (EU) to mitigate the risks of phototoxicity, SCC of the skin, and hepatic toxicity in patients using

	voriconazole.
Country(ies) of study	France, Germany, United Kingdom (UK), Italy, Netherlands, Hungary, Austria, Denmark, Ireland, Spain
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Marketing Authorisation Holder(s)

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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
CIOMS	Council for International Organizations of Medical Sciences
CIs	Confidence Intervals
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HCPs	Healthcare Professionals
HSCT	Hematopoietic Stem Cell Transplant
IA	Invasive Aspergillosis
ID	Identifier
IEA	International Epidemiological Association
IEC	Independent Ethics Committees
IF	Invasive Fungal Infections
IRB	Institutional Review Board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISPE	International Society for Pharmacoepidemiology
IT	Information Technology
LFTs	Liver Function Tests
NIS	Non-Interventional Study

Abbreviation	Definition
PASS	Post-Authorisation Safety Study
PI	Prescribing Information
Q&A	Question & Answer
RM	Risk Minimisation
RMP	Risk Management Plan
aRMMs	Additional Risk Minimisation Measures
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCC	Squamous Cell Carcinoma
SDLC	System Development Life Cycle
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SPF	Sun Protection Factor
UBC	United BioSource Corporation
UK	United Kingdom
URL	Uniform Resource Locator
VFEND®	Voriconazole

3. INVESTIGATORS

Not applicable.

4. OTHER RESPONSIBLE PARTIES

The table below lists the names of the principal investigators of the protocol, ie, the Pfizer non-interventional study (NIS) lead and any external scientists responsible for the conduct of the study.

Responsible Party Name and Affiliation	Title/Role in Study
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5. MILESTONES

Milestone	Planned date	Actual date*	Comments
Date of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approval of protocol	None.	Austria: 07 Sep 2015 Denmark: 25 Aug 2015 France: N/A Germany: 03 Sep 2015 to 22 Oct 2015 Hungary: 21 Dec 2015 Ireland: 28 May 2015 to 18 Sep 2015 Italy: 09 Oct 2015 to 01 Sep 2015 Netherlands: N/A Spain: N/A UK: N/A	
Start of data collection**	Approximately 12 months after risk minimisation (RM) tools were mailed to HCPs in the 10 study countries.	02 Sep 2015***	
End of data collection	60 days after the start of data collection across the study countries.****	29 Feb 2016	
Final report of study results	3 months after the final data collection for the last study	05 May 2016	

Milestone	Planned date	Actual date*	Comments
	country that received the RM tools.		

* The country-specific IEC/IRB approval dates for the protocol and any amendments are provided in Appendix 3.2.
**The study was initiated after the distribution of the RM tools across the 10 study countries and protocol endorsement by EMA. Therefore, the planned timeline was contingent upon the date of the approval of the RM tools by the local Health Authorities and protocol endorsement by EMA.
***Data collection began on 02 Sep 2015 in France and the United Kingdom (UK). Data collection began in other countries on a rolling basis. The last country to begin data collection was Spain on 31 Dec 2015.
****Due to the varying start dates for data collection, the actual duration of the survey window in each country varied but was a minimum of 60 days.

6. RATIONALE AND BACKGROUND

Voriconazole (VFEND®) is a broad spectrum triazole antifungal agent used in the treatment of a range of serious fungal infections in both inpatient and outpatient settings. The clinical benefit of voriconazole has been demonstrated for the treatment of invasive aspergillosis (IA), candidemia in non neutropenic patients, fluconazole resistant serious invasive *Candida* infections (including *C. krusei*), serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. In the EU, voriconazole is indicated for the treatment of these infections and prophylaxis of invasive fungal infections (IFIs) in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

Phototoxicity, squamous cell carcinoma (SCC) of the skin, and hepatic toxicity have been designated as important 'identified' risks with administration of voriconazole in the Risk Management Plan (RMP) and are currently described in the Summary of Product Characteristics (SmPC).[2] To ensure that these risks are adequately managed, additional risk minimisation measures (aRMMs) were implemented initially in April 2014 based on rolling local health authority approvals in the following 33 countries: Albania, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, the Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, and the UK. These aRMMs target specialty care physicians who prescribe voriconazole, eg, infectious disease physicians, haematologists, oncologists, and solid organ transplant physicians (hereafter referred to as healthcare professionals [HCPs]). 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 voricanozole SmPC[2] (version date 28 October 2013).

Once local Health Authority approval was obtained, the RM tools were mailed to the country within 4 weeks. Additionally, in some of the countries, depending on local rules and regulations, the RM tools were posted to various webpages, including local Pfizer country offices and local National Health Authorities.

Table 1. RM Tools Distribution and Study Country Timelines

Study Country	Date RM Tools Submitted to Local Health Authority	Date RM Tools Mailed to HCPs	Actual Survey Open Date
UK	January 2014	April 2014	September 2015
France	January 2014	April 2014	September 2015
Austria	June 2014	August 2014	October 2015
Ireland	June 2014	August 2014	October 2015
Denmark	June 2014	December 2014	December 2015
Germany	June 2014	November 2014	December 2015
Spain	June 2014	December 2014	December 2015
Italy	June 2014	October 2014	December 2015
Netherlands	June 2014	November 2014	December 2015
Hungary	June 2014	September 2014	December 2015

Pfizer Inc. (hereafter referred to as Pfizer) conducted a survey of HCPs to evaluate the effectiveness of the aRMMs implemented across the EU to mitigate the risks mentioned above.

This NIS was designated as a Post-Authorisation Safety Study (PASS) and was a commitment to the EMA (EMEA/H/C/000387/MEA 087.2).

The Data Collection Tool (ie, survey instrument) can be found in Appendix 1.1 of the protocol (Appendix 2).

7. RESEARCH QUESTION AND OBJECTIVES

The overall objective of this PASS was to evaluate the effectiveness of the aRMMs in mitigating 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 distributed. 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 acknowledged 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 acknowledged reading and utilizing the tools.

3) Assess HCPs' knowledge of the risks of phototoxicity, SCC of the skin, and hepatic toxicity with VFEND 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 VFEND SmPC.[2] This was evaluated by estimating the proportion of targeted HCPs whose responses to the practice-related questions were consistent with the SmPC[2] prescribing information (PI).

    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.

8. AMENDMENTS AND UPDATES

None.

9. RESEARCH METHODS

The survey was designed in collaboration between Pfizer and a vendor, United BioSource Corporation (UBC), a wholly owned subsidiary of Express Scripts, Inc., and was administered and analysed by UBC. The survey was conducted according to the protocol provided in Appendix 2.

9.1. Study design

The study objectives were accomplished by means of a cross-sectional survey of all targeted HCPs who were mailed the RM tools and self-reported as prescribers of voriconazole in the following 10 EU 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 provided by 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.

9.2. 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 10 study countries listed above constituted the study population for the survey.

9.3. Subjects

This survey aimed to recruit approximately 750 voriconazole prescribers across the 10 study countries. All HCPs in the study countries that were mailed the RM tools were eligible to be invited to participate in the evaluation survey. Those HCPs who self-reported prescribing voriconazole at least once within 12 months of receiving the additional RM tools were eligible to complete the survey. The respondents' understanding of the appropriate use and risks of voriconazole was evaluated using an online survey. Each invitation included information on how to access the survey online, and included a unique code for each HCP to ensure that the invitation was used only once. Pursuant to local laws and country regulations, Pfizer could only reimburse HCPs in Spain for their time spent completing the survey.

To ensure comprehension of the invitation and survey, all of the HCP communication was conducted in the local country language. The survey and invitation as well as any reminder letters were translated by a certified translation vendor.

9.3.1. Inclusion criteria

The HCPs had to meet the following criteria to be eligible for inclusion in the survey:

- Willing/consent to participate in this self-administered survey.
- Prescribed voriconazole within the past 12 months preceding the survey.

9.3.2. Exclusion criteria

The HCPs who met any of the following criteria were not eligible for the survey:

- Participated in the User Testing of the RM tools (described in Section 7 Rationale and Background of the protocol; Appendix 2) and/or User Testing of the draft questions for the survey (described in Section 9.4 Data Sources of the protocol; Appendix 2).
- Employed in full time research or hospital administration (ie, non-practicing physicians).
- Employment by Pfizer Inc. or any research organization/vendor contracted by Pfizer to administer the survey.

9.4. Variables

The variables for analyses were derived from the survey data to address the objectives outlined as follows (the full survey is included as Appendix 1.1 of the protocol, Appendix 2 of this report):

1) Awareness of each of the RM tools among HCPs (Questions 9, 10, and 11)

2) Reading and utilisation of the RM tools (Questions 9, 9.1, 10, 11, 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)

   - Consent to participate
   - Whether the HCP managed patient(s) treated with voriconazole during the last 12-month period preceding the survey
   - Employment by Pfizer or any research organization/vendor contracted by Pfizer to administer the survey
   - Participation in User Testing of RM materials or survey questionnaire

6) Demographic characteristics (Questions 5, 6, and 12)

   - Location (city/country/suburb/urban)
   - HCP medical specialty type (eg, infectious disease physician, haematologist, oncologist, and solid organ transplant physician)
   - Number of years practicing medicine
   - Number of self-reported voriconazole treated patients the HCP managed in the last 12-month period preceding the survey

7) Usefulness of RM tools in clinical practice (Question 14)

9.5. Data sources and measurement

A structured self-administered questionnaire comprised of closed-ended questions or statements with multiple response choices (ie, questions or statements asking the HCPs to

choose from a defined list of responses) were used to collect the survey data. The questionnaire collected data on HCP characteristics and their responses to the risk knowledge questions. The data collected from the surveys were used to inform and evaluate the effectiveness of the aRMMs.

9.5.1. Prescriber recruitment

Eligible HCPs to whom the RM tools were mailed received a letter in the postal mail and by email (where it was available) inviting them to participate in the survey. Postal mail was used for each individual invitation. Email was used in addition to postal invitations in 3 countries where it was available (ie, France, UK, and Italy); it was also available in Spain but given the much higher response rate there and the concern about over-sampling in Spain, emails were not sent in Spain. The invitation letter included an overview of the rationale for the survey, reminder about the educational materials, the secure URL to be copied and pasted into their browser, and a unique user identifier (ID).

9.5.2. Subject withdrawal

The HCPs could withdraw from the survey at any point. However, only HCPs who completed the survey were included in the analysis.

9.5.3. Screening and survey administration

The questionnaire began with screening questions to confirm eligibility. Depending on the answers to the screening questions, survey participation was either terminated or continued.

9.5.4. Data collection process

The survey data collection opened for a minimum of 60 days in each of the 10 study countries. The survey start date was expected to begin approximately 12 months after the date of distribution of the RM tools in the individual study countries of Austria, Denmark, France, Germany, Hungary, Ireland, Italy, Netherlands, Spain, and UK (see Table 1 for study country timelines); however, this date varied by country based on the date of RM tools' approval by the local Health Authority.

Data were collected using an electronic data capture (EDC) system developed following a full validation process. A rigorous System Development Life Cycle (SDLC) was used for validation that complied with 23 internal IT Standard Operating Procedures (SOPs) of UBC. Unit testing and formal validation occurred on all appropriate systems and components during the build stage. The SDLC was fortified with SOPs addressing validation for all clinical and risk management-related applications. The internet-based repository was used to store survey data and other relevant programme information. The system was EU Annex 11 compliant. Healthcare professional identifying information was stored separately from survey data.

9.5.4.1. User testing of the survey questions

The proposed questions for the survey were User Tested in the UK for clarity and comprehension prior to survey launch in the study countries. The User testing of the survey

was completed on 12 December 2014. The testing included structured interviews with 12 HCPs in the UK. Findings from the testing along with HCPs' recommendations were used to improve clarity and comprehension of the survey questions. The final questionnaire with User Testing findings incorporated can be found in Appendix 1.1 of the protocol; Appendix 2.

9.5.4.2. Follow-up reminders

The HCP database was routinely updated with responders and after each mailing the database was cross-checked with any correspondence that had an invalid address (eg, incorrect contact details or an HCP who may have retired) or returned via postal mail or email. To determine if an HCP retired, when mail was returned a lookup was conducted via the Web or phone to follow-up with physicians' offices. No further correspondence was sent to the HCPs whose contact details were invalid or whose correspondence was returned as previously described. However, a survey reminder process was assessed using a target sample of HCPs who received the invitation (ie, those for whom there was no indication for not receiving, such as invalid address), but who did not respond within 30 days of the initial mailing.

Approximately 30 days following the initial invitation mailing, at least one reminder was sent to the above referenced target sample of HCPs for each country. The number of reminders was based on the response rate at predefined recruitment milestones identified by Pfizer. The interval between the reminders was approximately 15 days. Previous experience with similar surveys assessing programme effectiveness has shown that 30 days allows enough time for postal mailing to arrive, be routed through hospital, or be re-routed to another clinic location if necessary. This 30-day interval also minimised the potential for contacting the physician too soon without allotting sufficient time for review of the materials. In previous similar survey programmes, the majority of respondents took the initiative to log onto the survey within 72 hours of receiving the invitation.

Following the initial invitation mailing, at least 1 reminder was sent per non-responding HCP in each of the 10 study countries in which the effectiveness evaluation survey was implemented. Two postal reminders were sent in 9 of the 10 study countries with the exception of Germany where only 1 postal reminder was sent due to operational considerations based upon feedback to the local Pfizer Country Office by some HCPs. Additionally, email invitations and reminders were sent in 3 countries where it was available (ie, France, UK, and Italy).

The range of contact for the 10 participating countries was as follows:

- **Austria:** Invitation and 2 postal reminders;
- **Denmark:** Invitation and 2 postal reminders;
- **France:** Invitation and 2 postal reminders and email invitation with 1 email reminder;
- **Germany:** Invitation and 1 postal reminder;

- **Hungary:** Invitation and 2 postal reminders;
- **Ireland:** Invitation and 2 postal reminders;
- **Italy:** Invitation and 2 postal reminders and 1 email invitation;
- **Netherlands:** Invitation and 2 postal reminders;
- **Spain:** Invitation and 2 postal reminders;
- **UK:** Invitation and 2 postal reminders and 1 email invitation.

The variability in the contact metrics can, in large part, be attributed to the different timings of receipt of local regulatory approvals to implement the survey (Denmark, Hungary, Italy, the Netherlands, and Spain were all approved in November/December 2015). For these countries, there was not ample time to administer more than 2 reminders.

Another reason for different contact metrics is based on experience with other effectiveness evaluations which seek to balance the uptake in response rate versus the potential to antagonize HCPs with multiple outreaches for the same survey. Thus, every effort was made to strategically calibrate the timing of the postal versus email invitations and/or reminders to allow the postal letters to reach their recipients and allow HCPs a reasonable time to respond. The objective was to increase the response rate while at the same time maintaining sensitivity so as not to overwhelm the physicians with too many communications.

9.6. Bias

The data from this PASS are susceptible to a few potential biases as described below.

- **Volunteer bias.** Since the participation in the survey was voluntary, the HCPs were self-selected resulting in possible volunteer bias. The low response rate and a resulting non-response bias is another serious limitation of the survey as the HCPs willing to participate in the survey may differ in how they respond to survey questions from those who did not participate. Because of self-selection and low response rate, the results of this survey cannot be generalized to the entire population HCPs who prescribe voriconazole.
- **Recall bias.** A further limitation which is generally inherent in survey research is the reliance on a respondent's recall as to whether or not she/he has received materials. For the purposes of this PASS, the RM tools were the materials used to evaluate the effectiveness of the aRMMs. If the respondent replied that she/he did not receive a particular tool, the risk minimisation programme was evaluated as not having optimally disseminated material while it was possible that prescribers simply did not recall having received the tools that were sent and received. It is also important to keep in mind that the respondent may have had an acceptable understanding of the risks and appropriate behaviours despite not having received or recalled receipt of the tools.

- **Reporting bias.** All data from the survey are self-reported and therefore susceptible to possible reporting bias. This is also applicable to the prescribers' self-reporting of their practice behaviours to minimise the risks. There may be discrepancies between what HCPs would report about their practices and their actual behaviours. Therefore, it is difficult to validate whether HCP responses to practice-related questions are consistent with their actual behaviours in this self-reported survey.

9.6.1. Measures to minimize bias in the sample selection and increase response rate

The following measures were implemented to minimize bias and optimize response rate:

- Since there was no centralized registry or database of all HCPs who had prescribed voriconazole, it was not possible to invite a random sample of all prescribers to take the survey; however, the source of the potential prescriber sampling who opted in to be contacted for marketing and research purposes was quite comprehensive and a large number of voriconazole prescribers were expected to be captured in the database.

- In order to minimize differential recall by participants, prescribers were not eligible to participate in the survey if 1) they were employed in full-time research or hospital administration (ie, non-practising physicians), 2) were employed by Pfizer or UBC, or 3) had participated in the User Testing of the aRMMs.

- Reminder invitation letters/emails were sent to potential participants who did not respond to the initial survey invitation in order to reduce the number of non-respondents and potential non-response bias.

9.6.2. Procedures to minimise bias in survey administration

A number of controls were in place to ensure the survey was conducted in a professional manner and to minimize bias, including the following:

- The survey was programmed to ensure that questions were asked in the appropriate sequence and in a standard order with respect to receipt, reading, and comprehension.

- Lists of sub-items within a question were randomized to minimize the potential for positional bias.

- Skip patterns in the questionnaire were clearly indicated. Respondents could not go back to a question once the question had been answered. Respondents could not skip ahead.

- Programming was reviewed by quality control and simulated users prior to implementing the survey.

9.6.3. Procedures to minimise bias in survey results

A structured comprehension testing of the survey was undertaken before the administration of the survey as described in Section 9.5.4.1.

9.7. Study size

A sample size of approximately 750 completed surveys aggregated across 10 countries was targeted, which was based on both statistical and practical considerations. With a sample size of 750, the statistical precision around the estimate would be ±3.6%. It is to be noted that the final survey sample size depended on HCPs' willingness to participate in the survey. While the target was 750 respondents, all completed responses received by the cut-off date of 29 February 2016 were included in the analysis. The precision around the actual sample size of 332 was approximately ±5.4% around the estimate.

Table 2 presents sample size and precision of estimate calculations for various survey sample sizes. The precision of the estimate calculations were based on the following assumptions:

- The confidence intervals (CIs) around the estimate were 2-sided.
- The probability of type-I error (alpha) was 5%.
- At least 50% of the HCPs would correctly answer key questions about the risks of phototoxicity, hepatic toxicity, and SCC of the skin with the use of voriconazole (or 50% of HCPs' practices with regard to mitigating these risks were in accordance with the SmPC[2]/PI). Basing the sample size estimate on this assumption of 50% accurate risks comprehension (or 50% of HCPs practices in accordance with the SmPC[2]) was the most conservative approach, since either a higher or lower percentage than 50% would have led to higher statistical precision.

Table 2. Precision of the Estimate for a Range of Sample Sizes

Sample Size	Statistical Precision (%)
100	±9.8
150	±8.0
200	±6.9
250	±6.2
300	±5.7
350	±5.2

Sample Size	Statistical Precision (%)
400	±4.9
450	±4.6
500	±4.4
550	±4.2
600	±4.0
650	±3.8
700	±3.7
750	±3.6
800	±3.5
850	±3.4
900	±3.3
950	±3.2
1000	±3.1

9.8. Data transformation

Not applicable.

9.9. Statistical methods

Analyses performed as documented in the SAP, which was completed prior to the end of data collection.

9.9.1. Main summary measures

Descriptive statistics for categorical variables included the prescriber counts and percentages.

9.9.1.1. Statistical analyses

Assessment of HCPs' awareness of the RM tools (ie, HCP Checklist, Q&A Brochure, and Patient Alert Card) by estimating the proportion of targeted HCPs who acknowledge receiving the tools:

Frequency statistics were presented for all questions/items pertaining to the receipt of the RM tools. Exact 2-sided 95% CIs were calculated for the proportion of prescribers who reported receiving the RM tools.

Assessment of 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:

Frequency statistics were presented for all questions pertaining to the reading and utilizing the tools. The denominator for calculation of the percentages and the confidence intervals were the number of completers. Prescribers who reported not receiving the HCP Q&A Brochure were categorized as not having read the brochure.

Assessment of HCPs' knowledge of the risks of phototoxicity, SCC of the skin, and hepatic toxicity with the use of voriconazole:

The responses to all questions pertaining to the knowledge of the risks of phototoxicity, SCC of the skin, and hepatic toxicity with the use of voriconazole were presented by frequency statistics. The correct or desired response for each question was marked by a footnote in the results tables presented in this report and exact 2-sided 95% CIs were calculated for the percentages of respondents who gave the correct/desired response.

Counts and percentages were calculated for each question/item in the questionnaire. The minimum acceptable threshold of understanding, defined as a 80% correct response rate per risk question, was fulfilled if the correct response rate, ie, the actually observed correct response rate, was 80% or higher.

Assessment of the HCPs' knowledge of appropriate practice as well as self-reported behaviour aimed to minimize the risks of phototoxicity, SCC of the skin, and hepatic toxicity:

The responses to all questions pertaining to the HCPs' knowledge of appropriate practice and self-reported behaviour aimed to minimize the risks of phototoxicity, SCC of the skin, and hepatic toxicity were presented by frequency statistics. The correct or desired response for each question was marked by a footnote in the results tables presented in this report and the exact 2-sided 95% CIs were calculated for the percentages of respondents who gave the correct or desired response.

Sub-group analyses:

Sub-group analyses were performed for the following categories of questions:

- Receipt of the RM tools
- Reading and utilisation of the RM tools
- Knowledge questions about the risk of phototoxicity, SCC of the skin, and hepatic toxicity
- Knowledge of appropriate practice as well as self-reported behaviours/practices aimed to minimize the risks

The following were also reported as part of this analysis:

Survey administration statistics

- The number of invitations issued (I);
- The number of invitations returned as undeliverable (R)
- The number of respondents screened for participation (S);
- Survey response rate = S/(I-R);
- The number of respondents eligible for participation (E);
- Eligibility rate = E/S;
- The number of eligible respondents who completed the survey (C);
- Completion rate = C/E;

The survey administration statistics were performed by country and overall. The number of invitations issued and the number returned as undeliverable were also presented by medical specialty.

Prescriber eligibility questions

Responses to all eligibility questions were presented for the Screened Respondents Population. Prescriber eligibility was analysed by country and overall.

Demographic and other characteristics of respondents

Demography and other characteristics of respondents were presented for the Completers. Frequency statistics were presented for the following items:

- Country of practice
- Medical specialty (categories as in the survey)

- Years of practicing medicine
- Number of patients treated with voriconazole in the past 12 months

Country of practice and medical specialty were also compared between the survey responders and all invited HCPs.

9.9.2. Main statistical methods

The statistical analysis was mainly descriptive, ie, no formal hypotheses were tested. Descriptive statistics for categorical variables included counts and percentages.

Exact 2-sided 95% CIs were calculated for the correct/desired response rates by the method of Clopper-Pearson.[1]

Free text and verbatim responses were presented in data listings and, as appropriate, were categorized for categorical data analysis. For the categorized responses, counts and percentages were presented.

9.9.3. Missing values

Only completed surveys were analysed. The use of a web-based questionnaire did not result in any missing data with the exception of built-in skip logic/pattern.

9.9.4. Sensitivity analyses

None.

9.9.5. Amendments to the statistical analysis plan

None.

9.10. Quality control

The survey data were collected using a secure online EDC survey system. The proposed data entry system was validated and was secure for receiving and storing survey data. A web-based data repository was used to warehouse survey data and other relevant program information. This EDC system was an EU Annex 11 compliant platform for the entry, storage, manipulation, analysis, and transmission of electronic information. This platform ensured compliance with all relevant regulatory guidelines.

The EDC application is a core technology for capturing, managing and reporting data. Data may be exported in a variety of formats including Statistical Analysis Software (SAS) Transport®, Excel, and delimited ASCII files. Based on Microsoft's NET technologies, the EDC platform was integrated with reporting services to enable real-time access to data collected via the web. All data entered were single data entered by the respondent. Data were checked in real time against the programmed edit specifications as they were entered to ensure that data were being entered according to acceptable parameters and requirements.

The vendor had an independent Information Technology (IT) Quality Assurance Group that was responsible for managing and overseeing system/application development and validation, as well as related compliance functions.

9.11. Protection of human subjects

9.11.1. Informed consent

Not applicable.

9.11.2. Independent ethics committee (IEC)

The final prescriber survey protocol and survey questionnaire were submitted to local regulatory authorities such as ethics committees, where required.

9.11.3. Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and followed generally accepted research practices described in *Guidelines for Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), and Guide on Methodological Standards in Pharmacoepidemiology.

9.12. Safety reporting

See Section 11 of the protocol (Appendix 2) for management and reporting of adverse events/adverse reactions.

10. RESULTS

10.1. Participants

There were 27,396 HCPs 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 (Table 3 overall). Survey administration statistics by country can be found in Section 15 (Table 1.1).

Table 3. Survey Administration Statistics

Question	N	%
The number of invitations issued (I)	27,396	
The number of invitations returned as undeliverable (R)	661	
The number of respondents screened for participation (S)	447	
Survey response rate = S/(I-R)		1.7[a]
The number of respondents eligible for participation (E)	354	
Eligibility rate = (E/S)		79.2[b]
The number (deleted and percentages) of eligible respondents who completed the survey ("Completers") (C)[c]	332	
Completion rate = (C/E)		93.8[c]

[a] Survey response rate (S/[I-R]) was calculated as the percentage of the number of respondents screened for participation (S) divided by the invitations issued (I) minus the number of invitations returned as undeliverable (R).
[b] Eligibility rate (E/S) was calculated as the percentage of the screened respondents. The screened respondents consisted of all respondents who had accessed the survey using the unique code regardless of whether or not they answered any survey questions.
[c] The completion rate (C/E) was calculated using the number of eligible prescribers.
Source: Section 15; Table 1.1.

Of the 93 respondents who were ineligible to participate, 13 (14.0%) indicated they did not agree to take part in the survey, 26 (28.0%) reported they had not prescribed voriconazole in the previous 12 months, 1 (1.1%) reported they were currently employed by Pfizer or UBC, 2 (2.2%) reported they had participated in qualitative research of voriconazole RM materials, and 51 (54.8%) discontinued participation prior to completing the screening questions (Table 1.2a; Section 15).

10.2. Respondent demographic data

Of all completers (N=332), the largest proportions of participants who completed the survey were from Spain (57.5%, n=191) and France (12.7%, n=42) (Table 4). The largest proportion of primary medical specialty of prescribers was haematology (46.1%, n=153) followed by oncology (26.8%, n=89) (Figure 1). Almost half of the prescribers had been practicing medicine for 15 or more years (48.8%, n=162) (Figure 2) and had prescribed voriconazole for 1 to 5 patients during the last 12 months preceding the survey (47.6%, n=158) (Figure 3). Respondent demographic data are summarized in Table 2; Section 15.

Figure 1. Primary Medical Specialty (N=332) (Completed Surveys From All Countries Combined)

Source: Section 15, Table 2.

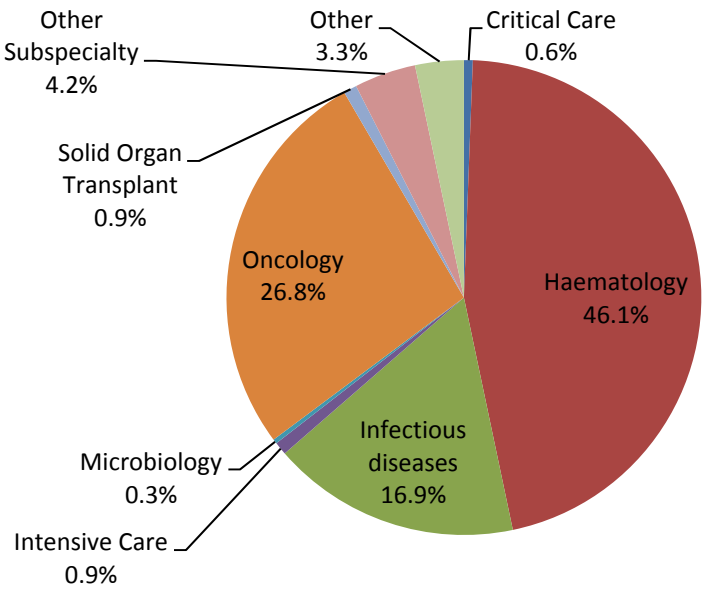


Figure 2. Number of Years Practicing Medicine (N=332) (Completed Surveys From All Countries Combined)

Source: Section 15, Table 2.

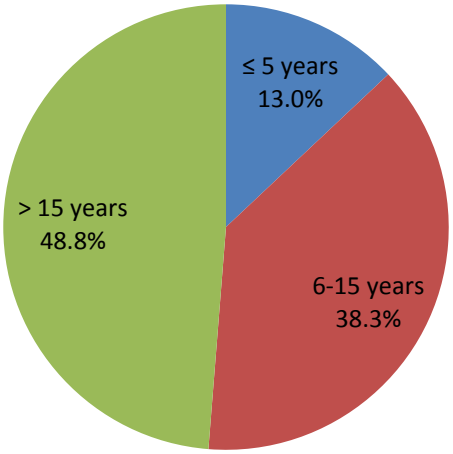
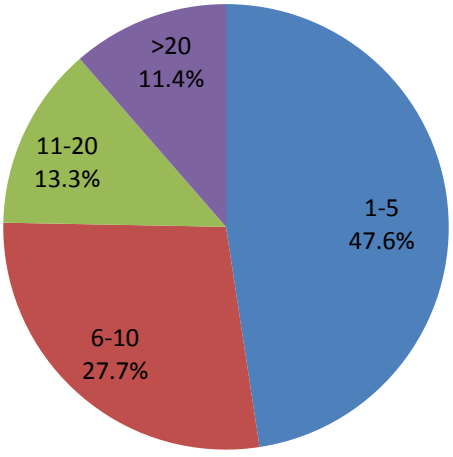


Figure 3. Number of Patients Treated with Voriconazole in the Past 12 Months (N=332) (Completed Surveys From All Countries Combined)

Source: Section 15, Table 2.



Comparison of country of practice and medical specialty between respondents and nonrespondents

To assess non-response bias, we evaluated the completers versus all invitees based on the 2 characteristics that were known on both populations: country of practice and medical specialty. The data indicate that the distribution of these 2 characteristics differ among respondents compared to all HCPs who were invited to take the survey. The largest proportion of invitations to HCPs were sent to France (22.7%) followed by Spain (17.6%) and the UK (17.4%). However, the largest proportions of participants who completed the survey were in Spain (57.5%) and the medical specialty of haematology (46.1%) followed by oncology (26.8%) (Table 4).

Table 4. Comparison of Country of Practice and Medical Specialty Between Respondents and the Invited HCP Population

Question	Prescribers Who Completed the Survey N=332 n (%)	Invited HCPs N=27,397 n (%)
Country of practice		
United Kingdom	21 (6.3)	4,780 (17.4)
France	42 (12.7)	6,229 (22.7)
Austria	2 (0.6)	373 (1.4)
Ireland	7 (2.1)	308 (1.1)
Denmark	5 (1.5)	871 (3.2)
Germany	16 (4.8)	3,136 (11.4)
Spain	191 (57.5)	4,823 (17.6)
Italy	14 (4.2)	2,375 (8.7)
The Netherlands	21 (6.3)	3,615 (13.2)
Hungary	13 (3.9)	887 (3.2)
Question 5: What is your primary medical specialty?		
Critical Care	2 (0.6)	13 (0.0)
Haematology	153 (46.1)	10,116 (36.9)
Infectious diseases	56 (16.9)	2,980 (10.9)
Intensive Care	3 (0.9)	275 (1.0)
Microbiology	1 (0.3)	44 (0.2)

Table 4. Comparison of Country of Practice and Medical Specialty Between Respondents and the Invited HCP Population

Question	Prescribers Who Completed the Survey N=332 n (%)	Invited HCPs N=27,397 n (%)
Oncology	89 (26.8)	8,723 (31.8)
Solid Organ Transplant	3 (0.9)	93 (0.3)
Other/Subspecialty (Specify)[1]	14 (4.2)	0
Other: (Specify)[2]	11 (3.3)	4,973 (18.2)
Not Reported	0	180 (0.7)

[1] Verbatim texts for other subspecialty for prescribers who completed the survey are reported in Listing 1.
[2] Verbatim texts for other specialty for prescribers who completed the survey are reported in Listing 2.
Source: Section 15; Table 2a.

10.3. Outcome data

Not applicable.

10.4. Main results

Results of the survey described below include responses from prescribers from all participating countries. Sample sizes of subgroups stratified by country, medical specialty, and the number of patients treated with voriconazole in the 12 months prior to survey participation were too small to permit comparisons and assess differences. Tables presenting survey results by subgroup are located in Section 15 (Tables 3.1 through 3.3 for receipt of RM tools, Tables 4.1 through 4.3 for reading and utilization of RM tools, Tables 5.1 through 5.4 for knowledge of the risks of phototoxicity, SCC of the skin, and hepatic toxicity with voriconazole, and Tables 6.1 through 6.4 for knowledge of the appropriate behaviours/practices and self-reported practice).

10.4.1. RM tools

10.4.1.1. Receipt of the RM tools for all countries combined

Table 5 presents responses to all questions about the receipt of the RM tools for VFEND for all countries combined.

Among all survey completers (N=332), about one quarter of prescribers who completed the survey reported they received the voriconazole HCP Q&A Brochure (19.6%, n=65), the voriconazole HCP Checklist (22.6%, n=75), or the voriconazole Patient Alert Card (25.9%, n=86). The majority of prescribers reported that they did not receive or did not remember receiving the respective RM tools.

Table 5. Receipt of the RM Tools – (Completed Surveys from All Countries Combined)

Question	Prescribers n=332 n (%) [95% CI][1]
Question 9: Did you or your hospital receive the VFEND (voriconazole) Healthcare Professional (HCP) Q&A Brochure?	
Yes[2]	65 (19.6) [15.4 - 24.3]
No	81 (24.4)
I don't remember receiving it	186 (56.0)
Question 10: Did you or your hospital receive copies of the VFEND (voriconazole) Healthcare Professional (HCP) Checklist?	
Yes[2]	75 (22.6) [18.2 - 27.5]
No	68 (20.5)
I don't remember receiving them	189 (56.9)
Question 11: Did you or your hospital receive copies of the VFEND (voriconazole) Patient Alert Card?	
Yes[2]	86 (25.9) [21.3 - 31.0]
No	90 (27.1)
I don't remember receiving them	156 (47.0)

[1] 95% exact 2-sided confidence intervals were calculated using the Clopper-Pearson[1] method.
[2] Desired response.
Source: Section 15; Table 3.

10.4.1.2. Reading and utilisation of the RM tools for all countries combined

Table 6 presents responses to all questions about reading and the utilisation of the RM tools for voriconazole among those completers from all countries combined who reported receiving the tools.

Out of those completers who reported receiving the voriconazole HCP Q&A Brochure (N=65), 57 prescribers (87.7%) reported that they read all (33.8%, n=22) or some (53.8%, n=35) of the voriconazole HCP Q&A Brochure. Out of those completers who reported receiving the voriconazole HCP Checklist (N=75), 49 prescribers (65.3%) used the voriconazole HCP Checklist always (17.3%, n=13) or sometimes (48.0%, n=36). Of those completers who reported receiving the voriconazole Patient Alert Card (N=86), 58 prescribers (67.4%) distributed and filled in the Patient Alert Card always (25.6%, n=22) or sometimes (41.9%, n=36). Responses to all questions about reading and utilization of the RM tools among all completers from all countries combined can be found in Section 15 Table 4.

Table 6. Reading and the Utilization of the RM Tools Based on the Receipt of Materials - (Completed Surveys From All Countries Combined)

Question	Prescribers n (%)
Question 9.1: Did you read the VFEND (voriconazole) HCP Q&A Brochure? (N=65)[1]	
Yes, all of it	22 (33.8)
Yes, some of it	35 (53.8)
No, I did not read it	4 (6.2)
I don't remember reading it	4 (6.2)
Read all of it or some of it[3]	57 (87.7)
Question 13: When treating patients with VFEND (voriconazole) in the past 12 months, how often did you use the VFEND HCP Checklist? (N=75)[1]	
Always	13 (17.3)
Sometimes	36 (48.0)
Never	20 (26.7)
I don't remember receiving copies of the HCP Checklist	6 (8.0)
Always or sometimes[3]	49 (65.3)
Question 15a: How frequently do you, or another member of your healthcare team (e.g. nurse, pharmacist or other), perform each of these activities when initiating treatment with VFEND (voriconazole)? (Please check one response for each activity below). (N=86)[1]	
Distribute and fill in the Patient Alert Card	
Always	22 (25.6)
Sometimes	36 (41.9)
Never	28 (32.6)
Always or sometimes[3]	58 (67.4)

[1] Counts and percentages were calculated based on receipt of the VFEND (voriconazole) HCP Q&A Brochure (ie, among those who answered "Yes" to survey Question 9).
[2] Desired response.
[3] Counts and percentages were calculated based on receipt of the VFEND (voriconazole) Healthcare Professional (HCP) Checklist (ie, among those who answered "Yes" to survey Question 10).
[4] Counts and percentages were calculated based on receipt of the VFEND (voriconazole) Patient Alert Card (ie, among those who answered "Yes" to survey Question 11).
Source: Section 15; Table 4a.

10.4.2. Risks of phototoxicity and SCC of the skin with voriconazole

Responses to questions about the knowledge of risks, knowledge of appropriate behaviour/practice with regard to strategies to mitigate risks, and self-reported practice with

regard to mitigating the risks of phototoxicity and SCC of the skin with voriconazole are presented in Table 7 for all countries combined.

10.4.2.1. Knowledge of the risks of phototoxicity and SCC of the skin with voriconazole

For Question 7, 294 (88.6%) prescribers correctly identified phototoxicity as a risk of voriconazole (according to the SmPC[2]/PI). Of all respondents (N=332), 147 (44.3%) correctly identified SCC of the skin as a risk; 120 (36.1%) responded that SCC of the skin is not a known risk associated with voriconazole, and 65 (19.6%) responded "I Don't Know".

10.4.2.2. Knowledge of appropriate behaviour/practice with regard to strategies to mitigate the risks of phototoxicity and SCC of the skin

For Question 8 items, 287 (86.4%) prescribers selected the desired response of "True" that if phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist. The correct-response rate was lower when asked to select "True" or "False" that voriconazole should not be discontinued if premalignant skin lesions or SCC of the skin are identified (75.6% "False"). A majority (93.7%, n=311) of all respondents correctly responded that long-term treatment (>6 months) with voriconazole should be considered only if the benefits outweigh the potential risks.

For Question 15, prescribers demonstrated a good understanding (with correct response rates of 81.6% to 92.2%) that patients should be informed about avoiding exposure to direct sunlight, detecting signs and symptoms of phototoxicity, and using sufficient sunscreen with high sun protection factor (SPF). The correct-response rate was lower when asked if patients should be informed about covering sun exposed areas of skin (62.0% "Yes").

The lowest scoring item for Question 15 pertained to the response option "dermatologic evaluation should be performed on a systematic and regular basis" (34.9% selected the correct response).

Question 18 asked about the same risk message using a complete statement from the RM tools. To that question, 160 (48.2%) of all respondents correctly answered that dermatologic evaluation should be performed on a systemic and regular basis (as opposed to weekly, monthly, or every 2 months) when voriconazole is continuously used despite the occurrence of phototoxicity-related lesions, while 42 (12.7%) responded that the dermatologic evaluation should be performed weekly, and 48 (14.5%) responded that it should be performed monthly; 58 (17.5%) selected the option "I Don't Know".

Question 19 asked about when voriconazole should be discontinued in a patient. Of all respondents, 254 (76.5%) correctly selected "all of the above" out of the following choices; phototoxicity, SCC of the skin, and premalignant lesions.

10.4.2.3. Self-reported practice with regard to strategies to mitigate the risks of phototoxicity and SCC of the skin

Question 15a assessed how frequently the respondent or another member of the healthcare team performed each of 6 risk mitigation activities when initiating treatment with

voriconazole. There were 230 (69.3%) respondents who said they always and 77 (23.2%) respondents who said they sometimes advise patients to avoid exposure to direct sunlight and/or to use measures such as protective clothing and sunscreen.

Additionally, in terms of additional Question 15 items pertaining to self-reported practice pertaining to risk mitigation in general, 226 (68.1%) respondents reported always advising patients of the importance of monitoring risks of voriconazole use and signs and symptoms of serious risks that warrant contacting a doctor immediately; 74 (22.3%) reported sometimes advising patients about these measures. With regard to self-reported discussion of the contents of the Patient Alert Cards, 41 (12.3%) reported always doing it, and 94 (28.3%) reported doing it sometimes.

There were no questions that pertained to self-reported practice to mitigate the risk of SCC of the skin.

Table 7. Knowledge of Risks, Appropriate Behaviour/Practice With Regard to Strategies to Mitigate Risks, and Self-Reported Practice With Regard to Mitigating the Risks of Phototoxicity and SCC of the Skin With VFEND (Completed Surveys From All Countries Combined)

Question		**Proportion of HCPs Who Provided Correct/Desirable Response N=332 n (%) [95% CI][1]**
Knowledge of risk	**Question 7: According to the SmPC/PI, the known risks for VFEND (voriconazole) are as follows (Yes/No/I Don't Know)**	
	Phototoxicity (eg, skin rash) (Yes)[2]	294 (88.6) [84.6 – 91.8]
	Squamous cell carcinoma (SCC) of the skin (Yes)[2]	147 (44.3) [38.9 – 49.8]
Knowledge of practice to mitigate risk	**Question 8: Please select only one response for each statement about VFEND below (True/False/I Don't Know):**	
	Long-term treatment (>6 months) with VFEND (voriconazole) should be considered only if the benefits outweigh the potential risks (True)[2]	311 (93.7) [90.5 – 96.0]
	If phototoxic reactions occur,	287 (86.4) [82.3-89.9]

Table 7. Knowledge of Risks, Appropriate Behaviour/Practice With Regard to Strategies to Mitigate Risks, and Self-Reported Practice With Regard to Mitigating the Risks of Phototoxicity and SCC of the Skin With VFEND (Completed Surveys From All Countries Combined)

	multidisciplinary advice should be sought and the patient should be referred to a dermatologist (True) [2]	
	VFEND should NOT be discontinued if premalignant skin lesions or skin squamous cell carconoma (SCC) are identified (False) [2]	251 (75.6) [70.6 – 80.1]
Knowledge of practice to mitigate risk	**Question 15: Which precautionary measures should physicians communicate to their patients for whom they have prescribed VFEND? (Check all that apply)**	
	Avoiding exposure to direct sunlight (Yes) [2]	297 (89.5) [85.6 – 92.5]
	Detecting signs and symptoms of phototoxicity (Yes) [2]	306 (92.2) [88.7 – 94.8]
	Covering sun-exposed areas of skin (Yes) [2]	206 (62.0) [56.6 – 67.3]
	Use sufficient sunscreen with high sun protection factor (SPF) (Yes) [2]	271 (81.6) [77.0 – 85.6]
	Dermatologic evaluation should be performed on a systematic and regular basis (Yes) [2]	116 (34.9) [29.8 – 40.3]
Self-reported practice	**Question 15a: How frequently do you or another member of your healthcare team perform each of these activities when initiating treatment with VFEND (Always/Sometimes/Never)?**	
	Advise patients to avoid exposure to direct sunlight and/or to use measures such as protective clothing and sunscreen	
	Always[2]	230 (69.3) [64.0 – 74.2]

Table 7. Knowledge of Risks, Appropriate Behaviour/Practice With Regard to Strategies to Mitigate Risks, and Self-Reported Practice With Regard to Mitigating the Risks of Phototoxicity and SCC of the Skin With VFEND (Completed Surveys From All Countries Combined)

	Sometimes	77 (23.2)
	Always or Sometimes	307 (92.5)
	Question 18: How often should a dermatologic evaluation be performed when VFEND (voriconazole) is continuously used despite the occurrence of phototoxicity-related lesions?	
	Weekly	42 (12.7)
	Monthly	48 (14.5)
	Every two months	24 (7.2)
	On systemic and regular basis[2]	160 (48.2) [42.7 – 53.7]
	I do not know	58 (17.5)
	Question 19: When should VFEND (voriconazole) be discontinued in a patient? (Select the one best response).	
	Phototoxicity	20 (6.0)
	Squamous Cell Carcinoma (SCC)	38 (11.4)
	Premalignant lesions	20 (6.0)
	All of the above[[2]	254 (76.5) [71.6 - 81.0]

[1] The 95% exact 2-sided confidence intervals were calculated using the Clopper-Pearson[1] method.
[2] Correct or desired response.
Source: Section 15; Tables 5 and 6.

10.4.2.4. Knowledge of the risks of phototoxicity and SCC of the skin with voriconazole by reading the HCP Q&A Brochure

The results of the subgroup analyses of HPC knowledge of risks of phototoxicity and SCC of the skin by reading/not reading or no receipt of the Q&A Brochure is presented in Table 8.

As seen in Table 8 and Table 6.4 (Section 15), the data indicate numeric trends of slightly greater knowledge of risks, knowledge of practice, and self-reported practice regarding recommended risk mitigation among those who read the voriconazole HCP Q&A Brochure compared to those who did not. However, the subgroup of those who reported reading the Q&A Brochure was small (ie, n=57) and meaningful comparisons were not possible.

Knowledge of risk

A larger proportion of prescribers who read some or all of the Q&A Brochure compared with those who did not receive or read it correctly identified phototoxicity (94.7% versus 87.3%, respectively) and SCC of the skin (61.4% versus 40.7%, respectively) as risks associated with voriconazole (Question 7) (Table 8).

Knowledge of practice to mitigate risk

Question 15 items relating to HCP knowledge of detecting signs and symptoms of phototoxicity covering sun-exposed areas of skin, and using sufficient sunscreen were all answered correctly by a larger proportion of prescribers who read some or all of the Q&A Brochure as compared with those who did not receive or read it (Section 15, Table 6.4). Results were the same between the subgroups for avoiding exposure to direct sunlight.

Question 8 items relating to the consideration of long-term treatment only if benefits outweigh potential risks and seeking multidisciplinary advice and referring to a dermatologist for phototoxic reactions were answered correctly by a larger proportion of prescribers who read some or all (100.0% and 96.5%, respectively) of the Q&A Brochure as compared with those who did not receive or read it (92.4% and 84.4%, respectively). Correct-response rates for a Question 8 item on discontinuing treatment if premalignant skin lesions or SCC of the skin are identified were similar for the 2 subgroups (75.4% versus 75.6%). A larger proportion of prescribers who read some or all (47.4% and 32.4%, respectively) of the Q&A Brochure correctly answered Question 18 on performing dermatologic evaluation on a systemic and regular basis (as opposed to weekly, monthly, or every 2 months) when voriconazole is continuously used despite the occurrence of phototoxicity-related lesions and Question 19 on discontinuing voriconazole when phototoxicity, SCC of the skin, or premalignant lesions occur by selecting “All of the above” (correct response) as compared with those who did not receive or read Q&A Brochure (80.7% versus 75.6%, respectively).

Self-reported practice

A larger proportion of prescribers who read some or all of the Q&A Brochure responded that they always advise patients to avoid exposure to direct sunlight and/or to use measures such

as protective clothing and sunscreen as compared with those who did not receive or read Q&A Brochure (80.7% versus 66.9%, respectively; Question 15a, Section 15, Table 6.4).

No question pertained to self-reported practice to mitigate the risk for SCC of the skin.

Table 8. Knowledge of the Risks of Phototoxicity, SCC of the Skin, and Hepatic Toxicity With VFEND by Reading the HCP Q&A Brochure - (Completed Surveys From All Countries Combined)

	Reading the HCP Q&A Brochure	
Question	**Read Some or All of It N=57 n (%) [95% CI][1]**	**Did Not Receive or Read It N=275 n (%) [95% CI][1]**
Question 7: According to the SmPC/PI, the known risks for VFEND (voriconazole) are as follows: (Please select only one response for each of the risks listed in the table below.)		
Phototoxicity (e.g. skin rash)		
Yes[2]	54 (94.7) [85.4 - 98.9]	240 (87.3) [82.7 - 91.0]
No	2 (3.5)	14 (5.1)
I Don't Know	1 (1.8)	21 (7.6)
Intestinal perforation		
Yes	8 (14.0)	16 (5.8)
No[2]	39 (68.4) [54.8 - 80.1]	189 (68.7) [62.9 - 74.2]
I Don't Know	10 (17.5)	70 (25.5)
Squamous cell carcinoma (SCC) of the skin		
Yes[2]	35 (61.4) [47.6 - 74.0]	112 (40.7) [34.9 - 46.8]
No	18 (31.6)	102 (37.1)
I Don't Know	4 (7.0)	61 (22.2)
Asthma		
Yes	5 (8.8)	34 (12.4)
No[2]	39 (68.4) [54.8 - 80.1]	157 (57.1) [51.0 - 63.0]
I Don't Know	13 (22.8)	84 (30.5)
Hepatic toxicity		

Table 8. Knowledge of the Risks of Phototoxicity, SCC of the Skin, and Hepatic Toxicity With VFEND by Reading the HCP Q&A Brochure - (Completed Surveys From All Countries Combined)

	Reading the HCP Q&A Brochure	
Question	**Read Some or All of It N=57 n (%) [95% CI][1]**	**Did Not Receive or Read It N=275 n (%) [95% CI][1]**
Yes[2]	56 (98.2) [90.6 - 100.0]	264 (96.0) [93.0 - 98.0]
No	1 (1.8)	6 (2.2)
I Don't Know	0	5 (1.8)
Cardiomyopathy		
Yes	19 (33.3)	77 (28.0)
No[2]	27 (47.4) [34.0 - 61.0]	115 (41.8) [35.9 - 47.9]
I Don't Know	11 (19.3)	83 (30.2)

[1] 95% exact 2-sided confidence intervals were calculated using the Clopper-Pearson[1] method.
[2] Correct response.
Abbreviations: Read some or all of it = Received it and read some of it or all of it; Did not receive or read it = Did not receive, does not remember receiving or did not read or does not remember reading it.
Source: Section 15, Table 5.4.

10.4.3. Risks of hepatic toxicity with voriconazole

Table 9 presents the responses to all questions about the knowledge of the risks, knowledge of appropriate behaviour/practice with regard to strategies to mitigate the risks, self-reported practice with regard to strategies to mitigate the risks of hepatic toxicity with voriconazole for all countries combined.

10.4.3.1. Knowledge of the risks of hepatic toxicity with voriconazole

Most prescribers correctly identified hepatic toxicity as a known risk of voriconazole (according to the SmPC[2]/PI) (96.4%, n=320) (Question 7).

10.4.3.2. Knowledge of appropriate behaviour/practice with regard to strategies to mitigate the risks of hepatic toxicity

For Question 8, which assessed knowledge of 5 risk-mitigation behaviours related to hepatic toxicity, 317 (95.5%) correctly identified as "False" the statement that "Laboratory evaluation of hepatic function (specifically AST and ALT) at initiation and during the first month of treatment with voriconazole is not necessary". Similarly, a high proportion of all respondents (94.3%, n=313) correctly identified as "True" the following statement: "If the liver function tests become markedly elevated, voriconazole should be discontinued, unless

the medical judgement of the risk-benefit balance of the treatment for the patients justified continued use".

Question 15 assessed knowledge of precautionary measures that physicians should communicate to their patients for whom they have prescribed voriconazole. There were 304 respondents (91.6%) who knew that physicians should communicate to their patients clinical signs of liver damage, such as jaundice that warrant contacting the doctor immediately.

Questions 16 and 17 pertained to the recommended frequency of liver function tests. Of all respondents, 239 (72.0%) knew that liver function tests should be performed at voriconazole treatment initiation and weekly thereafter for 1 month. There were 260 (78.3%) prescribers who correctly answered that if there are no changes in liver function tests after 1 month of initiation of voriconazole, the physician should monitor liver function on monthly basis.

10.4.3.3. Self-reported practice with regard to strategies to mitigate the risks of hepatic toxicity

There were no questions that pertained to self-reported practice to mitigate this risk.

Table 9. Knowledge of the Risks, Appropriate Behaviour/Practice With Regard to Strategies to Mitigate the Risks, and Self-Reported Practice With Regard to Strategies to Mitigate the Risks of Hepatic Toxicity With VFEND (Completed Surveys From All Countries Combined)

Question		Proportion of HCPs Who Provided Correct/Desirable Response N = 332 n (%) [95% CI][1]
Knowledge of risk	**Question 7: According to the SmPC/PI, the known risks for VFEND (voriconazole) are as follows (Yes/No/I Don't Know)**	
	Hepatic toxicity (Yes) [2]	320 (96.4) [93.8 – 98.1]
Knowledge of practice to mitigate risk	**Question 8: Please select only one response for each statement about VFEND below (True/False/I Don't Know):**	
	Laboratory evaluations of hepatic function (specifically AST and ALT) at initiation and during the first month of treatment with VFEND is	317 (95.5) [92.7 – 97.4]

Table 9. Knowledge of the Risks, Appropriate Behaviour/Practice With Regard to Strategies to Mitigate the Risks, and Self-Reported Practice With Regard to Strategies to Mitigate the Risks of Hepatic Toxicity With VFEND (Completed Surveys From All Countries Combined)

Question		Proportion of HCPs Who Provided Correct/Desirable Response N = 332 n (%) [95% CI][1]
	not necessary (False) [2]	
	If the Liver Function Tests become markedly elevated, VFEND should be discontinued, unless the medical judgment of the risk-benefit balance of the treatment for the patients justified continued use. (True) [2]	313 (94.3) [91.2 – 96.5]
	Question 15: Which precautionary measures should physicians communicate to their patients for whom they have prescribed VFEND? (Check all that apply)	
	Clinical signs of liver damage, such as jaundice that warrant contacting the doctor immediately (Yes) [2]	304 (91.6) [88.0 – 94.3]
	Question 16: How frequently should Liver Function Tests (specifically AST, ALT) be performed?	
	At VFEND treatment initiation and weekly thereafter for one month[2]	239 (72.0) [66.8 – 76.8]
	Every contact	38 (11.4)
	Monthly	44 (13.3)
	Other	2 (0.6)
	I Don't Know	9 (2.7)
	Question 17: If there are no changes in Liver Function Tests (LFTs) after one month of initiation of VFEND, how often should you monitor liver function during VFEND treatment	260 (78.3) [73.5 – 82.6]

Table 9. Knowledge of the Risks, Appropriate Behaviour/Practice With Regard to Strategies to Mitigate the Risks, and Self-Reported Practice With Regard to Strategies to Mitigate the Risks of Hepatic Toxicity With VFEND (Completed Surveys From All Countries Combined)

Question		Proportion of HCPs Who Provided Correct/Desirable Response N = 332 n (%) [95% CI][1]
	maintenance? (Monthly) [2]	
Self-reported practice	No question pertaining to self-reported practice asked about HCP's practice to monitor liver function during treatment with VFEND	

[1] The 95% exact 2-sided confidence intervals were calculated using the Clopper-Pearson[1] method.
[2] Correct or desired response.
Source: Section 15; Tables 5 and 6.

10.4.3.4. Knowledge of the risks of hepatic toxicity with voriconazole by reading the HCP Q&A Brochure

The results of the subgroup analyses of HCP knowledge of risks of hepatic toxicity by reading/not reading or no receipt of the Q&A Brochure is presented in Table 8.

As seen in Table 8, the data indicate no differencein knowledge of the risk of hepatic toxicity among those who read the voriconazole HCP Q&A Brochure (98.2%, n=56) compared to those who did not (96.0%, n=264). However, the subgroup of those who reported reading the Q&A Brochure was small (ie, n=57) and meaningful comparisons were not possible.

10.4.4. Overall risks associated with voriconazole

10.4.4.1. Knowledge of self-reported practice with regard to strategies to mitigate the risks associated with voriconazole

Question 15a assessed how frequently the respondent or another member of the healthcare team performed each of 6 risk mitigation activities when initiating treatment with voriconazole. There were 41 (12.3%) respondents who reported that they always discuss contents of the Patient Alert Card with their patients when initiating treatment with voriconazole. There were 94 (28.3%) respondents who said that they discuss the Patient Alert Card with patients sometimes. When asked how frequently prescribers advise patients of importance of monitoring risks of voriconazole use and signs and symptoms of serious risks that warrant contacting doctor immediately, 226 (68.1%) reported always doing that and 74 (22.3%) reported doing it sometimes (Table 10).

Table 10. Knowledge of Self-Reported Practice With Regard to Strategies to Mitigate The Risks of Toxicity With VFEND – (Completed Surveys From All Countries Combined)

Question		**Proportion of HCPs Who Provided Correct/Desirable Response n (%) [95% CI][1]**
Self-reported practice	**Question 15a: How frequently do you or another member of your healthcare team perform each of these activities when initiating treatment with VFEND (Always/Sometimes/Never).**	
	Discuss contents of the Patient Alert Card	
	Always[2]	41 (12.3) [9.0 – 16.4]
	Sometimes[2]	94 (28.3)
	Always/Sometimes[2]	135 (40.7)
	Advise patient of importance of monitoring risks of VFEND use and signs and symptoms of serious risks that warrant contacting doctor immediately	
	Always[2]	226 (68.1) [62.8 – 73.1]
	Sometimes[2]	74 (22.3)
	Never	32 (9.6)
	Always/Sometimes[2]	300 (90.4)

[1] The 95% exact 2-sided confidence intervals were calculated using the Clopper-Pearson[1] method.

[2] Correct or desired response.

Source: Section 15; Table 6.

10.5. Other analyses

10.5.1. Other survey questions

For Question 14, out of the those who completed the survey and reported receiving the RM tools, almost half found the following voriconazole RM tools to be very or extremely useful in their clinical practice: HCP Checklist (46.6%, n=35), HCP Q&A Brochure (41.5%, n=27), and Patient Alert Card (41.8%, n=36) (Table 11).

Table 11. Other Survey Questions Based on the Receipt of Materials – (Completed Surveys From All Countries Combined)

Question	Prescribers n (%)
Question 14: Did you find the VFEND (voriconazole) RM tools to be of use in your clinical practice? Please select only one rank for each RM tool listed below:	
HCP Checklist (N=75)[1]	
Not useful	5 (6.7)
Somewhat useful	21 (28.0)
No opinion/not sure	14 (18.7)
Very useful	34 (45.3)
Extremely useful	1 (1.3)
HCP Q&A Brochure (N=65)[2]	
Not useful	7 (10.8)
Somewhat useful	15 (23.1)
No opinion/not sure	16 (24.6)
Very useful	21 (32.3)
Extremely useful	6 (9.2)
Patient Alert Card (N=86)[3]	
Not useful	8 (9.3)
Somewhat useful	22 (25.6)
No opinion/not sure	20 (23.3)
Very useful	31 (36.0)
Extremely useful	5 (5.8)

Table 11. Other Survey Questions Based on the Receipt of Materials – (Completed Surveys From All Countries Combined)

Question	Prescribers n (%)

[1] Counts and percentages were calculated based on receipt of the VFEND (voriconazole) Healthcare Professional (HCP) Checklist (ie, among those who answered "Yes" to survey Question 10).
[2] Counts and percentages were calculated based on receipt of the VFEND (voriconazole) HCP Q&A Brochure (ie, among those who answered "Yes" to survey Question 9).
[3] Counts and percentages were calculated based on receipt of the VFEND (voriconazole) Patient Alert Card (ie, among those who answered "Yes" to survey Question 11).
Source: Section 15; Table 7a.

10.5.1.1. Subgroup analyses

As mentioned in Section 10.4, sample sizes of the subgroups stratified by country, medical specialty, and the numbers of patients treated with voriconazole in the 12 months prior to survey participation were too small to permit meaningful comparisons. Tables presenting other survey question results by subgroup are located in Table 7.1 in Section 15.

10.6. Adverse events/adverse reactions

No adverse events were reported (Listing 3).

11. DISCUSSION

11.1. Key results

Participants

There were 27,396 prescribers invited to participate in the survey and of those, 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 VFEND, 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.

11.2. 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[3] and that for surveys evaluating program effectiveness it was not uncommon for the response rate to be below 10%.[4]

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 voricanozole 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 VFEND cannot be known. Reliance on respondents' recall is another inherent limitation of survey research.

11.3. Interpretation

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 ≥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 (<±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 >±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.

11.4. 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.

12. OTHER INFORMATION

Not applicable.

13. 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%).

- The overall knowledge of risk mitigation practices was high (many met or exceeded the 80% threshold for success, and most others were ≥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.

14. REFERENCES

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[3]Galea, S & Tracy, M 2007, Participation Rates in Epidemiologic Studies. *Ann Epidemiol*, 17, 643-653.

[4]Food and Drug Administration 2012, 'Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge' (Docket No. FDA–2012–N–0408), Retrieved from http://www.fda.gov/downloads/Drugs/NewsEvents/UCM301966.pdf.

15. LIST OF SOURCE TABLES AND LISTINGS

15.1. Summary Tables

15.2. Data Listings

Table 1.1: Survey Administration Statistics

	Country										
Question	**UK n (%)**	**F n (%)**	**A n (%)**	**IRL n (%)**	**DK n (%)**	**D n (%)**	**E n (%)**	**I n (%)**	**NL n (%)**	**H n (%)**	**Overall n (%)**
The number of paper invitations issued to prescribers	4,779	6,229	373	308	870	3,136	4,823	2,375	3,615	888	27,396
The number of paper invitations undeliverable[1] (Undeliverable rate)[2]	191 (4.0)	205 (3.3)	32 (8.6)	23 (7.5)	35 (4.0)	94 (3.0)	6 (0.1)	3 (0.1)	47 (1.3)	25 (2.8)	661 (2.4)
The number of paper reminder letters sent[3]	14,278	12,418	744	604	1,715	3,124	9,417	4,735	7,284	1,761	56,080
The number of email invitations issued to prescribers	858	4,487	0	0	0	0	0	602	0	0	5,947
The number of email invitations undeliverable (Undeliverable rate)[2]	16 (1.9)	215 (4.8)	0	0	0	0	0	24 (4.0)	0	0	255 (4.3)
The number of email reminder letters sent	0	4,236	0	0	0	0	0	0	0	0	4,236

Table 1.1: Survey Administration Statistics

	Country										
Question	**UK n (%)**	**F n (%)**	**A n (%)**	**IRL n (%)**	**DK n (%)**	**D n (%)**	**E n (%)**	**I n (%)**	**NL n (%)**	**H n (%)**	**Overall n (%)**
The number of waves paper or email reminder letters sent	2	3	2	2	2	1	2	2	2	2	20
The number of screened respondents (Participation rate)[4]	30 (0.7)	57 (0.9)	2 (0.6)	7 (2.5)	8 (1.0)	21 (0.7)	203 (4.2)	17 (0.7)	35 (1.0)	20 (2.3)	447[5] (1.7)
The number of respondents eligible for participation (eligibility rate)[6]	23 (76.7)	48 (84.2)	2 (100.0)	7 (100.0)	5 (62.5)	18 (85.7)	196 (96.6)	15 (88.2)	26 (74.3)	14 (70.0)	354 (79.2)

Table 1.1: Survey Administration Statistics

	Country										
Question	**UK n (%)**	**F n (%)**	**A n (%)**	**IRL n (%)**	**DK n (%)**	**D n (%)**	**E n (%)**	**I n (%)**	**NL n (%)**	**H n (%)**	**Overall n (%)**
The number and percentages of eligible respondents who completed the survey; "Completers" (Completion rate)[7]	21 (91.3)	42 (87.5)	2 (100.0)	7 (100.0)	5 (100.0)	16 (88.9)	191 (97.4)	14 (93.3)	21 (80.8)	13 (92.9)	332 (93.8)

[1] Invitations returned as of March 4, 2016.
[2] Undeliverable rates are calculated as the percentage of the invitations issued.
[3] Total of one or more waves of reminder letters in each country.
[4] Participation rate is calculated as the percentage of the invited prescribers excluding the number of invitations returned as undeliverable.
[5] Includes 47 screened prescribers who did not progress far enough in the survey to indicate country.
[6] Eligibility rate is calculated as the percentage of the screened respondents. The screened respondents consists of all respondents who have accessed the survey using the unique code regardless of whether or not they answered any survey questions.
[7] The completion rates are calculated as percentage of the eligible prescribers.
Abbreviations: UK = United Kingdom; F = France; A = Austria; IRL = Ireland; DK = Denmark; D = Germany; E = Spain; I = Italy; NL = The Netherlands; H = Hungary.

Table 1.2: Survey Participant Screening Results - Screened Respondents

	Country										
Question	**UK N=30 n (%)**	**F N=57 n (%)**	**A N=2 n (%)**	**IRL N=7 n (%)**	**DK N=8 n (%)**	**D N=21 n (%)**	**E N=203 n (%)**	**I N=17 n (%)**	**NL N=35 n (%)**	**H N=20 n (%)**	**Overall N=447 n (%)**
Question 1: Do you agree to take part in this survey?											
Yes	27 (90.0)	56 (98.2)	2 (100.0)	7 (100.0)	6 (75.0)	19 (90.5)	203 (100.0)	17 (100.0)	32 (91.4)	18 (90.0)	387 (86.6)
No[1]	3 (10.0)	1 (1.8)	0	0	2 (25.0)	2 (9.5)	0	0	3 (8.6)	2 (10.0)	13 (2.9)
Discontinued[3]	0	0	0	0	0	0	0	0	0	0	47 (10.5)
Question 2: Have you prescribed VFEND (voriconazole) within the past 12 months?											
Yes	23 (76.7)	48 (84.2)	2 (100.0)	7 (100.0)	5 (62.5)	18 (85.7)	198 (97.5)	16 (94.1)	26 (74.3)	14 (70.0)	357 (79.9)
No[1]	4 (13.3)	7 (12.3)	0	0	1 (12.5)	0	4 (2.0)	1 (5.9)	6 (17.1)	3 (15.0)	26 (5.8)
Question not asked[2]	3 (10.0)	1 (1.8)	0	0	2 (25.0)	2 (9.5)	0	0	3 (8.6)	2 (10.0)	13 (2.9)
Discontinued[3]	0	1 (1.8)	0	0	0	1 (4.8)	1 (0.5)	0	0	1 (5.0)	51 (11.4)
Question 3: Are you currently employed by Pfizer or United BioSource Corporation?											
Yes[1]	0	0	0	0	0	0	0	1 (5.9)	0	0	1 (0.2)
No	23 (76.7)	48 (84.2)	2 (100.0)	7 (100.0)	5 (62.5)	18 (85.7)	198 (97.5)	15 (88.2)	26 (74.3)	14 (70.0)	356 (79.6)
Question not asked[2]	7 (23.3)	8 (14.0)	0	0	3 (37.5)	2 (9.5)	4 (2.0)	1 (5.9)	9 (25.7)	5 (25.0)	39 (8.7)
Discontinued[3]	0	1 (1.8)	0	0	0	1 (4.8)	1 (0.5)	0	0	1 (5.0)	51 (11.4)
Question 4: Have you ever participated in qualitative research of the VFEND (voriconazole) Risk Minimisation materials?											

Table 1.2: Survey Participant Screening Results - Screened Respondents

	Country										
Question	**UK N=30 n (%)**	**F N=57 n (%)**	**A N=2 n (%)**	**IRL N=7 n (%)**	**DK N=8 n (%)**	**D N=21 n (%)**	**E N=203 n (%)**	**I N=17 n (%)**	**NL N=35 n (%)**	**H N=20 n (%)**	**Overall N=447 n (%)**
Yes[1]	0	0	0	0	0	0	2 (1.0)	0	0	0	2 (0.4)
No	23 (76.7)	48 (84.2)	2 (100.0)	7 (100.0)	5 (62.5)	18 (85.7)	196 (96.6)	15 (88.2)	26 (74.3)	14 (70.0)	354 (79.2)
Question not asked[2]	7 (23.3)	8 (14.0)	0	0	3 (37.5)	2 (9.5)	4 (2.0)	2 (11.8)	9 (25.7)	5 (25.0)	40 (8.9)
Discontinued[3]	0	1 (1.8)	0	0	0	1 (4.8)	1 (0.5)	0	0	1 (5.0)	51 (11.4)

[1] Ineligible to participate in the survey.
[2] Question not asked due to a previous question elimination.
[3] Respondents who discontinued the survey before completing all eligibility questions without being identified as ineligible are counted as discontinued. Once a respondent is counted as discontinued, they will count as discontinued in all subsequent eligibility questions.
Note: The screened respondents consists all respondents who have accessed the survey using the unique code regardless of whether or not they answered any survey questions. The number of screened respondents are used for the calculation of all percentages in this table.
Abbreviations: UK = United Kingdom; F = France; A = Austria; IRL = Ireland; DK = Denmark; D = Germany; E = Spain; I = Italy; NL = The Netherlands; H = Hungary.

Table 1.2a: Survey Participant Screening Results – Ineligible Respondents

Question	N=93[2] n (%)
Question 1: Do you agree to take part in this survey?	
No[1]	13 (14.0)
Question 2: Have you prescribed VFEND (voriconazole) within the past 12 months?	
No[1]	26 (28.0)
Question 3: Are you currently employed by Pfizer or United BioSource Corporation?	
Yes[1]	1 (1.1)
Question 4: Have you ever participated in qualitative research of the VFEND (voriconazole) Risk Minimisation materials?	
Yes[1]	2 (2.2)

[1] Ineligible to participate in the survey.
[2] Total number of screened respondents minus the number of respondents eligible for participation as reported in Table 1.1.
Source: Table 1.2.

Table 2: Description of Survey Participants - Completed Surveys from All Countries Combined

Question	Prescribers N=332 n (%)
Country of practice	
United Kingdom	21 (6.3)
France	42 (12.7)
Austria	2 (0.6)
Ireland	7 (2.1)
Denmark	5 (1.5)
Germany	16 (4.8)
Spain	191 (57.5)
Italy	14 (4.2)
The Netherlands	21 (6.3)
Hungary	13 (3.9)
Question 5: What is your primary medical specialty?	
Critical Care	2 (0.6)
Haematology	153 (46.1)
Infectious diseases	56 (16.9)
Intensive Care	3 (0.9)
Microbiology	1 (0.3)
Oncology	89 (26.8)
Solid Organ Transplant	3 (0.9)
Other/Subspecialty (Specify)[1]	14 (4.2)
Other: (Specify)[2]	11 (3.3)
Question 6: How long have you been practicing medicine?	
≤ 5 years	43 (13.0)
6-15 years	127 (38.3)
> 15 years	162 (48.8)
Question 12: Approximately how many patients have you treated with VFEND (voriconazole) in the past 12 months?	
1-5	158 (47.6)

Table 2: Description of Survey Participants - Completed Surveys from All Countries Combined

Question	Prescribers N=332 n (%)
6-10	92 (27.7)
11-20	44 (13.3)
>20	38 (11.4)

[1] Verbatim texts for other subspecialty are reported in Listing 1.
[2] Verbatim texts for other specialty are reported in Listing 2.

Table 2a: Comparison of Country of Practice and Medical Specialty Between Respondents and the Invited HCP Population

Question	Prescribers Who Completed the Survey N=332 n (%)	Invited HCPs N=27,397 n (%)
Country of practice		
United Kingdom	21 (6.3)	4,780 (17.4)
France	42 (12.7)	6,229 (22.7)
Austria	2 (0.6)	373 (1.4)
Ireland	7 (2.1)	308 (1.1)
Denmark	5 (1.5)	871 (3.2)
Germany	16 (4.8)	3,136 (11.4)
Spain	191 (57.5)	4,823 (17.6)
Italy	14 (4.2)	2,375 (8.7)
The Netherlands	21 (6.3)	3,615 (13.2)
Hungary	13 (3.9)	887 (3.2)
Question 5: What is your primary medical specialty?		
Critical Care	2 (0.6)	13 (0.0)
Haematology	153 (46.1)	10,116 (36.9)
Infectious diseases	56 (16.9)	2,980 (10.9)
Intensive Care	3 (0.9)	275 (1.0)
Microbiology	1 (0.3)	44 (0.2)
Oncology	89 (26.8)	8,723 (31.8)
Solid Organ Transplant	3 (0.9)	93 (0.3)
Other/Subspecialty (Specify)[1]	14 (4.2)	0
Other: (Specify)[2]	11 (3.3)	4,973 (18.2)
Not Reported	0	180 (0.7)

[1] Verbatim texts for other subspecialty for prescribers who completed the survey are reported in Listing 1.
[2] Verbatim texts for other specialty for prescribers who completed the survey are reported in Listing 2.

Table 3: Responses to All Questions About the Receipt of the RM Tools - (Completed Surveys from All Countries Combined)

Question	Prescribers N=332 n (%) [95% CI][1]
Question 9: Did you or your hospital receive the VFEND (voriconazole) Healthcare Professional (HCP) Q&A Brochure?	
Yes[2]	65 (19.6) [15.4 - 24.3]
No	81 (24.4)
I don't remember receiving it	186 (56.0)
Question 10: Did you or your hospital receive copies of the VFEND (voriconazole) Healthcare Professional (HCP) Checklist?	
Yes[2]	75 (22.6) [18.2 - 27.5]
No	68 (20.5)
I don't remember receiving them	189 (56.9)
Question 11: Did you or your hospital receive copies of the VFEND (voriconazole) Patient Alert Card?	
Yes[2]	86 (25.9) [21.3 - 31.0]
No	90 (27.1)
I don't remember receiving them	156 (47.0)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Desired response.

Table 3.1: Responses to All Questions About the Receipt of the RM Tools by Country - (Completed Surveys from All Countries Combined)

	Country									
Question	UK N=21 n (%) [95% CI][1]	F N=42 n (%) [95% CI][1]	A N=2 n (%) [95% CI][1]	IRL N=7 n (%) [95% CI][1]	DK N=5 n (%) [95% CI][1]	D N=16 n (%) [95% CI][1]	E N=191 n (%) [95% CI][1]	I N=14 n (%) [95% CI][1]	NL N=21 n (%) [95% CI][1]	H N=13 n (%) [95% CI][1]
Question 9: Did you or your hospital receive the VFEND (voriconazole) Healthcare Professional (HCP) Q&A Brochure?										
Yes[2]	4 (19.0) [5.4 - 41.9]	8 (19.0) [8.6 - 34.1]	0	2 (28.6) [3.7 - 71.0]	0	3 (18.8) [4.0 - 45.6]	37 (19.4) [14.0 - 25.7]	3 (21.4) [4.7 - 50.8]	4 (19.0) [5.4 - 41.9]	4 (30.8) [9.1 - 61.4]
No	4 (19.0)	12 (28.6)	1 (50.0)	0	0	5 (31.3)	53 (27.7)	1 (7.1)	4 (19.0)	1 (7.7)
I don't remember receiving it	13 (61.9)	22 (52.4)	1 (50.0)	5 (71.4)	5 (100.0)	8 (50.0)	101 (52.9)	10 (71.4)	13 (61.9)	8 (61.5)
Question 10: Did you or your hospital receive copies of the VFEND (voriconazole) Healthcare Professional (HCP) Checklist?										
Yes[2]	5 (23.8) [8.2 - 47.2]	10 (23.8) [12.1 - 39.5]	0	1 (14.3) [0.4 - 57.9]	0	3 (18.8) [4.0 - 45.6]	45 (23.6) [17.7 - 30.2]	4 (28.6) [8.4 - 58.1]	3 (14.3) [3.0 - 36.3]	4 (30.8) [9.1 - 61.4]
No	2 (9.5)	14 (33.3)	0	0	0	5 (31.3)	42 (22.0)	1 (7.1)	3 (14.3)	1 (7.7)
I don't remember receiving them	14 (66.7)	18 (42.9)	2 (100.0)	6 (85.7)	5 (100.0)	8 (50.0)	104 (54.5)	9 (64.3)	15 (71.4)	8 (61.5)
Question 11: Did you or your hospital receive copies of the VFEND (voriconazole) Patient Alert Card?										
Yes[2]	5 (23.8) [8.2 - 47.2]	16 (38.1) [23.6 - 54.4]	0	1 (14.3) [0.4 - 57.9]	1 (20.0) [0.5 - 71.6]	3 (18.8) [4.0 - 45.6]	46 (24.1) [18.2 - 30.8]	6 (42.9) [17.7 - 71.1]	2 (9.5) [1.2 - 30.4]	6 (46.2) [19.2 - 74.9]
No	2 (9.5)	14 (33.3)	1 (50.0)	1 (14.3)	0	9 (56.3)	58 (30.4)	0	4 (19.0)	1 (7.7)

Table 3.1: Responses to All Questions About the Receipt of the RM Tools by Country - (Completed Surveys from All Countries Combined)

	Country									
Question	**UK N=21 n (%) [95% CI][1]**	**F N=42 n (%) [95% CI][1]**	**A N=2 n (%) [95% CI][1]**	**IRL N=7 n (%) [95% CI][1]**	**DK N=5 n (%) [95% CI][1]**	**D N=16 n (%) [95% CI][1]**	**E N=191 n (%) [95% CI][1]**	**I N=14 n (%) [95% CI][1]**	**NL N=21 n (%) [95% CI][1]**	**H N=13 n (%) [95% CI][1]**
I don't remember receiving them	14 (66.7)	12 (28.6)	1 (50.0)	5 (71.4)	4 (80.0)	4 (25.0)	87 (45.5)	8 (57.1)	15 (71.4)	6 (46.2)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Desired response.
Abbreviations: UK = United Kingdom; F = France; A = Austria; IRL = Ireland; DK = Denmark; D = Germany; E = Spain; I = Italy; NL = The Netherlands; H = Hungary.

Table 3.2: Responses to All Questions About the Receipt of the RM Tools by Medical Specialty - (Completed Surveys from All Countries Combined)

Question	Medical Specialty				
	Critical Care / Intensive Care N=5 n (%) [95% CI][1]	Oncology / Hematology N=242 n (%) [95% CI][1]	Infectious Disease / Microbiology N=57 n (%) [95% CI][1]	Solid Organ Transplant Physician N=3 n (%) [95% CI][1]	Other/Other Subspecialty N=25 n (%) [95% CI][1]
Question 9: Did you or your hospital receive the VFEND (voriconazole) Healthcare Professional (HCP) Q&A Brochure?					
Yes[2]	0	45 (18.6) [13.9 - 24.1]	15 (26.3) [15.5 - 39.7]	0	5 (20.0) [6.8 - 40.7]
No	0	57 (23.6)	15 (26.3)	1 (33.3)	8 (32.0)
I don't remember receiving it	5 (100.0)	140 (57.9)	27 (47.4)	2 (66.7)	12 (48.0)
Question 10: Did you or your hospital receive copies of the VFEND (voriconazole) Healthcare Professional (HCP) Checklist?					
Yes[2]	0	57 (23.6) [18.4 - 29.4]	13 (22.8) [12.7 - 35.8]	2 (66.7) [9.4 - 99.2]	3 (12.0) [2.5 - 31.2]
No	0	49 (20.2)	12 (21.1)	0	7 (28.0)
I don't remember receiving them	5 (100.0)	136 (56.2)	32 (56.1)	1 (33.3)	15 (60.0)
Question 11: Did you or your hospital receive copies of the VFEND (voriconazole) Patient Alert Card?					
Yes[2]	0	60 (24.8) [19.5 - 30.7]	18 (31.6) [19.9 - 45.2]	1 (33.3) [0.8 - 90.6]	7 (28.0) [12.1 - 49.4]
No	1 (20.0)	67 (27.7)	13 (22.8)	1 (33.3)	8 (32.0)
I don't remember receiving them	4 (80.0)	115 (47.5)	26 (45.6)	1 (33.3)	10 (40.0)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Desired response.

Table 3.3: Responses to All Questions About the Receipt of the RM Tools by Number of Patients Treated in the Last 12 Months - (Completed Surveys from All Countries Combined)

Question	Number of Patients Treated in the Last 12 Months			
	1-5 Patients N=158 n (%) [95% CI][1]	6-10 Patients N=92 n (%) [95% CI][1]	11-20 Patients N=44 n (%) [95% CI][1]	More Than 20 Patients N=38 n (%) [95% CI][1]
Question 9: Did you or your hospital receive the VFEND (voriconazole) Healthcare Professional (HCP) Q&A Brochure?				
Yes[2]	34 (21.5) [15.4 - 28.8]	15 (16.3) [9.4 - 25.5]	6 (13.6) [5.2 - 27.4]	10 (26.3) [13.4 - 43.1]
No	34 (21.5)	18 (19.6)	15 (34.1)	14 (36.8)
I don't remember receiving it	90 (57.0)	59 (64.1)	23 (52.3)	14 (36.8)
Question 10: Did you or your hospital receive copies of the VFEND (voriconazole) Healthcare Professional (HCP) Checklist?				
Yes[2]	30 (19.0) [13.2 - 26.0]	22 (23.9) [15.6 - 33.9]	12 (27.3) [15.0 - 42.8]	11 (28.9) [15.4 - 45.9]
No	28 (17.7)	17 (18.5)	12 (27.3)	11 (28.9)
I don't remember receiving them	100 (63.3)	53 (57.6)	20 (45.5)	16 (42.1)
Question 11: Did you or your hospital receive copies of the VFEND (voriconazole) Patient Alert Card?				
Yes[2]	36 (22.8) [16.5 - 30.1]	25 (27.2) [18.4 - 37.4]	13 (29.5) [16.8 - 45.2]	12 (31.6) [17.5 - 48.7]
No	43 (27.2)	23 (25.0)	14 (31.8)	10 (26.3)
I don't remember receiving them	79 (50.0)	44 (47.8)	17 (38.6)	16 (42.1)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Desired response.

Table 4: Responses to All Questions About Reading and the Utilization of the RM Tools - (Completed Surveys From All Countries Combined)

Question	Prescribers N=332 n (%) [95% CI][1]
Question 9.1: Did you read the VFEND (voriconazole) HCP Q&A Brochure?	
Yes, all of it	22 (6.6)
Yes, some of it	35 (10.5)
No, I did not read it	4 (1.2)
I don't remember reading it	4 (1.2)
Did not receive it[2]	267 (80.4)
Read all of it or some of it[3]	57 (17.2) [13.3 - 21.7]
Question 13: When treating patients with VFEND (voriconazole) in the past 12 months, how often did you use the VFEND HCP Checklist?	
Always	21 (6.3)
Sometimes	69 (20.8)
Never	98 (29.5)
I don't remember receiving copies of the HCP Checklist	144 (43.4)
Always or sometimes[3]	90 (27.1) [22.4 - 32.2]
Question 15a: How frequently do you, or another member of your healthcare team (e.g. nurse, pharmacist or other), perform each of these activities when initiating treatment with VFEND (voriconazole)? (Please check one response for each activity below).	
Distribute and fill in the Patient Alert Card	
Always	38 (11.4)
Sometimes	82 (24.7)
Never	212 (63.9)
Always or sometimes[3]	120 (36.1) [31.0 - 41.6]
Question 20: Did you or another staff member request additional copies of the VFEND (voriconazole) RM tools?	
Yes	16 (4.8)
No	316 (95.2)
Question 21: Did you or another staff member obtain the VFEND (voriconazole) RM tools by downloading them from a website?	
Yes	30 (9.0)

Table 4: Responses to All Questions About Reading and the Utilization of the RM Tools - (Completed Surveys From All Countries Combined)

Question	Prescribers N=332 n (%) [95% CI][1]
No	302 (91.0)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Respondents who answered 'No' or 'I don't remember receiving it' to Question 9.
[3] Desired response.

Table 4a: Responses to All Questions About Reading and the Utilization of the RM Tools Based on the Receipt of Materials - (Completed Surveys From All Countries Combined)

Question	Prescribers n (%)
Question 9.1: Did you read the VFEND (voriconazole) HCP Q&A Brochure? (N=65)[1]	
Yes, all of it	22 (33.8)
Yes, some of it	35 (53.8)
No, I did not read it	4 (6.2)
I don't remember reading it	4 (6.2)
Read all of it or some of it[2]	57 (87.7)
Question 13: When treating patients with VFEND (voriconazole) in the past 12 months, how often did you use the VFEND HCP Checklist? (N=75)[3]	
Always	13 (17.3)
Sometimes	36 (48.0)
Never	20 (26.7)
I don't remember receiving copies of the HCP Checklist	6 (8.0)
Always or sometimes[2]	49 (65.3)
Question 15a: How frequently do you, or another member of your healthcare team (e.g. nurse, pharmacist or other), perform each of these activities when initiating treatment with VFEND (voriconazole)? (Please check one response for each activity below). (N=86)[4]	
Distribute and fill in the Patient Alert Card	
Always	22 (25.6)
Sometimes	36 (41.9)
Never	28 (32.6)
Always or sometimes[2]	58 (67.4)

[1] Counts and percentages are calculated based on receipt of the VFEND (voriconazole) HCP Q&A Brochure (i.e. among those who answered "yes" to survey question 9).
[2] Desired response.
[3] Counts and percentages are calculated based on receipt of the VFEND (voriconazole) Healthcare Professional (HCP) Checklist (i.e. among those who answered "yes" to survey question 10).
[4] Counts and percentages are calculated based on receipt of the VFEND (voriconazole) Patient Alert Card (i.e. among those who answered "yes" to survey question 11).

Table 4.1: Responses to All Questions About Reading and the Utilization of the RM Tools by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	**UK N=21 n (%) [95% CI][1]**	**F N=42 n (%) [95% CI][1]**	**A N=2 n (%) [95% CI][1]**	**IRL N=7 n (%) [95% CI][1]**	**DK N=5 n (%) [95% CI][1]**	**D N=16 n (%) [95% CI][1]**	**E N=191 n (%) [95% CI][1]**	**I N=14 n (%) [95% CI][1]**	**NL N=21 n (%) [95% CI][1]**	**H N=13 n (%) [95% CI][1]**
Question 9.1: Did you read the VFEND (voriconazole) HCP Q&A Brochure?										
Yes, all of it	0	1 (2.4)	0	0	0	0	17 (8.9)	1 (7.1)	0	3 (23.1)
Yes, some of it	4 (19.0)	5 (11.9)	0	2 (28.6)	0	3 (18.8)	17 (8.9)	1 (7.1)	3 (14.3)	0
No, I did not read it	0	2 (4.8)	0	0	0	0	2 (1.0)	0	0	0
I don't remember reading it	0	0	0	0	0	0	1 (0.5)	1 (7.1)	1 (4.8)	1 (7.7)
Did not receive it[2]	17 (81.0)	34 (81.0)	2 (100.0)	5 (71.4)	5 (100.0)	13 (81.3)	154 (80.6)	11 (78.6)	17 (81.0)	9 (69.2)
Read all of it or some of it[3]	4 (19.0) [5.4 - 41.9]	6 (14.3) [5.4 - 28.5]	0	2 (28.6) [3.7 - 71.0]	0	3 (18.8) [4.0 - 45.6]	34 (17.8) [12.7 - 24.0]	2 (14.3) [1.8 - 42.8]	3 (14.3) [3.0 - 36.3]	3 (23.1) [5.0 - 53.8]
Question 13: When treating patients with VFEND (voriconazole) in the past 12 months, how often did you use the VFEND HCP Checklist?										
Always	0	2 (4.8)	0	1 (14.3)	0	1 (6.3)	13 (6.8)	1 (7.1)	0	3 (23.1)
Sometimes	6 (28.6)	9 (21.4)	1 (50.0)	1 (14.3)	0	3 (18.8)	43 (22.5)	4 (28.6)	2 (9.5)	0
Never	4 (19.0)	20 (47.6)	0	3 (42.9)	1 (20.0)	7 (43.8)	47 (24.6)	2 (14.3)	10 (47.6)	4 (30.8)
I don't remember receiving copies of the HCP Checklist	11 (52.4)	11 (26.2)	1 (50.0)	2 (28.6)	4 (80.0)	5 (31.3)	88 (46.1)	7 (50.0)	9 (42.9)	6 (46.2)

Table 4.1: Responses to All Questions About Reading and the Utilization of the RM Tools by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	**UK N=21 n (%) [95% CI][1]**	**F N=42 n (%) [95% CI][1]**	**A N=2 n (%) [95% CI][1]**	**IRL N=7 n (%) [95% CI][1]**	**DK N=5 n (%) [95% CI][1]**	**D N=16 n (%) [95% CI][1]**	**E N=191 n (%) [95% CI][1]**	**I N=14 n (%) [95% CI][1]**	**NL N=21 n (%) [95% CI][1]**	**H N=13 n (%) [95% CI][1]**
Always or sometimes[3]	6 (28.6) [11.3 - 52.2]	11 (26.2) [13.9 - 42.0]	1 (50.0) [1.3 - 98.7]	2 (28.6) [3.7 - 71.0]	0	4 (25.0) [7.3 - 52.4]	56 (29.3) [23.0 - 36.3]	5 (35.7) [12.8 - 64.9]	2 (9.5) [1.2 - 30.4]	3 (23.1) [5.0 - 53.8]
Question 15a: How frequently do you, or another member of your healthcare team (e.g. nurse, pharmacist or other), perform each of these activities when initiating treatment with VFEND (voriconazole)? (Please check one response for each activity below).										
Distribute and fill in the Patient Alert Card										
Always	2 (9.5)	7 (16.7)	0	1 (14.3)	0	2 (12.5)	16 (8.4)	3 (21.4)	3 (14.3)	4 (30.8)
Sometimes	4 (19.0)	9 (21.4)	0	2 (28.6)	2 (40.0)	6 (37.5)	52 (27.2)	4 (28.6)	1 (4.8)	2 (15.4)
Never	15 (71.4)	26 (61.9)	2 (100.0)	4 (57.1)	3 (60.0)	8 (50.0)	123 (64.4)	7 (50.0)	17 (81.0)	7 (53.8)
Always or sometimes[3]	6 (28.6) [11.3 - 52.2]	16 (38.1) [23.6 - 54.4]	0	3 (42.9) [9.9 - 81.6]	2 (40.0) [5.3 - 85.3]	8 (50.0) [24.7 - 75.3]	68 (35.6) [28.8 - 42.8]	7 (50.0) [23.0 - 77.0]	4 (19.0) [5.4 - 41.9]	6 (46.2) [19.2 - 74.9]
Question 20: Did you or another staff member request additional copies of the VFEND (voriconazole) RM tools?										
Yes	1 (4.8)	0	0	0	0	1 (6.3)	10 (5.2)	1 (7.1)	1 (4.8)	2 (15.4)
No	20 (95.2)	42 (100.0)	2 (100.0)	7 (100.0)	5 (100.0)	15 (93.8)	181 (94.8)	13 (92.9)	20 (95.2)	11 (84.6)
Question 21: Did you or another staff member obtain the VFEND (voriconazole) RM tools by downloading them from a website?										
Yes	0	2 (4.8)	0	1 (14.3)	0	0	22 (11.5)	3 (21.4)	1 (4.8)	1 (7.7)

Table 4.1: Responses to All Questions About Reading and the Utilization of the RM Tools by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	**UK N=21 n (%) [95% CI][1]**	**F N=42 n (%) [95% CI][1]**	**A N=2 n (%) [95% CI][1]**	**IRL N=7 n (%) [95% CI][1]**	**DK N=5 n (%) [95% CI][1]**	**D N=16 n (%) [95% CI][1]**	**E N=191 n (%) [95% CI][1]**	**I N=14 n (%) [95% CI][1]**	**NL N=21 n (%) [95% CI][1]**	**H N=13 n (%) [95% CI][1]**
No	21 (100.0)	40 (95.2)	2 (100.0)	6 (85.7)	5 (100.0)	16 (100.0)	169 (88.5)	11 (78.6)	20 (95.2)	12 (92.3)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Respondents who answered 'No' or 'I don't remember receiving it' to Question 9.
[3] Desired response.
Abbreviations: UK = United Kingdom; F = France; A = Austria; IRL = Ireland; DK = Denmark; D = Germany; E = Spain; I = Italy; NL = The Netherlands; H = Hungary.

Table 4.2: Responses to All Questions About Reading and the Utilization of the RM Tools by Medical Specialty - (Completed Surveys From All Countries Combined)

Question	Medical Specialty				
	Critical Care / Intensive Care N=5 n (%) [95% CI][1]	Oncology / Hematology N=242 n (%) [95% CI][1]	Infectious Disease / Microbiology N=57 n (%) [95% CI][1]	Solid Organ Transplant Physician N=3 n (%) [95% CI][1]	Other/Other Subspecialty N=25 n (%) [95% CI][1]
Question 9.1: Did you read the VFEND (voriconazole) HCP Q&A Brochure?					
Yes, all of it	0	20 (8.3)	1 (1.8)	0	1 (4.0)
Yes, some of it	0	21 (8.7)	11 (19.3)	0	3 (12.0)
No, I did not read it	0	3 (1.2)	1 (1.8)	0	0
I don't remember reading it	0	1 (0.4)	2 (3.5)	0	1 (4.0)
Did not receive it[2]	5 (100.0)	197 (81.4)	42 (73.7)	3 (100.0)	20 (80.0)
Read all of it or some of it[3]	0	41 (16.9) [12.4 - 22.3]	12 (21.1) [11.4 - 33.9]	0	4 (16.0) [4.5 - 36.1]
Question 13: When treating patients with VFEND (voriconazole) in the past 12 months, how often did you use the VFEND HCP Checklist?					
Always	0	17 (7.0)	2 (3.5)	1 (33.3)	1 (4.0)
Sometimes	0	57 (23.6)	11 (19.3)	0	1 (4.0)
Never	2 (40.0)	67 (27.7)	15 (26.3)	2 (66.7)	12 (48.0)
I don't remember receiving copies of the HCP Checklist	3 (60.0)	101 (41.7)	29 (50.9)	0	11 (44.0)
Always or sometimes[3]	0	74 (30.6) [24.8 - 36.8]	13 (22.8) [12.7 - 35.8]	1 (33.3) [0.8 - 90.6]	2 (8.0) [1.0 - 26.0]
Question 15a: How frequently do you, or another member of your healthcare team (e.g. nurse, pharmacist or other), perform each of these activities when initiating treatment with VFEND (voriconazole)? (Please check one response for each activity below).					
Distribute and fill in the Patient Alert Card					
Always	0	27 (11.2)	6 (10.5)	1 (33.3)	4 (16.0)
Sometimes	0	67 (27.7)	12 (21.1)	0	3 (12.0)
Never	5 (100.0)	148 (61.2)	39 (68.4)	2 (66.7)	18 (72.0)
Always or sometimes[3]	0	94 (38.8) [32.7 - 45.3]	18 (31.6) [19.9 - 45.2]	1 (33.3) [0.8 - 90.6]	7 (28.0) [12.1 - 49.4]

Table 4.2: Responses to All Questions About Reading and the Utilization of the RM Tools by Medical Specialty - (Completed Surveys From All Countries Combined)

Question	Medical Specialty				
	Critical Care / Intensive Care N=5 n (%) [95% CI][1]	Oncology / Hematology N=242 n (%) [95% CI][1]	Infectious Disease / Microbiology N=57 n (%) [95% CI][1]	Solid Organ Transplant Physician N=3 n (%) [95% CI][1]	Other/Other Subspecialty N=25 n (%) [95% CI][1]
Question 20: Did you or another staff member request additional copies of the VFEND (voriconazole) RM tools?					
Yes	0	12 (5.0)	1 (1.8)	0	3 (12.0)
No	5 (100.0)	230 (95.0)	56 (98.2)	3 (100.0)	22 (88.0)
Question 21: Did you or another staff member obtain the VFEND (voriconazole) RM tools by downloading them from a website?					
Yes	0	26 (10.7)	3 (5.3)	0	1 (4.0)
No	5 (100.0)	216 (89.3)	54 (94.7)	3 (100.0)	24 (96.0)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Respondents who answered 'No' or 'I don't remember receiving it' to Question 9.
[3] Desired response.

Table 4.3: Responses to All Questions About Reading and the Utilization of the RM Tools by Number of Patients Treated in the Last 12 Months - (Completed Surveys From All Countries Combined)

Question	Number of Patients Treated in the Last 12 Months			
	1-5 Patients N=158 n (%) [95% CI][1]	6-10 Patients N=92 n (%) [95% CI][1]	11-20 Patients N=44 n (%) [95% CI][1]	More Than 20 Patients N=38 n (%) [95% CI][1]
Question 9.1: Did you read the VFEND (voriconazole) HCP Q&A Brochure?				
Yes, all of it	10 (6.3)	4 (4.3)	5 (11.4)	3 (7.9)
Yes, some of it	20 (12.7)	9 (9.8)	1 (2.3)	5 (13.2)
No, I did not read it	3 (1.9)	0	0	1 (2.6)
I don't remember reading it	1 (0.6)	2 (2.2)	0	1 (2.6)
Did not receive it[2]	124 (78.5)	77 (83.7)	38 (86.4)	28 (73.7)
Read all of it or some of it[3]	30 (19.0) [13.2 - 26.0]	13 (14.1) [7.7 - 23.0]	6 (13.6) [5.2 - 27.4]	8 (21.1) [9.6 - 37.3]
Question 13: When treating patients with VFEND (voriconazole) in the past 12 months, how often did you use the VFEND HCP Checklist?				
Always	12 (7.6)	4 (4.3)	3 (6.8)	2 (5.3)
Sometimes	22 (13.9)	25 (27.2)	8 (18.2)	14 (36.8)
Never	51 (32.3)	19 (20.7)	14 (31.8)	14 (36.8)
I don't remember receiving copies of the HCP Checklist	73 (46.2)	44 (47.8)	19 (43.2)	8 (21.1)
Always or sometimes[3]	34 (21.5) [15.4 - 28.8]	29 (31.5) [22.2 - 42.0]	11 (25.0) [13.2 - 40.3]	16 (42.1) [26.3 - 59.2]
Question 15a: How frequently do you, or another member of your healthcare team (e.g. nurse, pharmacist or other), perform each of these activities when initiating treatment with VFEND (voriconazole)? (Please check one response for each activity below).				
Distribute and fill in the Patient Alert Card				
Always	17 (10.8)	7 (7.6)	8 (18.2)	6 (15.8)
Sometimes	36 (22.8)	19 (20.7)	13 (29.5)	14 (36.8)
Never	105 (66.5)	66 (71.7)	23 (52.3)	18 (47.4)
Always or sometimes[3]	53 (33.5) [26.2 - 41.5]	26 (28.3) [19.4 - 38.6]	21 (47.7) [32.5 - 63.3]	20 (52.6) [35.8 - 69.0]

Table 4.3: Responses to All Questions About Reading and the Utilization of the RM Tools by Number of Patients Treated in the Last 12 Months - (Completed Surveys From All Countries Combined)

Question	Number of Patients Treated in the Last 12 Months			
	1-5 Patients N=158 n (%) [95% CI][1]	6-10 Patients N=92 n (%) [95% CI][1]	11-20 Patients N=44 n (%) [95% CI][1]	More Than 20 Patients N=38 n (%) [95% CI][1]
Question 20: Did you or another staff member request additional copies of the VFEND (voriconazole) RM tools?				
Yes	6 (3.8)	3 (3.3)	5 (11.4)	2 (5.3)
No	152 (96.2)	89 (96.7)	39 (88.6)	36 (94.7)
Question 21: Did you or another staff member obtain the VFEND (voriconazole) RM tools by downloading them from a website?				
Yes	20 (12.7)	6 (6.5)	1 (2.3)	3 (7.9)
No	138 (87.3)	86 (93.5)	43 (97.7)	35 (92.1)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Respondents who answered 'No' or 'I don't remember receiving it' to Question 9.
[3] Desired response.

Table 5: Responses to All Questions About the Knowledge of the Risks of Phototoxicity, SCC of the Skin and Hepatic Toxicity With Voriconazole - (Completed Surveys From All Countries Combined)

Question	Prescribers N=332 n (%) [95% CI][1]
Question 7: According to the SmPC/PI, the known risks for VFEND (voriconazole) are as follows: (Please select only one response for each of the risks listed in the table below.)	
Phototoxicity (e.g. skin rash)	
Yes[2]	294 (88.6) [84.6 - 91.8]
No	16 (4.8)
I Don't Know	22 (6.6)
Intestinal perforation	
Yes	24 (7.2)
No[2]	228 (68.7) [63.4 - 73.6]
I Don't Know	80 (24.1)
Squamous cell carcinoma (SCC) of the skin	
Yes[2]	147 (44.3) [38.9 - 49.8]
No	120 (36.1)
I Don't Know	65 (19.6)
Asthma	
Yes	39 (11.7)
No[2]	196 (59.0) [53.5 - 64.4]
I Don't Know	97 (29.2)
Hepatic toxicity	
Yes[2]	320 (96.4) [93.8 - 98.1]
No	7 (2.1)
I Don't Know	5 (1.5)
Cardiomyopathy	
Yes	96 (28.9)
No[2]	142 (42.8) [37.4 - 48.3]

Table 5: Responses to All Questions About the Knowledge of the Risks of Phototoxicity, SCC of the Skin and Hepatic Toxicity With Voriconazole - (Completed Surveys From All Countries Combined)

Question	Prescribers N=332 n (%) [95% CI][1]
I Don't Know	94 (28.3)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 5.1: Responses to All Questions About the Knowledge of the Risks of Phototoxicity, SCC of the Skin and Hepatic Toxicity With Voriconazole by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	UK N=21 n (%) [95% CI][1]	F N=42 n (%) [95% CI][1]	A N=2 n (%) [95% CI][1]	IRL N=7 n (%) [95% CI][1]	DK N=5 n (%) [95% CI][1]	D N=16 n (%) [95% CI][1]	E N=191 n (%) [95% CI][1]	I N=14 n (%) [95% CI][1]	NL N=21 n (%) [95% CI][1]	H N=13 n (%) [95% CI][1]
Question 7: According to the SmPC/PI, the known risks for VFEND (voriconazole) are as follows: (Please select only one response for each of the risks listed in the table below.)										
Phototoxicity (e.g. skin rash)										
Yes[2]	19 (90.5) [69.6 - 98.8]	37 (88.1) [74.4 - 96.0]	2 (100.0) [15.8 - 100.0]	7 (100.0) [59.0 - 100.0]	4 (80.0) [28.4 - 99.5]	13 (81.3) [54.4 - 96.0]	175 (91.6) [86.8 - 95.1]	12 (85.7) [57.2 - 98.2]	16 (76.2) [52.8 - 91.8]	9 (69.2) [38.6 - 90.9]
No	1 (4.8)	4 (9.5)	0	0	1 (20.0)	0	6 (3.1)	1 (7.1)	1 (4.8)	2 (15.4)
I Don't Know	1 (4.8)	1 (2.4)	0	0	0	3 (18.8)	10 (5.2)	1 (7.1)	4 (19.0)	2 (15.4)
Intestinal perforation										
Yes	1 (4.8)	1 (2.4)	0	0	0	3 (18.8)	17 (8.9)	0	1 (4.8)	1 (7.7)
No[2]	15 (71.4) [47.8 - 88.7]	35 (83.3) [68.6 - 93.0]	2 (100.0) [15.8 - 100.0]	5 (71.4) [29.0 - 96.3]	3 (60.0) [14.7 - 94.7]	12 (75.0) [47.6 - 92.7]	121 (63.4) [56.1 - 70.2]	12 (85.7) [57.2 - 98.2]	12 (57.1) [34.0 - 78.2]	11 (84.6) [54.6 - 98.1]
I Don't Know	5 (23.8)	6 (14.3)	0	2 (28.6)	2 (40.0)	1 (6.3)	53 (27.7)	2 (14.3)	8 (38.1)	1 (7.7)
Squamous cell carcinoma (SCC) of the skin										
Yes[2]	10 (47.6) [25.7 - 70.2]	23 (54.8) [38.7 - 70.2]	1 (50.0) [1.3 - 98.7]	6 (85.7) [42.1 - 99.6]	1 (20.0) [0.5 - 71.6]	6 (37.5) [15.2 - 64.6]	81 (42.4) [35.3 - 49.8]	5 (35.7) [12.8 - 64.9]	9 (42.9) [21.8 - 66.0]	5 (38.5) [13.9 - 68.4]
No	8 (38.1)	15 (35.7)	1 (50.0)	0	2 (40.0)	6 (37.5)	68 (35.6)	6 (42.9)	6 (28.6)	8 (61.5)

Table 5.1: Responses to All Questions About the Knowledge of the Risks of Phototoxicity, SCC of the Skin and Hepatic Toxicity With Voriconazole by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	UK N=21 n (%) [95% CI][1]	F N=42 n (%) [95% CI][1]	A N=2 n (%) [95% CI][1]	IRL N=7 n (%) [95% CI][1]	DK N=5 n (%) [95% CI][1]	D N=16 n (%) [95% CI][1]	E N=191 n (%) [95% CI][1]	I N=14 n (%) [95% CI][1]	NL N=21 n (%) [95% CI][1]	H N=13 n (%) [95% CI][1]
I Don't Know	3 (14.3)	4 (9.5)	0	1 (14.3)	2 (40.0)	4 (25.0)	42 (22.0)	3 (21.4)	6 (28.6)	0
Asthma										
Yes	2 (9.5)	5 (11.9)	0	2 (28.6)	0	4 (25.0)	23 (12.0)	0	2 (9.5)	1 (7.7)
No[2]	12 (57.1) [34.0 - 78.2]	28 (66.7) [50.5 - 80.4]	2 (100.0) [15.8 - 100.0]	2 (28.6) [3.7 - 71.0]	3 (60.0) [14.7 - 94.7]	8 (50.0) [24.7 - 75.3]	113 (59.2) [51.8 - 66.2]	8 (57.1) [28.9 - 82.3]	10 (47.6) [25.7 - 70.2]	10 (76.9) [46.2 - 95.0]
I Don't Know	7 (33.3)	9 (21.4)	0	3 (42.9)	2 (40.0)	4 (25.0)	55 (28.8)	6 (42.9)	9 (42.9)	2 (15.4)
Hepatic toxicity										
Yes[2]	20 (95.2) [76.2 - 99.9]	39 (92.9) [80.5 - 98.5]	1 (50.0) [1.3 - 98.7]	7 (100.0) [59.0 - 100.0]	5 (100.0) [47.8 - 100.0]	16 (100.0) [79.4 - 100.0]	186 (97.4) [94.0 - 99.1]	14 (100.0) [76.8 - 100.0]	21 (100.0) [83.9 - 100.0]	11 (84.6) [54.6 - 98.1]
No	0	1 (2.4)	1 (50.0)	0	0	0	4 (2.1)	0	0	1 (7.7)
I Don't Know	1 (4.8)	2 (4.8)	0	0	0	0	1 (0.5)	0	0	1 (7.7)
Cardiomyopathy										
Yes	1 (4.8)	5 (11.9)	0	0	0	4 (25.0)	73 (38.2)	4 (28.6)	5 (23.8)	4 (30.8)
No[2]	10 (47.6) [25.7 - 70.2]	23 (54.8) [38.7 - 70.2]	2 (100.0) [15.8 - 100.0]	3 (42.9) [9.9 - 81.6]	3 (60.0) [14.7 - 94.7]	8 (50.0) [24.7 - 75.3]	77 (40.3) [33.3 - 47.6]	5 (35.7) [12.8 - 64.9]	4 (19.0) [5.4 - 41.9]	7 (53.8) [25.1 - 80.8]

Table 5.1: Responses to All Questions About the Knowledge of the Risks of Phototoxicity, SCC of the Skin and Hepatic Toxicity With Voriconazole by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	**UK N=21 n (%) [95% CI][1]**	**F N=42 n (%) [95% CI][1]**	**A N=2 n (%) [95% CI][1]**	**IRL N=7 n (%) [95% CI][1]**	**DK N=5 n (%) [95% CI][1]**	**D N=16 n (%) [95% CI][1]**	**E N=191 n (%) [95% CI][1]**	**I N=14 n (%) [95% CI][1]**	**NL N=21 n (%) [95% CI][1]**	**H N=13 n (%) [95% CI][1]**
I Don't Know	10 (47.6)	14 (33.3)	0	4 (57.1)	2 (40.0)	4 (25.0)	41 (21.5)	5 (35.7)	12 (57.1)	2 (15.4)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.
Abbreviations: UK = United Kingdom; F = France; A = Austria; IRL = Ireland; DK = Denmark; D = Germany; E = Spain; I = Italy; NL = The Netherlands; H = Hungary.

Table 5.2: Responses to All Questions About the Knowledge of the Risks of Phototoxicity, SCC of the Skin and Hepatic Toxicity With Voriconazole by Medical Specialty - (Completed Surveys From All Countries Combined)

Question	Medical Specialty				
	Critical Care / Intensive Care N=5 n (%) [95% CI][1]	Oncology / Hematology N=242 n (%) [95% CI][1]	Infectious Disease / Microbiology N=57 n (%) [95% CI][1]	Solid Organ Transplant Physician N=3 n (%) [95% CI][1]	Other/Other Subspecialty N=25 n (%) [95% CI][1]
Question 7: According to the SmPC/PI, the known risks for VFEND (voriconazole) are as follows: (Please select only one response for each of the risks listed in the table below.)					
Phototoxicity (e.g. skin rash)					
Yes[2]	3 (60.0) [14.7 - 94.7]	217 (89.7) [85.1 - 93.2]	52 (91.2) [80.7 - 97.1]	1 (33.3) [0.8 - 90.6]	21 (84.0) [63.9 - 95.5]
No	0	9 (3.7)	4 (7.0)	1 (33.3)	2 (8.0)
I Don't Know	2 (40.0)	16 (6.6)	1 (1.8)	1 (33.3)	2 (8.0)
Intestinal perforation					
Yes	1 (20.0)	22 (9.1)	1 (1.8)	0	0
No[2]	3 (60.0) [14.7 - 94.7]	157 (64.9) [58.5 - 70.9]	48 (84.2) [72.1 - 92.5]	2 (66.7) [9.4 - 99.2]	18 (72.0) [50.6 - 87.9]
I Don't Know	1 (20.0)	63 (26.0)	8 (14.0)	1 (33.3)	7 (28.0)
Squamous cell carcinoma (SCC) of the skin					
Yes[2]	2 (40.0) [5.3 - 85.3]	96 (39.7) [33.5 - 46.1]	33 (57.9) [44.1 - 70.9]	0	16 (64.0) [42.5 - 82.0]
No	0	92 (38.0)	18 (31.6)	3 (100.0)	7 (28.0)
I Don't Know	3 (60.0)	54 (22.3)	6 (10.5)	0	2 (8.0)
Asthma					
Yes	1 (20.0)	31 (12.8)	4 (7.0)	1 (33.3)	2 (8.0)
No[2]	2 (40.0) [5.3 - 85.3]	140 (57.9) [51.4 - 64.1]	38 (66.7) [52.9 - 78.6]	1 (33.3) [0.8 - 90.6]	15 (60.0) [38.7 - 78.9]
I Don't Know	2 (40.0)	71 (29.3)	15 (26.3)	1 (33.3)	8 (32.0)
Hepatic toxicity					
Yes[2]	5 (100.0) [47.8 - 100.0]	233 (96.3) [93.1 - 98.3]	57 (100.0) [93.7 - 100.0]	3 (100.0) [29.2 - 100.0]	22 (88.0) [68.8 - 97.5]
No	0	5 (2.1)	0	0	2 (8.0)

Table 5.2: Responses to All Questions About the Knowledge of the Risks of Phototoxicity, SCC of the Skin and Hepatic Toxicity With Voriconazole by Medical Specialty - (Completed Surveys From All Countries Combined)

Question	Medical Specialty				
	Critical Care / Intensive Care N=5 n (%) [95% CI][1]	Oncology / Hematology N=242 n (%) [95% CI][1]	Infectious Disease / Microbiology N=57 n (%) [95% CI][1]	Solid Organ Transplant Physician N=3 n (%) [95% CI][1]	Other/Other Subspecialty N=25 n (%) [95% CI][1]
I Don't Know	0	4 (1.7)	0	0	1 (4.0)
Cardiomyopathy					
Yes	2 (40.0)	74 (30.6)	14 (24.6)	2 (66.7)	4 (16.0)
No[2]	1 (20.0) [0.5 - 71.6]	103 (42.6) [36.3 - 49.1]	28 (49.1) [35.6 - 62.7]	0	10 (40.0) [21.1 - 61.3]
I Don't Know	2 (40.0)	65 (26.9)	15 (26.3)	1 (33.3)	11 (44.0)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 5.3: Responses to All Questions About the Knowledge of the Risks of Phototoxicity, SCC of the Skin and Hepatic Toxicity With Voriconazole by Number of Patients Treated in the Last 12 Months - (Completed Surveys From All Countries Combined)

Question	Number of Patients Treated in the Last 12 Months			
	1-5 Patients N=158 n (%) [95% CI][1]	6-10 Patients N=92 n (%) [95% CI][1]	11-20 Patients N=44 n (%) [95% CI][1]	More Than 20 Patients N=38 n (%) [95% CI][1]
Question 7: According to the SmPC/PI, the known risks for VFEND (voriconazole) are as follows: (Please select only one response for each of the risks listed in the table below.)				
Phototoxicity (e.g. skin rash)				
Yes[2]	142 (89.9) [84.1 - 94.1]	81 (88.0) [79.6 - 93.9]	36 (81.8) [67.3 - 91.8]	35 (92.1) [78.6 - 98.3]
No	8 (5.1)	6 (6.5)	2 (4.5)	0
I Don't Know	8 (5.1)	5 (5.4)	6 (13.6)	3 (7.9)
Intestinal perforation				
Yes	8 (5.1)	7 (7.6)	4 (9.1)	5 (13.2)
No[2]	107 (67.7) [59.8 - 74.9]	66 (71.7) [61.4 - 80.6]	30 (68.2) [52.4 - 81.4]	25 (65.8) [48.6 - 80.4]
I Don't Know	43 (27.2)	19 (20.7)	10 (22.7)	8 (21.1)
Squamous cell carcinoma (SCC) of the skin				
Yes[2]	73 (46.2) [38.2 - 54.3]	41 (44.6) [34.2 - 55.3]	20 (45.5) [30.4 - 61.2]	13 (34.2) [19.6 - 51.4]
No	54 (34.2)	34 (37.0)	19 (43.2)	13 (34.2)
I Don't Know	31 (19.6)	17 (18.5)	5 (11.4)	12 (31.6)
Asthma				
Yes	20 (12.7)	9 (9.8)	6 (13.6)	4 (10.5)
No[2]	86 (54.4) [46.3 - 62.4]	60 (65.2) [54.6 - 74.9]	26 (59.1) [43.2 - 73.7]	24 (63.2) [46.0 - 78.2]
I Don't Know	52 (32.9)	23 (25.0)	12 (27.3)	10 (26.3)
Hepatic toxicity				
Yes[2]	153 (96.8) [92.8 - 99.0]	88 (95.7) [89.2 - 98.8]	42 (95.5) [84.5 - 99.4]	37 (97.4) [86.2 - 99.9]
No	3 (1.9)	2 (2.2)	2 (4.5)	0
I Don't Know	2 (1.3)	2 (2.2)	0	1 (2.6)

Table 5.3: Responses to All Questions About the Knowledge of the Risks of Phototoxicity, SCC of the Skin and Hepatic Toxicity With Voriconazole by Number of Patients Treated in the Last 12 Months - (Completed Surveys From All Countries Combined)

Question	Number of Patients Treated in the Last 12 Months			
	1-5 Patients N=158 n (%) [95% CI][1]	**6-10 Patients N=92 n (%) [95% CI][1]**	**11-20 Patients N=44 n (%) [95% CI][1]**	**More Than 20 Patients N=38 n (%) [95% CI][1]**
Cardiomyopathy				
Yes	53 (33.5)	26 (28.3)	9 (20.5)	8 (21.1)
No[2]	54 (34.2) [26.8 - 42.1]	45 (48.9) [38.3 - 59.6]	21 (47.7) [32.5 - 63.3]	22 (57.9) [40.8 - 73.7]
I Don't Know	51 (32.3)	21 (22.8)	14 (31.8)	8 (21.1)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 5.4: Responses to All Questions About the Knowledge of the Risks of Phototoxicity, SCC of the Skin and Hepatic Toxicity With Voriconazole by Reading the HCP Q&A Brochure - (Completed Surveys From All Countries Combined)

Question	Reading the HCP Q&A Brochure	
	Read Some or All of It N=57 n (%) [95% CI][1]	Did Not Receive or Read It N=275 n (%) [95% CI][1]
Question 7: According to the SmPC/PI, the known risks for VFEND (voriconazole) are as follows: (Please select only one response for each of the risks listed in the table below.)		
Phototoxicity (e.g. skin rash)		
Yes[2]	54 (94.7) [85.4 - 98.9]	240 (87.3) [82.7 - 91.0]
No	2 (3.5)	14 (5.1)
I Don't Know	1 (1.8)	21 (7.6)
Intestinal perforation		
Yes	8 (14.0)	16 (5.8)
No[2]	39 (68.4) [54.8 - 80.1]	189 (68.7) [62.9 - 74.2]
I Don't Know	10 (17.5)	70 (25.5)
Squamous cell carcinoma (SCC) of the skin		
Yes[2]	35 (61.4) [47.6 - 74.0]	112 (40.7) [34.9 - 46.8]
No	18 (31.6)	102 (37.1)
I Don't Know	4 (7.0)	61 (22.2)
Asthma		
Yes	5 (8.8)	34 (12.4)
No[2]	39 (68.4) [54.8 - 80.1]	157 (57.1) [51.0 - 63.0]
I Don't Know	13 (22.8)	84 (30.5)
Hepatic toxicity		
Yes[2]	56 (98.2) [90.6 - 100.0]	264 (96.0) [93.0 - 98.0]
No	1 (1.8)	6 (2.2)
I Don't Know	0	5 (1.8)
Cardiomyopathy		

Table 5.4: Responses to All Questions About the Knowledge of the Risks of Phototoxicity, SCC of the Skin and Hepatic Toxicity With Voriconazole by Reading the HCP Q&A Brochure - (Completed Surveys From All Countries Combined)

Question	Reading the HCP Q&A Brochure	
	Read Some or All of It N=57 n (%) [95% CI][1]	Did Not Receive or Read It N=275 n (%) [95% CI][1]
Yes	19 (33.3)	77 (28.0)
No[2]	27 (47.4) [34.0 - 61.0]	115 (41.8) [35.9 - 47.9]
I Don't Know	11 (19.3)	83 (30.2)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.
Abbreviations: Read some or all of it = Received it and read some of it or all of it; Did not receive or read it = Did not receive, does not remember receiving or did not read or does not remember reading it

Table 6: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks - (Completed Surveys From All Countries Combined)

Question	Prescribers N=332 n (%) [95% CI][1]
Question 8: Please select only one response for each statement about VFEND (voriconazole) below:	
Long-term treatment (> 6 months) with VFEND (voriconazole) should be considered only if the benefits outweigh the potential risks	
True[2]	311 (93.7) [90.5 - 96.0]
False	15 (4.5)
I Don't Know	6 (1.8)
If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist	
True[2]	287 (86.4) [82.3 - 89.9]
False	31 (9.3)
I Don't Know	14 (4.2)
VFEND (voriconazole) should not be discontinued if premalignant skin lesions or skin Squamous Cell Carcinoma are identified	
True	25 (7.5)
False[2]	251 (75.6) [70.6 - 80.1]
I Don't Know	56 (16.9)
Laboratory evaluation of hepatic function (specifically AST and ALT) at initiation and during the first month of treatment with VFEND (voriconazole) is not necessary	
True	12 (3.6)
False[2]	317 (95.5) [92.7 - 97.4]
I Don't Know	3 (0.9)
If the Liver Function Tests become markedly elevated, VFEND (voriconazole) should be discontinued, unless the medical judgment of the risk-benefit balance of the treatment for the patient justifies continued use	
True[2]	313 (94.3) [91.2 - 96.5]
False	16 (4.8)
I Don't Know	3 (0.9)

Table 6: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks - (Completed Surveys From All Countries Combined)

Question	Prescribers N=332 n (%) [95% CI][1]
Question 15: Which precautionary measures should physicians communicate to their patients for whom they have prescribed VFEND (voriconazole)? Please check all that apply.[3]	
Avoiding exposure to direct sunlight	
Yes[2]	297 (89.5) [85.6 - 92.5]
No	35 (10.5)
Detecting signs and symptoms of phototoxicity	
Yes[2]	306 (92.2) [88.7 - 94.8]
No	26 (7.8)
Use with caution in patients with previous history of intestinal ulceration or diverticulitis	
Yes	110 (33.1)
No[2]	222 (66.9) [61.5 - 71.9]
Dermatologic evaluation should be performed on a systematic and regular basis	
Yes[2]	116 (34.9) [29.8 - 40.3]
No	216 (65.1)
Intensified monitoring of blood glucose level	
Yes	40 (12.0)
No[2]	292 (88.0) [84.0 - 91.3]
Covering sun exposed areas of skin	
Yes[2]	206 (62.0) [56.6 - 67.3]
No	126 (38.0)
Use sufficient sunscreen with high sun protection factor (SPF)	
Yes[2]	271 (81.6) [77.0 - 85.6]
No	61 (18.4)
Clinical signs of liver damage, such as jaundice that warrant contacting the doctor immediately	
Yes[2]	304 (91.6) [88.0 - 94.3]
No	28 (8.4)

Table 6: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks - (Completed Surveys From All Countries Combined)

Question	Prescribers N=332 n (%) [95% CI][1]
International Normalized Ratio regular monitoring	
Yes	67 (20.2)
No[2]	265 (79.8) [75.1 - 84.0]
Avoid invasive dental procedures	
Yes	45 (13.6)
No[2]	287 (86.4) [82.3 - 89.9]
Question 15a: How frequently do you, or another member of your healthcare team (e.g. nurse, pharmacist or other), perform each of these activities when initiating treatment with VFEND (voriconazole)? (Please check one response for each activity below).	
Discuss contents of the Patient Alert Card	
Always[2]	41 (12.3) [9.0 - 16.4]
Sometimes	94 (28.3)
Never	197 (59.3)
Advise patient to avoid exposure to direct sunlight and/or to use measures such as protective clothing and sunscreen	
Always[2]	230 (69.3) [64.0 - 74.2]
Sometimes	77 (23.2)
Never	25 (7.5)
Discuss risk of lymphoma	
Always	32 (9.6)
Sometimes	68 (20.5)
Never[2]	232 (69.9) [64.6 - 74.8]
Discuss risk of gastric perforation	
Always	34 (10.2)
Sometimes	94 (28.3)
Never[2]	204 (61.4) [56.0 - 66.7]
Advise patient of importance of monitoring risks of VFEND (voriconazole) use and signs and symptoms of serious risks that warrant contacting doctor immediately	

Table 6: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks - (Completed Surveys From All Countries Combined)

Question	Prescribers N=332 n (%) [95% CI][1]
Always[2]	226 (68.1) [62.8 - 73.1]
Sometimes	74 (22.3)
Never	32 (9.6)
Discuss risk of amyloidosis	
Always	15 (4.5)
Sometimes	48 (14.5)
Never[2]	269 (81.0) [76.4 - 85.1]
Question 16: How frequently should Liver Function Tests (specifically AST, ALT) be performed?	
At VFEND (voriconazole) treatment initiation and weekly thereafter for one month[2]	239 (72.0) [66.8 - 76.8]
Every contact	38 (11.4)
Monthly	44 (13.3)
Other	2 (0.6)
I do not know	9 (2.7)
Question 17: If there are no changes in Liver Function Tests (LFTs) after one month of initiation of VFEND (voriconazole), how often should you monitor liver function during VFEND treatment maintenance?	
Weekly	41 (12.3)
Monthly[2]	260 (78.3) [73.5 - 82.6]
Other	12 (3.6)
I do not know	19 (5.7)
Question 18: How often should a dermatologic evaluation be performed when VFEND (voriconazole) is continuously used despite the occurrence of phototoxicity-related lesions?	
Weekly	42 (12.7)
Monthly	48 (14.5)
Every two months	24 (7.2)
On systemic and regular basis[2]	160 (48.2) [42.7 - 53.7]

Table 6: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks - (Completed Surveys From All Countries Combined)

Question	Prescribers N=332 n (%) [95% CI][1]
I do not know	58 (17.5)
Question 19: When should VFEND (voriconazole) be discontinued in a patient? (Select the one best response).	
Phototoxicity	20 (6.0)
Squamous Cell Carcinoma (SCC)	38 (11.4)
Premalignant lesions	20 (6.0)
All of the above[2]	254 (76.5) [71.6 - 81.0]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct or desired response.
[3] If the response option is checked the response is presented as 'Yes' answer, if it is not checked as 'No' answer.

Table 6.1: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	UK N=21 n (%) [95% CI][1]	F N=42 n (%) [95% CI][1]	A N=2 n (%) [95% CI][1]	IRL N=7 n (%) [95% CI][1]	DK N=5 n (%) [95% CI][1]	D N=16 n (%) [95% CI][1]	E N=191 n (%) [95% CI][1]	I N=14 n (%) [95% CI][1]	NL N=21 n (%) [95% CI][1]	H N=13 n (%) [95% CI][1]
Question 8: Please select only one response for each statement about VFEND (voriconazole) below:										
Long-term treatment (> 6 months) with VFEND (voriconazole) should be considered only if the benefits outweigh the potential risks										
True[2]	21 (100.0) [83.9 - 100.0]	39 (92.9) [80.5 - 98.5]	2 (100.0) [15.8 - 100.0]	6 (85.7) [42.1 - 99.6]	5 (100.0) [47.8 - 100.0]	16 (100.0) [79.4 - 100.0]	177 (92.7) [88.0 - 95.9]	14 (100.0) [76.8 - 100.0]	19 (90.5) [69.6 - 98.8]	12 (92.3) [64.0 - 99.8]
False	0	3 (7.1)	0	0	0	0	11 (5.8)	0	1 (4.8)	0
I Don't Know	0	0	0	1 (14.3)	0	0	3 (1.6)	0	1 (4.8)	1 (7.7)
If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist										
True[2]	19 (90.5) [69.6 - 98.8]	32 (76.2) [60.5 - 87.9]	1 (50.0) [1.3 - 98.7]	7 (100.0) [59.0 - 100.0]	2 (40.0) [5.3 - 85.3]	15 (93.8) [69.8 - 99.8]	171 (89.5) [84.3 - 93.5]	12 (85.7) [57.2 - 98.2]	18 (85.7) [63.7 - 97.0]	10 (76.9) [46.2 - 95.0]
False	0	8 (19.0)	1 (50.0)	0	1 (20.0)	1 (6.3)	15 (7.9)	2 (14.3)	0	3 (23.1)
I Don't Know	2 (9.5)	2 (4.8)	0	0	2 (40.0)	0	5 (2.6)	0	3 (14.3)	0
VFEND (voriconazole) should not be discontinued if premalignant skin lesions or skin Squamous Cell Carcinoma are identified										
True	4 (19.0)	3 (7.1)	1 (50.0)	2 (28.6)	0	0	13 (6.8)	2 (14.3)	0	0
False[2]	12 (57.1) [34.0 - 78.2]	33 (78.6) [63.2 - 89.7]	1 (50.0) [1.3 - 98.7]	3 (42.9) [9.9 - 81.6]	5 (100.0) [47.8 - 100.0]	14 (87.5) [61.7 - 98.4]	145 (75.9) [69.2 - 81.8]	11 (78.6) [49.2 - 95.3]	15 (71.4) [47.8 - 88.7]	12 (92.3) [64.0 - 99.8]

Table 6.1: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	**UK N=21 n (%) [95% CI][1]**	**F N=42 n (%) [95% CI][1]**	**A N=2 n (%) [95% CI][1]**	**IRL N=7 n (%) [95% CI][1]**	**DK N=5 n (%) [95% CI][1]**	**D N=16 n (%) [95% CI][1]**	**E N=191 n (%) [95% CI][1]**	**I N=14 n (%) [95% CI][1]**	**NL N=21 n (%) [95% CI][1]**	**H N=13 n (%) [95% CI][1]**
I Don't Know	5 (23.8)	6 (14.3)	0	2 (28.6)	0	2 (12.5)	33 (17.3)	1 (7.1)	6 (28.6)	1 (7.7)
Laboratory evaluation of hepatic function (specifically AST and ALT) at initiation and during the first month of treatment with VFEND (voriconazole) is not necessary										
True	2 (9.5)	2 (4.8)	2 (100.0)	0	0	0	3 (1.6)	1 (7.1)	0	2 (15.4)
False[2]	19 (90.5) [69.6 - 98.8]	39 (92.9) [80.5 - 98.5]	0	7 (100.0) [59.0 - 100.0]	5 (100.0) [47.8 - 100.0]	16 (100.0) [79.4 - 100.0]	188 (98.4) [95.5 - 99.7]	13 (92.9) [66.1 - 99.8]	19 (90.5) [69.6 - 98.8]	11 (84.6) [54.6 - 98.1]
I Don't Know	0	1 (2.4)	0	0	0	0	0	0	2 (9.5)	0
If the Liver Function Tests become markedly elevated, VFEND (voriconazole) should be discontinued, unless the medical judgment of the risk-benefit balance of the treatment for the patient justifies continued use										
True[2]	20 (95.2) [76.2 - 99.9]	37 (88.1) [74.4 - 96.0]	2 (100.0) [15.8 - 100.0]	7 (100.0) [59.0 - 100.0]	5 (100.0) [47.8 - 100.0]	16 (100.0) [79.4 - 100.0]	184 (96.3) [92.6 - 98.5]	14 (100.0) [76.8 - 100.0]	19 (90.5) [69.6 - 98.8]	9 (69.2) [38.6 - 90.9]
False	1 (4.8)	3 (7.1)	0	0	0	0	6 (3.1)	0	2 (9.5)	4 (30.8)
I Don't Know	0	2 (4.8)	0	0	0	0	1 (0.5)	0	0	0
Question 15: Which precautionary measures should physicians communicate to their patients for whom they have prescribed VFEND (voriconazole)? Please check all that apply.[3]										
Avoiding exposure to direct sunlight										

Table 6.1: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	UK N=21 n (%) [95% CI][1]	F N=42 n (%) [95% CI][1]	A N=2 n (%) [95% CI][1]	IRL N=7 n (%) [95% CI][1]	DK N=5 n (%) [95% CI][1]	D N=16 n (%) [95% CI][1]	E N=191 n (%) [95% CI][1]	I N=14 n (%) [95% CI][1]	NL N=21 n (%) [95% CI][1]	H N=13 n (%) [95% CI][1]
Yes[2]	19 (90.5) [69.6 - 98.8]	38 (90.5) [77.4 - 97.3]	2 (100.0) [15.8 - 100.0]	6 (85.7) [42.1 - 99.6]	5 (100.0) [47.8 - 100.0]	14 (87.5) [61.7 - 98.4]	174 (91.1) [86.1 - 94.7]	11 (78.6) [49.2 - 95.3]	16 (76.2) [52.8 - 91.8]	12 (92.3) [64.0 - 99.8]
No	2 (9.5)	4 (9.5)	0	1 (14.3)	0	2 (12.5)	17 (8.9)	3 (21.4)	5 (23.8)	1 (7.7)
Detecting signs and symptoms of phototoxicity										
Yes[2]	20 (95.2) [76.2 - 99.9]	38 (90.5) [77.4 - 97.3]	2 (100.0) [15.8 - 100.0]	5 (71.4) [29.0 - 96.3]	5 (100.0) [47.8 - 100.0]	15 (93.8) [69.8 - 99.8]	178 (93.2) [88.6 - 96.3]	13 (92.9) [66.1 - 99.8]	19 (90.5) [69.6 - 98.8]	11 (84.6) [54.6 - 98.1]
No	1 (4.8)	4 (9.5)	0	2 (28.6)	0	1 (6.3)	13 (6.8)	1 (7.1)	2 (9.5)	2 (15.4)
Use with caution in patients with previous history of intestinal ulceration or diverticulitis										
Yes	6 (28.6)	12 (28.6)	1 (50.0)	3 (42.9)	1 (20.0)	10 (62.5)	65 (34.0)	1 (7.1)	8 (38.1)	3 (23.1)
No[2]	15 (71.4) [47.8 - 88.7]	30 (71.4) [55.4 - 84.3]	1 (50.0) [1.3 - 98.7]	4 (57.1) [18.4 - 90.1]	4 (80.0) [28.4 - 99.5]	6 (37.5) [15.2 - 64.6]	126 (66.0) [58.8 - 72.7]	13 (92.9) [66.1 - 99.8]	13 (61.9) [38.4 - 81.9]	10 (76.9) [46.2 - 95.0]
Dermatologic evaluation should be performed on a systematic and regular basis										
Yes[2]	2 (9.5) [1.2 - 30.4]	18 (42.9) [27.7 - 59.0]	0	2 (28.6) [3.7 - 71.0]	0	9 (56.3) [29.9 - 80.2]	70 (36.6) [29.8 - 43.9]	5 (35.7) [12.8 - 64.9]	3 (14.3) [3.0 - 36.3]	7 (53.8) [25.1 - 80.8]
No	19 (90.5)	24 (57.1)	2 (100.0)	5 (71.4)	5 (100.0)	7 (43.8)	121 (63.4)	9 (64.3)	18 (85.7)	6 (46.2)

Table 6.1: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	UK N=21 n (%) [95% CI][1]	F N=42 n (%) [95% CI][1]	A N=2 n (%) [95% CI][1]	IRL N=7 n (%) [95% CI][1]	DK N=5 n (%) [95% CI][1]	D N=16 n (%) [95% CI][1]	E N=191 n (%) [95% CI][1]	I N=14 n (%) [95% CI][1]	NL N=21 n (%) [95% CI][1]	H N=13 n (%) [95% CI][1]
Intensified monitoring of blood glucose level										
Yes	1 (4.8)	5 (11.9)	0	1 (14.3)	0	4 (25.0)	23 (12.0)	1 (7.1)	3 (14.3)	2 (15.4)
No[2]	20 (95.2) [76.2 - 99.9]	37 (88.1) [74.4 - 96.0]	2 (100.0) [15.8 - 100.0]	6 (85.7) [42.1 - 99.6]	5 (100.0) [47.8 - 100.0]	12 (75.0) [47.6 - 92.7]	168 (88.0) [82.5 - 92.2]	13 (92.9) [66.1 - 99.8]	18 (85.7) [63.7 - 97.0]	11 (84.6) [54.6 - 98.1]
Covering sun exposed areas of skin										
Yes[2]	19 (90.5) [69.6 - 98.8]	34 (81.0) [65.9 - 91.4]	0	5 (71.4) [29.0 - 96.3]	4 (80.0) [28.4 - 99.5]	12 (75.0) [47.6 - 92.7]	100 (52.4) [45.0 - 59.6]	7 (50.0) [23.0 - 77.0]	15 (71.4) [47.8 - 88.7]	10 (76.9) [46.2 - 95.0]
No	2 (9.5)	8 (19.0)	2 (100.0)	2 (28.6)	1 (20.0)	4 (25.0)	91 (47.6)	7 (50.0)	6 (28.6)	3 (23.1)
Use sufficient sunscreen with high sun protection factor (SPF)										
Yes[2]	19 (90.5) [69.6 - 98.8]	27 (64.3) [48.0 - 78.4]	1 (50.0) [1.3 - 98.7]	5 (71.4) [29.0 - 96.3]	4 (80.0) [28.4 - 99.5]	15 (93.8) [69.8 - 99.8]	165 (86.4) [80.7 - 90.9]	10 (71.4) [41.9 - 91.6]	14 (66.7) [43.0 - 85.4]	11 (84.6) [54.6 - 98.1]
No	2 (9.5)	15 (35.7)	1 (50.0)	2 (28.6)	1 (20.0)	1 (6.3)	26 (13.6)	4 (28.6)	7 (33.3)	2 (15.4)
Clinical signs of liver damage, such as jaundice that warrant contacting the doctor immediately										
Yes[2]	19 (90.5) [69.6 - 98.8]	35 (83.3) [68.6 - 93.0]	1 (50.0) [1.3 - 98.7]	7 (100.0) [59.0 - 100.0]	5 (100.0) [47.8 - 100.0]	15 (93.8) [69.8 - 99.8]	179 (93.7) [89.3 - 96.7]	13 (92.9) [66.1 - 99.8]	18 (85.7) [63.7 - 97.0]	12 (92.3) [64.0 - 99.8]

Table 6.1: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	**UK N=21 n (%) [95% CI][1]**	**F N=42 n (%) [95% CI][1]**	**A N=2 n (%) [95% CI][1]**	**IRL N=7 n (%) [95% CI][1]**	**DK N=5 n (%) [95% CI][1]**	**D N=16 n (%) [95% CI][1]**	**E N=191 n (%) [95% CI][1]**	**I N=14 n (%) [95% CI][1]**	**NL N=21 n (%) [95% CI][1]**	**H N=13 n (%) [95% CI][1]**
No	2 (9.5)	7 (16.7)	1 (50.0)	0	0	1 (6.3)	12 (6.3)	1 (7.1)	3 (14.3)	1 (7.7)
International Normalized Ratio regular monitoring										
Yes	6 (28.6)	7 (16.7)	0	0	2 (40.0)	5 (31.3)	32 (16.8)	4 (28.6)	8 (38.1)	3 (23.1)
No[2]	15 (71.4) [47.8 - 88.7]	35 (83.3) [68.6 - 93.0]	2 (100.0) [15.8 - 100.0]	7 (100.0) [59.0 - 100.0]	3 (60.0) [14.7 - 94.7]	11 (68.8) [41.3 - 89.0]	159 (83.2) [77.2 - 88.2]	10 (71.4) [41.9 - 91.6]	13 (61.9) [38.4 - 81.9]	10 (76.9) [46.2 - 95.0]
Avoid invasive dental procedures										
Yes	1 (4.8)	3 (7.1)	0	2 (28.6)	1 (20.0)	3 (18.8)	28 (14.7)	1 (7.1)	4 (19.0)	2 (15.4)
No[2]	20 (95.2) [76.2 - 99.9]	39 (92.9) [80.5 - 98.5]	2 (100.0) [15.8 - 100.0]	5 (71.4) [29.0 - 96.3]	4 (80.0) [28.4 - 99.5]	13 (81.3) [54.4 - 96.0]	163 (85.3) [79.5 - 90.0]	13 (92.9) [66.1 - 99.8]	17 (81.0) [58.1 - 94.6]	11 (84.6) [54.6 - 98.1]
Question 15a: How frequently do you, or another member of your healthcare team (e.g. nurse, pharmacist or other), perform each of these activities when initiating treatment with VFEND (voriconazole)? (Please check one response for each activity below).										
Discuss contents of the Patient Alert Card										
Always[2]	2 (9.5) [1.2 - 30.4]	6 (14.3) [5.4 - 28.5]	0	1 (14.3) [0.4 - 57.9]	0	2 (12.5) [1.6 - 38.3]	23 (12.0) [7.8 - 17.5]	4 (28.6) [8.4 - 58.1]	1 (4.8) [0.1 - 23.8]	2 (15.4) [1.9 - 45.4]
Sometimes	4 (19.0)	12 (28.6)	0	2 (28.6)	2 (40.0)	6 (37.5)	55 (28.8)	5 (35.7)	4 (19.0)	4 (30.8)
Never	15 (71.4)	24 (57.1)	2 (100.0)	4 (57.1)	3 (60.0)	8 (50.0)	113 (59.2)	5 (35.7)	16 (76.2)	7 (53.8)

Table 6.1: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	**UK N=21 n (%) [95% CI][1]**	**F N=42 n (%) [95% CI][1]**	**A N=2 n (%) [95% CI][1]**	**IRL N=7 n (%) [95% CI][1]**	**DK N=5 n (%) [95% CI][1]**	**D N=16 n (%) [95% CI][1]**	**E N=191 n (%) [95% CI][1]**	**I N=14 n (%) [95% CI][1]**	**NL N=21 n (%) [95% CI][1]**	**H N=13 n (%) [95% CI][1]**
Advise patient to avoid exposure to direct sunlight and/or to use measures such as protective clothing and sunscreen										
Always[2]	12 (57.1) [34.0 - 78.2]	30 (71.4) [55.4 - 84.3]	1 (50.0) [1.3 - 98.7]	3 (42.9) [9.9 - 81.6]	3 (60.0) [14.7 - 94.7]	11 (68.8) [41.3 - 89.0]	136 (71.2) [64.2 - 77.5]	11 (78.6) [49.2 - 95.3]	11 (52.4) [29.8 - 74.3]	12 (92.3) [64.0 - 99.8]
Sometimes	7 (33.3)	9 (21.4)	1 (50.0)	3 (42.9)	2 (40.0)	3 (18.8)	45 (23.6)	3 (21.4)	3 (14.3)	1 (7.7)
Never	2 (9.5)	3 (7.1)	0	1 (14.3)	0	2 (12.5)	10 (5.2)	0	7 (33.3)	0
Discuss risk of lymphoma										
Always	0	2 (4.8)	0	0	0	4 (25.0)	22 (11.5)	2 (14.3)	1 (4.8)	1 (7.7)
Sometimes	2 (9.5)	9 (21.4)	0	2 (28.6)	1 (20.0)	3 (18.8)	39 (20.4)	4 (28.6)	5 (23.8)	3 (23.1)
Never[2]	19 (90.5) [69.6 - 98.8]	31 (73.8) [58.0 - 86.1]	2 (100.0) [15.8 - 100.0]	5 (71.4) [29.0 - 96.3]	4 (80.0) [28.4 - 99.5]	9 (56.3) [29.9 - 80.2]	130 (68.1) [60.9 - 74.6]	8 (57.1) [28.9 - 82.3]	15 (71.4) [47.8 - 88.7]	9 (69.2) [38.6 - 90.9]
Discuss risk of gastric perforation										
Always	0	2 (4.8)	0	0	0	3 (18.8)	24 (12.6)	2 (14.3)	2 (9.5)	1 (7.7)
Sometimes	3 (14.3)	11 (26.2)	0	3 (42.9)	1 (20.0)	5 (31.3)	60 (31.4)	5 (35.7)	3 (14.3)	3 (23.1)
Never[2]	18 (85.7) [63.7 - 97.0]	29 (69.0) [52.9 - 82.4]	2 (100.0) [15.8 - 100.0]	4 (57.1) [18.4 - 90.1]	4 (80.0) [28.4 - 99.5]	8 (50.0) [24.7 - 75.3]	107 (56.0) [48.7 - 63.2]	7 (50.0) [23.0 - 77.0]	16 (76.2) [52.8 - 91.8]	9 (69.2) [38.6 - 90.9]

Table 6.1: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	**UK N=21 n (%) [95% CI][1]**	**F N=42 n (%) [95% CI][1]**	**A N=2 n (%) [95% CI][1]**	**IRL N=7 n (%) [95% CI][1]**	**DK N=5 n (%) [95% CI][1]**	**D N=16 n (%) [95% CI][1]**	**E N=191 n (%) [95% CI][1]**	**I N=14 n (%) [95% CI][1]**	**NL N=21 n (%) [95% CI][1]**	**H N=13 n (%) [95% CI][1]**
Advise patient of importance of monitoring risks of VFEND (voriconazole) use and signs and symptoms of serious risks that warrant contacting doctor immediately										
Always[2]	13 (61.9) [38.4 - 81.9]	31 (73.8) [58.0 - 86.1]	2 (100.0) [15.8 - 100.0]	4 (57.1) [18.4 - 90.1]	4 (80.0) [28.4 - 99.5]	14 (87.5) [61.7 - 98.4]	127 (66.5) [59.3 - 73.1]	11 (78.6) [49.2 - 95.3]	9 (42.9) [21.8 - 66.0]	11 (84.6) [54.6 - 98.1]
Sometimes	6 (28.6)	7 (16.7)	0	2 (28.6)	0	1 (6.3)	49 (25.7)	3 (21.4)	4 (19.0)	2 (15.4)
Never	2 (9.5)	4 (9.5)	0	1 (14.3)	1 (20.0)	1 (6.3)	15 (7.9)	0	8 (38.1)	0
Discuss risk of amyloidosis										
Always	0	3 (7.1)	0	0	0	1 (6.3)	6 (3.1)	2 (14.3)	2 (9.5)	1 (7.7)
Sometimes	1 (4.8)	6 (14.3)	0	1 (14.3)	1 (20.0)	3 (18.8)	27 (14.1)	4 (28.6)	2 (9.5)	3 (23.1)
Never[2]	20 (95.2) [76.2 - 99.9]	33 (78.6) [63.2 - 89.7]	2 (100.0) [15.8 - 100.0]	6 (85.7) [42.1 - 99.6]	4 (80.0) [28.4 - 99.5]	12 (75.0) [47.6 - 92.7]	158 (82.7) [76.6 - 87.8]	8 (57.1) [28.9 - 82.3]	17 (81.0) [58.1 - 94.6]	9 (69.2) [38.6 - 90.9]
Question 16: How frequently should Liver Function Tests (specifically AST, ALT) be performed?										
At VFEND (voriconazole) treatment initiation and weekly thereafter for one month[2]	10 (47.6) [25.7 - 70.2]	32 (76.2) [60.5 - 87.9]	1 (50.0) [1.3 - 98.7]	6 (85.7) [42.1 - 99.6]	1 (20.0) [0.5 - 71.6]	14 (87.5) [61.7 - 98.4]	142 (74.3) [67.5 - 80.4]	12 (85.7) [57.2 - 98.2]	12 (57.1) [34.0 - 78.2]	9 (69.2) [38.6 - 90.9]

Table 6.1: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	UK N=21 n (%) [95% CI][1]	F N=42 n (%) [95% CI][1]	A N=2 n (%) [95% CI][1]	IRL N=7 n (%) [95% CI][1]	DK N=5 n (%) [95% CI][1]	D N=16 n (%) [95% CI][1]	E N=191 n (%) [95% CI][1]	I N=14 n (%) [95% CI][1]	NL N=21 n (%) [95% CI][1]	H N=13 n (%) [95% CI][1]
Every contact	4 (19.0)	1 (2.4)	0	0	3 (60.0)	1 (6.3)	23 (12.0)	0	5 (23.8)	1 (7.7)
Monthly	4 (19.0)	8 (19.0)	1 (50.0)	0	1 (20.0)	1 (6.3)	23 (12.0)	2 (14.3)	1 (4.8)	3 (23.1)
Other	0	0	0	0	0	0	1 (0.5)	0	1 (4.8)	0
I do not know	3 (14.3)	1 (2.4)	0	1 (14.3)	0	0	2 (1.0)	0	2 (9.5)	0
Question 17: If there are no changes in Liver Function Tests (LFTs) after one month of initiation of VFEND (voriconazole), how often should you monitor liver function during VFEND treatment maintenance?										
Weekly	3 (14.3)	2 (4.8)	0	0	0	2 (12.5)	31 (16.2)	1 (7.1)	2 (9.5)	0
Monthly[2]	15 (71.4) [47.8 - 88.7]	35 (83.3) [68.6 - 93.0]	1 (50.0) [1.3 - 98.7]	6 (85.7) [42.1 - 99.6]	4 (80.0) [28.4 - 99.5]	12 (75.0) [47.6 - 92.7]	150 (78.5) [72.0 - 84.1]	13 (92.9) [66.1 - 99.8]	13 (61.9) [38.4 - 81.9]	11 (84.6) [54.6 - 98.1]
Other	2 (9.5)	3 (7.1)	0	0	0	0	7 (3.7)	0	0	0
I do not know	1 (4.8)	2 (4.8)	1 (50.0)	1 (14.3)	1 (20.0)	2 (12.5)	3 (1.6)	0	6 (28.6)	2 (15.4)
Question 18: How often should a dermatologic evaluation be performed when VFEND (voriconazole) is continuously used despite the occurrence of phototoxicity-related lesions?										
Weekly	1 (4.8)	5 (11.9)	0	0	0	5 (31.3)	23 (12.0)	4 (28.6)	1 (4.8)	3 (23.1)
Monthly	3 (14.3)	9 (21.4)	0	1 (14.3)	0	2 (12.5)	24 (12.6)	4 (28.6)	1 (4.8)	4 (30.8)
Every two months	0	9 (21.4)	1 (50.0)	0	1 (20.0)	1 (6.3)	11 (5.8)	0	1 (4.8)	0

Table 6.1: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Country - (Completed Surveys From All Countries Combined)

	Country									
Question	**UK N=21 n (%) [95% CI][1]**	**F N=42 n (%) [95% CI][1]**	**A N=2 n (%) [95% CI][1]**	**IRL N=7 n (%) [95% CI][1]**	**DK N=5 n (%) [95% CI][1]**	**D N=16 n (%) [95% CI][1]**	**E N=191 n (%) [95% CI][1]**	**I N=14 n (%) [95% CI][1]**	**NL N=21 n (%) [95% CI][1]**	**H N=13 n (%) [95% CI][1]**
On systemic and regular basis[2]	9 (42.9) [21.8 - 66.0]	15 (35.7) [21.6 - 52.0]	1 (50.0) [1.3 - 98.7]	5 (71.4) [29.0 - 96.3]	2 (40.0) [5.3 - 85.3]	8 (50.0) [24.7 - 75.3]	105 (55.0) [47.6 - 62.2]	3 (21.4) [4.7 - 50.8]	8 (38.1) [18.1 - 61.6]	4 (30.8) [9.1 - 61.4]
I do not know	8 (38.1)	4 (9.5)	0	1 (14.3)	2 (40.0)	0	28 (14.7)	3 (21.4)	10 (47.6)	2 (15.4)
Question 19: When should VFEND (voriconazole) be discontinued in a patient? (Select the one best response).										
Phototoxicity	2 (9.5)	5 (11.9)	1 (50.0)	0	1 (20.0)	0	6 (3.1)	1 (7.1)	3 (14.3)	1 (7.7)
Squamous Cell Carcinoma (SCC)	0	12 (28.6)	1 (50.0)	1 (14.3)	1 (20.0)	2 (12.5)	18 (9.4)	0	3 (14.3)	0
Premalignant lesions	3 (14.3)	5 (11.9)	0	0	0	2 (12.5)	8 (4.2)	0	1 (4.8)	1 (7.7)
All of the above[2]	16 (76.2) [52.8 - 91.8]	20 (47.6) [32.0 - 63.6]	0	6 (85.7) [42.1 - 99.6]	3 (60.0) [14.7 - 94.7]	12 (75.0) [47.6 - 92.7]	159 (83.2) [77.2 - 88.2]	13 (92.9) [66.1 - 99.8]	14 (66.7) [43.0 - 85.4]	11 (84.6) [54.6 - 98.1]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct or desired response.
[3] If the response option is checked the response is presented as 'Yes' answer, if it is not checked as 'No' answer.
Abbreviations: UK = United Kingdom; F = France; A = Austria; IRL = Ireland; DK = Denmark; D = Germany; E = Spain; I = Italy; NL = The Netherlands; H = Hungary.

Table 6.2: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Medical Specialty - (Completed Surveys From All Countries Combined)

Question	Medical Specialty				
	Critical Care / Intensive Care N=5 n (%) [95% CI][1]	Oncology / Hematology N=242 n (%) [95% CI][1]	Infectious Disease / Microbiology N=57 n (%) [95% CI][1]	Solid Organ Transplant Physician N=3 n (%) [95% CI][1]	Other/Other Subspecialty N=25 n (%) [95% CI][1]
Question 8: Please select only one response for each statement about VFEND (voriconazole) below:					
Long-term treatment (> 6 months) with VFEND (voriconazole) should be considered only if the benefits outweigh the potential risks					
True[2]	5 (100.0) [47.8 - 100.0]	227 (93.8) [90.0 - 96.5]	54 (94.7) [85.4 - 98.9]	3 (100.0) [29.2 - 100.0]	22 (88.0) [68.8 - 97.5]
False	0	10 (4.1)	3 (5.3)	0	2 (8.0)
I Don't Know	0	5 (2.1)	0	0	1 (4.0)
If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist					
True[2]	4 (80.0) [28.4 - 99.5]	211 (87.2) [82.3 - 91.1]	47 (82.5) [70.1 - 91.3]	2 (66.7) [9.4 - 99.2]	23 (92.0) [74.0 - 99.0]
False	0	21 (8.7)	8 (14.0)	0	2 (8.0)
I Don't Know	1 (20.0)	10 (4.1)	2 (3.5)	1 (33.3)	0
VFEND (voriconazole) should not be discontinued if premalignant skin lesions or skin Squamous Cell Carcinoma are identified					
True	0	21 (8.7)	4 (7.0)	0	0
False[2]	4 (80.0) [28.4 - 99.5]	180 (74.4) [68.4 - 79.8]	44 (77.2) [64.2 - 87.3]	3 (100.0) [29.2 - 100.0]	20 (80.0) [59.3 - 93.2]
I Don't Know	1 (20.0)	41 (16.9)	9 (15.8)	0	5 (20.0)
Laboratory evaluation of hepatic function (specifically AST and ALT) at initiation and during the first month of treatment with VFEND (voriconazole) is not necessary					
True	0	8 (3.3)	2 (3.5)	0	2 (8.0)
False[2]	5 (100.0) [47.8 - 100.0]	233 (96.3) [93.1 - 98.3]	55 (96.5) [87.9 - 99.6]	3 (100.0) [29.2 - 100.0]	21 (84.0) [63.9 - 95.5]
I Don't Know	0	1 (0.4)	0	0	2 (8.0)
If the Liver Function Tests become markedly elevated, VFEND (voriconazole) should be discontinued, unless the medical judgment of the risk-benefit balance of the treatment for the patient justifies continued use					

Table 6.2: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Medical Specialty - (Completed Surveys From All Countries Combined)

Question	Medical Specialty				
	Critical Care / Intensive Care N=5 n (%) [95% CI][1]	Oncology / Hematology N=242 n (%) [95% CI][1]	Infectious Disease / Microbiology N=57 n (%) [95% CI][1]	Solid Organ Transplant Physician N=3 n (%) [95% CI][1]	Other/Other Subspecialty N=25 n (%) [95% CI][1]
True[2]	5 (100.0) [47.8 - 100.0]	230 (95.0) [91.5 - 97.4]	55 (96.5) [87.9 - 99.6]	2 (66.7) [9.4 - 99.2]	21 (84.0) [63.9 - 95.5]
False	0	10 (4.1)	1 (1.8)	1 (33.3)	4 (16.0)
I Don't Know	0	2 (0.8)	1 (1.8)	0	0
Question 15: Which precautionary measures should physicians communicate to their patients for whom they have prescribed VFEND (voriconazole)? Please check all that apply.[3]					
Avoiding exposure to direct sunlight					
Yes[2]	5 (100.0) [47.8 - 100.0]	217 (89.7) [85.1 - 93.2]	50 (87.7) [76.3 - 94.9]	3 (100.0) [29.2 - 100.0]	22 (88.0) [68.8 - 97.5]
No	0	25 (10.3)	7 (12.3)	0	3 (12.0)
Detecting signs and symptoms of phototoxicity					
Yes[2]	5 (100.0) [47.8 - 100.0]	221 (91.3) [87.0 - 94.5]	54 (94.7) [85.4 - 98.9]	3 (100.0) [29.2 - 100.0]	23 (92.0) [74.0 - 99.0]
No	0	21 (8.7)	3 (5.3)	0	2 (8.0)
Use with caution in patients with previous history of intestinal ulceration or diverticulitis					
Yes	2 (40.0)	87 (36.0)	13 (22.8)	0	8 (32.0)
No[2]	3 (60.0) [14.7 - 94.7]	155 (64.0) [57.7 - 70.1]	44 (77.2) [64.2 - 87.3]	3 (100.0) [29.2 - 100.0]	17 (68.0) [46.5 - 85.1]
Dermatologic evaluation should be performed on a systematic and regular basis					
Yes[2]	1 (20.0) [0.5 - 71.6]	89 (36.8) [30.7 - 43.2]	19 (33.3) [21.4 - 47.1]	2 (66.7) [9.4 - 99.2]	5 (20.0) [6.8 - 40.7]
No	4 (80.0)	153 (63.2)	38 (66.7)	1 (33.3)	20 (80.0)
Intensified monitoring of blood glucose level					
Yes	1 (20.0)	31 (12.8)	4 (7.0)	0	4 (16.0)
No[2]	4 (80.0) [28.4 - 99.5]	211 (87.2) [82.3 - 91.1]	53 (93.0) [83.0 - 98.1]	3 (100.0) [29.2 - 100.0]	21 (84.0) [63.9 - 95.5]
Covering sun exposed areas of skin					

Table 6.2: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Medical Specialty - (Completed Surveys From All Countries Combined)

Question	Medical Specialty				
	Critical Care / Intensive Care N=5 n (%) [95% CI][1]	Oncology / Hematology N=242 n (%) [95% CI][1]	Infectious Disease / Microbiology N=57 n (%) [95% CI][1]	Solid Organ Transplant Physician N=3 n (%) [95% CI][1]	Other/Other Subspecialty N=25 n (%) [95% CI][1]
Yes[2]	4 (80.0) [28.4 - 99.5]	142 (58.7) [52.2 - 64.9]	40 (70.2) [56.6 - 81.6]	2 (66.7) [9.4 - 99.2]	18 (72.0) [50.6 - 87.9]
No	1 (20.0)	100 (41.3)	17 (29.8)	1 (33.3)	7 (28.0)
Use sufficient sunscreen with high sun protection factor (SPF)					
Yes[2]	4 (80.0) [28.4 - 99.5]	195 (80.6) [75.0 - 85.4]	49 (86.0) [74.2 - 93.7]	3 (100.0) [29.2 - 100.0]	20 (80.0) [59.3 - 93.2]
No	1 (20.0)	47 (19.4)	8 (14.0)	0	5 (20.0)
Clinical signs of liver damage, such as jaundice that warrant contacting the doctor immediately					
Yes[2]	5 (100.0) [47.8 - 100.0]	222 (91.7) [87.5 - 94.9]	50 (87.7) [76.3 - 94.9]	3 (100.0) [29.2 - 100.0]	24 (96.0) [79.6 - 99.9]
No	0	20 (8.3)	7 (12.3)	0	1 (4.0)
International Normalized Ratio regular monitoring					
Yes	2 (40.0)	46 (19.0)	10 (17.5)	1 (33.3)	8 (32.0)
No[2]	3 (60.0) [14.7 - 94.7]	196 (81.0) [75.5 - 85.7]	47 (82.5) [70.1 - 91.3]	2 (66.7) [9.4 - 99.2]	17 (68.0) [46.5 - 85.1]
Avoid invasive dental procedures					
Yes	2 (40.0)	38 (15.7)	3 (5.3)	0	2 (8.0)
No[2]	3 (60.0) [14.7 - 94.7]	204 (84.3) [79.1 - 88.6]	54 (94.7) [85.4 - 98.9]	3 (100.0) [29.2 - 100.0]	23 (92.0) [74.0 - 99.0]
Question 15a: How frequently do you, or another member of your healthcare team (e.g. nurse, pharmacist or other), perform each of these activities when initiating treatment with VFEND (voriconazole)? (Please check one response for each activity below).					
Discuss contents of the Patient Alert Card					
Always[2]	0	30 (12.4) [8.5 - 17.2]	6 (10.5) [4.0 - 21.5]	1 (33.3) [0.8 - 90.6]	4 (16.0) [4.5 - 36.1]
Sometimes	0	75 (31.0)	16 (28.1)	0	3 (12.0)
Never	5 (100.0)	137 (56.6)	35 (61.4)	2 (66.7)	18 (72.0)

Table 6.2: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Medical Specialty - (Completed Surveys From All Countries Combined)

Question	Medical Specialty				
	Critical Care / Intensive Care N=5 n (%) [95% CI][1]	Oncology / Hematology N=242 n (%) [95% CI][1]	Infectious Disease / Microbiology N=57 n (%) [95% CI][1]	Solid Organ Transplant Physician N=3 n (%) [95% CI][1]	Other/Other Subspecialty N=25 n (%) [95% CI][1]
Advise patient to avoid exposure to direct sunlight and/or to use measures such as protective clothing and sunscreen					
Always[2]	0	169 (69.8) [63.6 - 75.5]	41 (71.9) [58.5 - 83.0]	1 (33.3) [0.8 - 90.6]	19 (76.0) [54.9 - 90.6]
Sometimes	0	58 (24.0)	14 (24.6)	2 (66.7)	3 (12.0)
Never	5 (100.0)	15 (6.2)	2 (3.5)	0	3 (12.0)
Discuss risk of lymphoma					
Always	0	23 (9.5)	6 (10.5)	1 (33.3)	2 (8.0)
Sometimes	0	52 (21.5)	10 (17.5)	1 (33.3)	5 (20.0)
Never[2]	5 (100.0) [47.8 - 100.0]	167 (69.0) [62.8 - 74.8]	41 (71.9) [58.5 - 83.0]	1 (33.3) [0.8 - 90.6]	18 (72.0) [50.6 - 87.9]
Discuss risk of gastric perforation					
Always	1 (20.0)	27 (11.2)	3 (5.3)	0	3 (12.0)
Sometimes	0	73 (30.2)	15 (26.3)	1 (33.3)	5 (20.0)
Never[2]	4 (80.0) [28.4 - 99.5]	142 (58.7) [52.2 - 64.9]	39 (68.4) [54.8 - 80.1]	2 (66.7) [9.4 - 99.2]	17 (68.0) [46.5 - 85.1]
Advise patient of importance of monitoring risks of VFEND (voriconazole) use and signs and symptoms of serious risks that warrant contacting doctor immediately					
Always[2]	0	165 (68.2) [61.9 - 74.0]	43 (75.4) [62.2 - 85.9]	2 (66.7) [9.4 - 99.2]	16 (64.0) [42.5 - 82.0]
Sometimes	0	57 (23.6)	12 (21.1)	1 (33.3)	4 (16.0)
Never	5 (100.0)	20 (8.3)	2 (3.5)	0	5 (20.0)
Discuss risk of amyloidosis					
Always	0	9 (3.7)	3 (5.3)	1 (33.3)	2 (8.0)
Sometimes	0	35 (14.5)	8 (14.0)	0	5 (20.0)
Never[2]	5 (100.0) [47.8 - 100.0]	198 (81.8) [76.4 - 86.5]	46 (80.7) [68.1 - 90.0]	2 (66.7) [9.4 - 99.2]	18 (72.0) [50.6 - 87.9]

Table 6.2: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Medical Specialty - (Completed Surveys From All Countries Combined)

Question	Medical Specialty				
	Critical Care / Intensive Care N=5 n (%) [95% CI][1]	Oncology / Hematology N=242 n (%) [95% CI][1]	Infectious Disease / Microbiology N=57 n (%) [95% CI][1]	Solid Organ Transplant Physician N=3 n (%) [95% CI][1]	Other/Other Subspecialty N=25 n (%) [95% CI][1]
Question 16: How frequently should Liver Function Tests (specifically AST, ALT) be performed?					
At VFEND (voriconazole) treatment initiation and weekly thereafter for one month[2]	4 (80.0) [28.4 - 99.5]	175 (72.3) [66.2 - 77.9]	44 (77.2) [64.2 - 87.3]	3 (100.0) [29.2 - 100.0]	13 (52.0) [31.3 - 72.2]
Every contact	0	31 (12.8)	3 (5.3)	0	4 (16.0)
Monthly	0	31 (12.8)	8 (14.0)	0	5 (20.0)
Other	1 (20.0)	0	1 (1.8)	0	0
I do not know	0	5 (2.1)	1 (1.8)	0	3 (12.0)
Question 17: If there are no changes in Liver Function Tests (LFTs) after one month of initiation of VFEND (voriconazole), how often should you monitor liver function during VFEND treatment maintenance?					
Weekly	0	35 (14.5)	3 (5.3)	0	3 (12.0)
Monthly[2]	2 (40.0) [5.3 - 85.3]	190 (78.5) [72.8 - 83.5]	48 (84.2) [72.1 - 92.5]	3 (100.0) [29.2 - 100.0]	17 (68.0) [46.5 - 85.1]
Other	0	7 (2.9)	5 (8.8)	0	0
I do not know	3 (60.0)	10 (4.1)	1 (1.8)	0	5 (20.0)
Question 18: How often should a dermatologic evaluation be performed when VFEND (voriconazole) is continuously used despite the occurrence of phototoxicity-related lesions?					
Weekly	0	31 (12.8)	9 (15.8)	1 (33.3)	1 (4.0)
Monthly	0	37 (15.3)	6 (10.5)	0	5 (20.0)
Every two months	0	17 (7.0)	6 (10.5)	0	1 (4.0)
On systemic and regular basis[2]	2 (40.0) [5.3 - 85.3]	120 (49.6) [43.1 - 56.1]	26 (45.6) [32.4 - 59.3]	2 (66.7) [9.4 - 99.2]	10 (40.0) [21.1 - 61.3]
I do not know	3 (60.0)	37 (15.3)	10 (17.5)	0	8 (32.0)
Question 19: When should VFEND (voriconazole) be discontinued in a patient? (Select the one best response).					

Table 6.2: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Medical Specialty - (Completed Surveys From All Countries Combined)

Question	Medical Specialty				
	Critical Care / Intensive Care N=5 n (%) [95% CI][1]	Oncology / Hematology N=242 n (%) [95% CI][1]	Infectious Disease / Microbiology N=57 n (%) [95% CI][1]	Solid Organ Transplant Physician N=3 n (%) [95% CI][1]	Other/Other Subspecialty N=25 n (%) [95% CI][1]
Phototoxicity	0	13 (5.4)	5 (8.8)	2 (66.7)	0
Squamous Cell Carcinoma (SCC)	1 (20.0)	26 (10.7)	4 (7.0)	1 (33.3)	6 (24.0)
Premalignant lesions	1 (20.0)	15 (6.2)	4 (7.0)	0	0
All of the above[2]	3 (60.0) [14.7 - 94.7]	188 (77.7) [71.9 - 82.8]	44 (77.2) [64.2 - 87.3]	0	19 (76.0) [54.9 - 90.6]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct or desired response.
[3] If the response option is checked the response is presented as 'Yes' answer, if it is not checked as 'No' answer.

Table 6.3: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Number of Patients Treated in the Last 12 Months - (Completed Surveys From All Countries Combined)

Question	Number of Patients Treated in the Last 12 Months			
	1-5 Patients N=158 n (%) [95% CI][1]	6-10 Patients N=92 n (%) [95% CI][1]	11-20 Patients N=44 n (%) [95% CI][1]	More Than 20 Patients N=38 n (%) [95% CI][1]
Question 8: Please select only one response for each statement about VFEND (voriconazole) below:				
Long-term treatment (> 6 months) with VFEND (voriconazole) should be considered only if the benefits outweigh the potential risks				
True[2]	151 (95.6) [91.1 - 98.2]	85 (92.4) [84.9 - 96.9]	40 (90.9) [78.3 - 97.5]	35 (92.1) [78.6 - 98.3]
False	2 (1.3)	6 (6.5)	4 (9.1)	3 (7.9)
I Don't Know	5 (3.2)	1 (1.1)	0	0
If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist				
True[2]	136 (86.1) [79.7 - 91.1]	82 (89.1) [80.9 - 94.7]	34 (77.3) [62.2 - 88.5]	35 (92.1) [78.6 - 98.3]
False	13 (8.2)	9 (9.8)	6 (13.6)	3 (7.9)
I Don't Know	9 (5.7)	1 (1.1)	4 (9.1)	0
VFEND (voriconazole) should not be discontinued if premalignant skin lesions or skin Squamous Cell Carcinoma are identified				
True	10 (6.3)	7 (7.6)	4 (9.1)	4 (10.5)
False[2]	121 (76.6) [69.2 - 82.9]	72 (78.3) [68.4 - 86.2]	28 (63.6) [47.8 - 77.6]	30 (78.9) [62.7 - 90.4]
I Don't Know	27 (17.1)	13 (14.1)	12 (27.3)	4 (10.5)
Laboratory evaluation of hepatic function (specifically AST and ALT) at initiation and during the first month of treatment with VFEND (voriconazole) is not necessary				
True	5 (3.2)	4 (4.3)	0	3 (7.9)
False[2]	151 (95.6) [91.1 - 98.2]	88 (95.7) [89.2 - 98.8]	43 (97.7) [88.0 - 99.9]	35 (92.1) [78.6 - 98.3]
I Don't Know	2 (1.3)	0	1 (2.3)	0
If the Liver Function Tests become markedly elevated, VFEND (voriconazole) should be discontinued, unless the medical judgment of the risk-benefit balance of the treatment for the patient justifies continued use				

Table 6.3: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Number of Patients Treated in the Last 12 Months - (Completed Surveys From All Countries Combined)

Question	Number of Patients Treated in the Last 12 Months			
	1-5 Patients N=158 n (%) [95% CI][1]	6-10 Patients N=92 n (%) [95% CI][1]	11-20 Patients N=44 n (%) [95% CI][1]	More Than 20 Patients N=38 n (%) [95% CI][1]
True[2]	151 (95.6) [91.1 - 98.2]	88 (95.7) [89.2 - 98.8]	39 (88.6) [75.4 - 96.2]	35 (92.1) [78.6 - 98.3]
False	6 (3.8)	3 (3.3)	4 (9.1)	3 (7.9)
I Don't Know	1 (0.6)	1 (1.1)	1 (2.3)	0
Question 15: Which precautionary measures should physicians communicate to their patients for whom they have prescribed VFEND (voriconazole)? Please check all that apply.[3]				
Avoiding exposure to direct sunlight				
Yes[2]	139 (88.0) [81.9 - 92.6]	86 (93.5) [86.3 - 97.6]	38 (86.4) [72.6 - 94.8]	34 (89.5) [75.2 - 97.1]
No	19 (12.0)	6 (6.5)	6 (13.6)	4 (10.5)
Detecting signs and symptoms of phototoxicity				
Yes[2]	145 (91.8) [86.3 - 95.5]	87 (94.6) [87.8 - 98.2]	39 (88.6) [75.4 - 96.2]	35 (92.1) [78.6 - 98.3]
No	13 (8.2)	5 (5.4)	5 (11.4)	3 (7.9)
Use with caution in patients with previous history of intestinal ulceration or diverticulitis				
Yes	46 (29.1)	32 (34.8)	16 (36.4)	16 (42.1)
No[2]	112 (70.9) [63.1 - 77.8]	60 (65.2) [54.6 - 74.9]	28 (63.6) [47.8 - 77.6]	22 (57.9) [40.8 - 73.7]
Dermatologic evaluation should be performed on a systematic and regular basis				
Yes[2]	52 (32.9) [25.7 - 40.8]	35 (38.0) [28.1 - 48.8]	13 (29.5) [16.8 - 45.2]	16 (42.1) [26.3 - 59.2]
No	106 (67.1)	57 (62.0)	31 (70.5)	22 (57.9)
Intensified monitoring of blood glucose level				
Yes	15 (9.5)	11 (12.0)	6 (13.6)	8 (21.1)
No[2]	143 (90.5) [84.8 - 94.6]	81 (88.0) [79.6 - 93.9]	38 (86.4) [72.6 - 94.8]	30 (78.9) [62.7 - 90.4]
Covering sun exposed areas of skin				

Table 6.3: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Number of Patients Treated in the Last 12 Months - (Completed Surveys From All Countries Combined)

Question	Number of Patients Treated in the Last 12 Months			
	1-5 Patients N=158 n (%) [95% CI][1]	6-10 Patients N=92 n (%) [95% CI][1]	11-20 Patients N=44 n (%) [95% CI][1]	More Than 20 Patients N=38 n (%) [95% CI][1]
Yes[2]	106 (67.1) [59.2 - 74.3]	49 (53.3) [42.6 - 63.7]	27 (61.4) [45.5 - 75.6]	24 (63.2) [46.0 - 78.2]
No	52 (32.9)	43 (46.7)	17 (38.6)	14 (36.8)
Use sufficient sunscreen with high sun protection factor (SPF)				
Yes[2]	133 (84.2) [77.5 - 89.5]	76 (82.6) [73.3 - 89.7]	33 (75.0) [59.7 - 86.8]	29 (76.3) [59.8 - 88.6]
No	25 (15.8)	16 (17.4)	11 (25.0)	9 (23.7)
Clinical signs of liver damage, such as jaundice that warrant contacting the doctor immediately				
Yes[2]	147 (93.0) [87.9 - 96.5]	85 (92.4) [84.9 - 96.9]	37 (84.1) [69.9 - 93.4]	35 (92.1) [78.6 - 98.3]
No	11 (7.0)	7 (7.6)	7 (15.9)	3 (7.9)
International Normalized Ratio regular monitoring				
Yes	35 (22.2)	15 (16.3)	10 (22.7)	7 (18.4)
No[2]	123 (77.8) [70.6 - 84.1]	77 (83.7) [74.5 - 90.6]	34 (77.3) [62.2 - 88.5]	31 (81.6) [65.7 - 92.3]
Avoid invasive dental procedures				
Yes	18 (11.4)	13 (14.1)	8 (18.2)	6 (15.8)
No[2]	140 (88.6) [82.6 - 93.1]	79 (85.9) [77.0 - 92.3]	36 (81.8) [67.3 - 91.8]	32 (84.2) [68.7 - 94.0]
Question 15a: How frequently do you, or another member of your healthcare team (e.g. nurse, pharmacist or other), perform each of these activities when initiating treatment with VFEND (voriconazole)? (Please check one response for each activity below).				
Discuss contents of the Patient Alert Card				
Always[2]	18 (11.4) [6.9 - 17.4]	7 (7.6) [3.1 - 15.1]	9 (20.5) [9.8 - 35.3]	7 (18.4) [7.7 - 34.3]
Sometimes	43 (27.2)	25 (27.2)	13 (29.5)	13 (34.2)
Never	97 (61.4)	60 (65.2)	22 (50.0)	18 (47.4)

Table 6.3: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Number of Patients Treated in the Last 12 Months - (Completed Surveys From All Countries Combined)

Question	Number of Patients Treated in the Last 12 Months			
	1-5 Patients N=158 n (%) [95% CI][1]	6-10 Patients N=92 n (%) [95% CI][1]	11-20 Patients N=44 n (%) [95% CI][1]	More Than 20 Patients N=38 n (%) [95% CI][1]
Advise patient to avoid exposure to direct sunlight and/or to use measures such as protective clothing and sunscreen				
Always[2]	119 (75.3) [67.8 - 81.8]	62 (67.4) [56.8 - 76.8]	24 (54.5) [38.8 - 69.6]	25 (65.8) [48.6 - 80.4]
Sometimes	30 (19.0)	24 (26.1)	15 (34.1)	8 (21.1)
Never	9 (5.7)	6 (6.5)	5 (11.4)	5 (13.2)
Discuss risk of lymphoma				
Always	18 (11.4)	7 (7.6)	2 (4.5)	5 (13.2)
Sometimes	32 (20.3)	20 (21.7)	8 (18.2)	8 (21.1)
Never[2]	108 (68.4) [60.5 - 75.5]	65 (70.7) [60.2 - 79.7]	34 (77.3) [62.2 - 88.5]	25 (65.8) [48.6 - 80.4]
Discuss risk of gastric perforation				
Always	21 (13.3)	5 (5.4)	3 (6.8)	5 (13.2)
Sometimes	41 (25.9)	32 (34.8)	11 (25.0)	10 (26.3)
Never[2]	96 (60.8) [52.7 - 68.4]	55 (59.8) [49.0 - 69.9]	30 (68.2) [52.4 - 81.4]	23 (60.5) [43.4 - 76.0]
Advise patient of importance of monitoring risks of VFEND (voriconazole) use and signs and symptoms of serious risks that warrant contacting doctor immediately				
Always[2]	107 (67.7) [59.8 - 74.9]	69 (75.0) [64.9 - 83.4]	26 (59.1) [43.2 - 73.7]	24 (63.2) [46.0 - 78.2]
Sometimes	34 (21.5)	18 (19.6)	12 (27.3)	10 (26.3)
Never	17 (10.8)	5 (5.4)	6 (13.6)	4 (10.5)
Discuss risk of amyloidosis				
Always	6 (3.8)	3 (3.3)	1 (2.3)	5 (13.2)
Sometimes	23 (14.6)	13 (14.1)	8 (18.2)	4 (10.5)
Never[2]	129 (81.6) [74.7 - 87.3]	76 (82.6) [73.3 - 89.7]	35 (79.5) [64.7 - 90.2]	29 (76.3) [59.8 - 88.6]

Table 6.3: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Number of Patients Treated in the Last 12 Months - (Completed Surveys From All Countries Combined)

Question	Number of Patients Treated in the Last 12 Months			
	1-5 Patients N=158 n (%) [95% CI][1]	6-10 Patients N=92 n (%) [95% CI][1]	11-20 Patients N=44 n (%) [95% CI][1]	More Than 20 Patients N=38 n (%) [95% CI][1]
Question 16: How frequently should Liver Function Tests (specifically AST, ALT) be performed?				
At VFEND (voriconazole) treatment initiation and weekly thereafter for one month[2]	121 (76.6) [69.2 - 82.9]	59 (64.1) [53.5 - 73.9]	36 (81.8) [67.3 - 91.8]	23 (60.5) [43.4 - 76.0]
Every contact	11 (7.0)	15 (16.3)	4 (9.1)	8 (21.1)
Monthly	17 (10.8)	17 (18.5)	4 (9.1)	6 (15.8)
Other	1 (0.6)	0	0	1 (2.6)
I do not know	8 (5.1)	1 (1.1)	0	0
Question 17: If there are no changes in Liver Function Tests (LFTs) after one month of initiation of VFEND (voriconazole), how often should you monitor liver function during VFEND treatment maintenance?				
Weekly	18 (11.4)	12 (13.0)	5 (11.4)	6 (15.8)
Monthly[2]	126 (79.7) [72.6 - 85.7]	74 (80.4) [70.9 - 88.0]	34 (77.3) [62.2 - 88.5]	26 (68.4) [51.3 - 82.5]
Other	4 (2.5)	2 (2.2)	2 (4.5)	4 (10.5)
I do not know	10 (6.3)	4 (4.3)	3 (6.8)	2 (5.3)
Question 18: How often should a dermatologic evaluation be performed when VFEND (voriconazole) is continuously used despite the occurrence of phototoxicity-related lesions?				
Weekly	22 (13.9)	11 (12.0)	5 (11.4)	4 (10.5)
Monthly	24 (15.2)	11 (12.0)	4 (9.1)	9 (23.7)
Every two months	8 (5.1)	8 (8.7)	6 (13.6)	2 (5.3)
On systemic and regular basis[2]	72 (45.6) [37.6 - 53.7]	45 (48.9) [38.3 - 59.6]	23 (52.3) [36.7 - 67.5]	20 (52.6) [35.8 - 69.0]
I do not know	32 (20.3)	17 (18.5)	6 (13.6)	3 (7.9)
Question 19: When should VFEND (voriconazole) be discontinued in a patient? (Select the one best response).				

Table 6.3: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Number of Patients Treated in the Last 12 Months - (Completed Surveys From All Countries Combined)

Question	Number of Patients Treated in the Last 12 Months			
	1-5 Patients N=158 n (%) [95% CI][1]	6-10 Patients N=92 n (%) [95% CI][1]	11-20 Patients N=44 n (%) [95% CI][1]	More Than 20 Patients N=38 n (%) [95% CI][1]
Phototoxicity	8 (5.1)	7 (7.6)	0	5 (13.2)
Squamous Cell Carcinoma (SCC)	19 (12.0)	8 (8.7)	9 (20.5)	2 (5.3)
Premalignant lesions	7 (4.4)	5 (5.4)	4 (9.1)	4 (10.5)
All of the above[2]	124 (78.5) [71.2 - 84.6]	72 (78.3) [68.4 - 86.2]	31 (70.5) [54.8 - 83.2]	27 (71.1) [54.1 - 84.6]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct or desired response.
[3] If the response option is checked the response is presented as 'Yes' answer, if it is not checked as 'No' answer.

Table 6.4: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Reading the HCP Q&A Brochure - (Completed Surveys From All Countries Combined)

Question	Reading the HCP Q&A Brochure	
	Read Some or All of It N=57 n (%) [95% CI][1]	Did Not Receive or Read It N=275 n (%) [95% CI][1]
Question 8: Please select only one response for each statement about VFEND (voriconazole) below:		
Long-term treatment (> 6 months) with VFEND (voriconazole) should be considered only if the benefits outweigh the potential risks		
True[2]	57 (100.0) [93.7 - 100.0]	254 (92.4) [88.6 - 95.2]
False	0	15 (5.5)
I Don't Know	0	6 (2.2)
If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist		
True[2]	55 (96.5) [87.9 - 99.6]	232 (84.4) [79.5 - 88.4]
False	2 (3.5)	29 (10.5)
I Don't Know	0	14 (5.1)
VFEND (voriconazole) should not be discontinued if premalignant skin lesions or skin Squamous Cell Carcinoma are identified		
True	7 (12.3)	18 (6.5)
False[2]	43 (75.4) [62.2 - 85.9]	208 (75.6) [70.1 - 80.6]
I Don't Know	7 (12.3)	49 (17.8)
Laboratory evaluation of hepatic function (specifically AST and ALT) at initiation and during the first month of treatment with VFEND (voriconazole) is not necessary		
True	3 (5.3)	9 (3.3)
False[2]	54 (94.7) [85.4 - 98.9]	263 (95.6) [92.5 - 97.7]
I Don't Know	0	3 (1.1)
If the Liver Function Tests become markedly elevated, VFEND (voriconazole) should be discontinued, unless the medical judgment of the risk-benefit balance of the treatment for the patient justifies continued use		
True[2]	55 (96.5) [87.9 - 99.6]	258 (93.8) [90.3 - 96.4]

Table 6.4: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Reading the HCP Q&A Brochure - (Completed Surveys From All Countries Combined)

Question	Reading the HCP Q&A Brochure	
	Read Some or All of It N=57 n (%) [95% CI][1]	**Did Not Receive or Read It N=275 n (%) [95% CI][1]**
False	2 (3.5)	14 (5.1)
I Don't Know	0	3 (1.1)
Question 15: Which precautionary measures should physicians communicate to their patients for whom they have prescribed VFEND (voriconazole)? Please check all that apply.[3]		
Avoiding exposure to direct sunlight		
Yes[2]	51 (89.5) [78.5 - 96.0]	246 (89.5) [85.2 - 92.8]
No	6 (10.5)	29 (10.5)
Detecting signs and symptoms of phototoxicity		
Yes[2]	55 (96.5) [87.9 - 99.6]	251 (91.3) [87.3 - 94.3]
No	2 (3.5)	24 (8.7)
Use with caution in patients with previous history of intestinal ulceration or diverticulitis		
Yes	23 (40.4)	87 (31.6)
No[2]	34 (59.6) [45.8 - 72.4]	188 (68.4) [62.5 - 73.8]
Dermatologic evaluation should be performed on a systematic and regular basis		
Yes[2]	27 (47.4) [34.0 - 61.0]	89 (32.4) [26.9 - 38.2]
No	30 (52.6)	186 (67.6)
Intensified monitoring of blood glucose level		
Yes	10 (17.5)	30 (10.9)
No[2]	47 (82.5) [70.1 - 91.3]	245 (89.1) [84.8 - 92.5]
Covering sun exposed areas of skin		
Yes[2]	45 (78.9) [66.1 - 88.6]	161 (58.5) [52.5 - 64.4]
No	12 (21.1)	114 (41.5)

Table 6.4: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Reading the HCP Q&A Brochure - (Completed Surveys From All Countries Combined)

Question	Reading the HCP Q&A Brochure	
	Read Some or All of It N=57 n (%) [95% CI][1]	Did Not Receive or Read It N=275 n (%) [95% CI][1]
Use sufficient sunscreen with high sun protection factor (SPF)		
Yes[2]	54 (94.7) [85.4 - 98.9]	217 (78.9) [73.6 - 83.6]
No	3 (5.3)	58 (21.1)
Clinical signs of liver damage, such as jaundice that warrant contacting the doctor immediately		
Yes[2]	52 (91.2) [80.7 - 97.1]	252 (91.6) [87.7 - 94.6]
No	5 (8.8)	23 (8.4)
International Normalized Ratio regular monitoring		
Yes	15 (26.3)	52 (18.9)
No[2]	42 (73.7) [60.3 - 84.5]	223 (81.1) [76.0 - 85.5]
Avoid invasive dental procedures		
Yes	8 (14.0)	37 (13.5)
No[2]	49 (86.0) [74.2 - 93.7]	238 (86.5) [81.9 - 90.3]
Question 15a: How frequently do you, or another member of your healthcare team (e.g. nurse, pharmacist or other), perform each of these activities when initiating treatment with VFEND (voriconazole)? (Please check one response for each activity below).		
Discuss contents of the Patient Alert Card		
Always[2]	12 (21.1) [11.4 - 33.9]	29 (10.5) [7.2 - 14.8]
Sometimes	24 (42.1)	70 (25.5)
Never	21 (36.8)	176 (64.0)
Advise patient to avoid exposure to direct sunlight and/or to use measures such as protective clothing and sunscreen		
Always[2]	46 (80.7) [68.1 - 90.0]	184 (66.9) [61.0 - 72.4]
Sometimes	9 (15.8)	68 (24.7)

Table 6.4: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Reading the HCP Q&A Brochure - (Completed Surveys From All Countries Combined)

Question	Reading the HCP Q&A Brochure	
	Read Some or All of It N=57 n (%) [95% CI][1]	Did Not Receive or Read It N=275 n (%) [95% CI][1]
Never	2 (3.5)	23 (8.4)
Discuss risk of lymphoma		
Always	5 (8.8)	27 (9.8)
Sometimes	14 (24.6)	54 (19.6)
Never[2]	38 (66.7) [52.9 - 78.6]	194 (70.5) [64.8 - 75.9]
Discuss risk of gastric perforation		
Always	8 (14.0)	26 (9.5)
Sometimes	18 (31.6)	76 (27.6)
Never[2]	31 (54.4) [40.7 - 67.6]	173 (62.9) [56.9 - 68.6]
Advise patient of importance of monitoring risks of VFEND (voriconazole) use and signs and symptoms of serious risks that warrant contacting doctor immediately		
Always[2]	43 (75.4) [62.2 - 85.9]	183 (66.5) [60.6 - 72.1]
Sometimes	12 (21.1)	62 (22.5)
Never	2 (3.5)	30 (10.9)
Discuss risk of amyloidosis		
Always	4 (7.0)	11 (4.0)
Sometimes	9 (15.8)	39 (14.2)
Never[2]	44 (77.2) [64.2 - 87.3]	225 (81.8) [76.7 - 86.2]
Question 16: How frequently should Liver Function Tests (specifically AST, ALT) be performed?		
At VFEND (voriconazole) treatment initiation and weekly thereafter for one month[2]	42 (73.7) [60.3 - 84.5]	197 (71.6) [65.9 - 76.9]
Every contact	6 (10.5)	32 (11.6)
Monthly	7 (12.3)	37 (13.5)

Table 6.4: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Reading the HCP Q&A Brochure - (Completed Surveys From All Countries Combined)

Question	Reading the HCP Q&A Brochure	
	Read Some or All of It N=57 n (%) [95% CI][1]	Did Not Receive or Read It N=275 n (%) [95% CI][1]
Other	1 (1.8)	1 (0.4)
I do not know	1 (1.8)	8 (2.9)
Question 17: If there are no changes in Liver Function Tests (LFTs) after one month of initiation of VFEND (voriconazole), how often should you monitor liver function during VFEND treatment maintenance?		
Weekly	8 (14.0)	33 (12.0)
Monthly[2]	47 (82.5) [70.1 - 91.3]	213 (77.5) [72.1 - 82.3]
Other	2 (3.5)	10 (3.6)
I do not know	0	19 (6.9)
Question 18: How often should a dermatologic evaluation be performed when VFEND (voriconazole) is continuously used despite the occurrence of phototoxicity-related lesions?		
Weekly	8 (14.0)	34 (12.4)
Monthly	9 (15.8)	39 (14.2)
Every two months	4 (7.0)	20 (7.3)
On systemic and regular basis[2]	28 (49.1) [35.6 - 62.7]	132 (48.0) [42.0 - 54.1]
I do not know	8 (14.0)	50 (18.2)
Question 19: When should VFEND (voriconazole) be discontinued in a patient? (Select the one best response).		
Phototoxicity	3 (5.3)	17 (6.2)
Squamous Cell Carcinoma (SCC)	5 (8.8)	33 (12.0)
Premalignant lesions	3 (5.3)	17 (6.2)

Table 6.4: Responses to All Questions About the Knowledge of Appropriate Behavior/Practice and Self-reported Behaviors With Regard to Strategies to Mitigate the Risks by Reading the HCP Q&A Brochure - (Completed Surveys From All Countries Combined)

Question	Reading the HCP Q&A Brochure	
	Read Some or All of It N=57 n (%) [95% CI][1]	Did Not Receive or Read It N=275 n (%) [95% CI][1]
All of the above[2]	46 (80.7) [68.1 - 90.0]	208 (75.6) [70.1 - 80.6]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct or desired response.
[3] If the response option is checked the response is presented as 'Yes' answer, if it is not checked as 'No' answer.
Abbreviations: Read some or all of it = Received it and read some of it or all of it; Did not receive or read it = Did not receive, does not remember receiving or did not read or does not remember reading it

Table 7: Responses to Other Survey Questions – (Completed Surveys From All Countries Combined)

Question	Prescribers N=332 n (%)
Question 14: Did you find the VFEND (voriconazole) RM tools to be of use in your clinical practice? Please select only one rank for each RM tool listed below:	
HCP Checklist	
Not useful	24 (7.2)
Somewhat useful	44 (13.3)
No opinion/not sure	190 (57.2)
Very useful	69 (20.8)
Extremely useful	5 (1.5)
HCP Q&A Brochure	
Not useful	27 (8.1)
Somewhat useful	43 (13.0)
No opinion/not sure	198 (59.6)
Very useful	54 (16.3)
Extremely useful	10 (3.0)
Patient Alert Card	
Not useful	26 (7.8)
Somewhat useful	44 (13.3)
No opinion/not sure	198 (59.6)
Very useful	56 (16.9)
Extremely useful	8 (2.4)

Note: Percentages are calculated based on the number of completed surveys from all countries combined.

Table 7a: Responses to Other Survey Questions Based on the Receipt of Materials – (Completed Surveys From All Countries Combined)

Question	Prescribers n (%)
Question 14: Did you find the VFEND (voriconazole) RM tools to be of use in your clinical practice? Please select only one rank for each RM tool listed below:	
HCP Checklist (N=75)[1]	
Not useful	5 (6.7)
Somewhat useful	21 (28.0)
No opinion/not sure	14 (18.7)
Very useful	34 (45.3)
Extremely useful	1 (1.3)
HCP Q&A Brochure (N=65)[2]	
Not useful	7 (10.8)
Somewhat useful	15 (23.1)
No opinion/not sure	16 (24.6)
Very useful	21 (32.3)
Extremely useful	6 (9.2)
Patient Alert Card (N=86)[3]	
Not useful	8 (9.3)
Somewhat useful	22 (25.6)
No opinion/not sure	20 (23.3)
Very useful	31 (36.0)
Extremely useful	5 (5.8)

[1] Counts and percentages are calculated based on receipt of the VFEND (voriconazole) Healthcare Professional (HCP) Checklist (i.e. among those who answered "yes" to survey question 10).
[2] Counts and percentages are calculated based on receipt of the VFEND (voriconazole) HCP Q&A Brochure (i.e. among those who answered "yes" to survey question 9).
[3] Counts and percentages are calculated based on receipt of the VFEND (voriconazole) Patient Alert Card (i.e. among those who answered "yes" to survey question 11).

Table 7.1: Responses to Other Survey Questions by Country – (Completed Surveys From All Countries Combined)

	Country									
Question	UK N=21 n (%)	F N=42 n (%)	A N=2 n (%)	IRL N=7 n (%)	DK N=5 n (%)	D N=16 n (%)	E N=191 n (%)	I N=14 n (%)	NL N=21 n (%)	H N=13 n (%)
Question 14: Did you find the VFEND (voriconazole) RM tools to be of use in your clinical practice? Please select only one rank for each RM tool listed below:										
HCP Checklist										
Not useful	4 (19.0)	6 (14.3)	0	0	0	2 (12.5)	9 (4.7)	3 (21.4)	0	0
Somewhat useful	4 (19.0)	2 (4.8)	0	0	0	2 (12.5)	29 (15.2)	2 (14.3)	2 (9.5)	3 (23.1)
No opinion/not sure	11 (52.4)	23 (54.8)	1 (50.0)	5 (71.4)	5 (100.0)	8 (50.0)	107 (56.0)	7 (50.0)	17 (81.0)	6 (46.2)
Very useful	2 (9.5)	11 (26.2)	1 (50.0)	2 (28.6)	0	3 (18.8)	42 (22.0)	2 (14.3)	2 (9.5)	4 (30.8)
Extremely useful	0	0	0	0	0	1 (6.3)	4 (2.1)	0	0	0
HCP Q&A Brochure										
Not useful	4 (19.0)	7 (16.7)	0	0	0	2 (12.5)	10 (5.2)	2 (14.3)	2 (9.5)	0
Somewhat useful	4 (19.0)	4 (9.5)	1 (50.0)	1 (14.3)	0	3 (18.8)	24 (12.6)	2 (14.3)	2 (9.5)	2 (15.4)
No opinion/not sure	11 (52.4)	21 (50.0)	1 (50.0)	5 (71.4)	5 (100.0)	8 (50.0)	119 (62.3)	7 (50.0)	15 (71.4)	6 (46.2)
Very useful	2 (9.5)	8 (19.0)	0	1 (14.3)	0	2 (12.5)	31 (16.2)	3 (21.4)	2 (9.5)	5 (38.5)
Extremely useful	0	2 (4.8)	0	0	0	1 (6.3)	7 (3.7)	0	0	0
Patient Alert Card										
Not useful	3 (14.3)	8 (19.0)	0	0	0	2 (12.5)	10 (5.2)	1 (7.1)	1 (4.8)	1 (7.7)
Somewhat useful	5 (23.8)	5 (11.9)	0	0	0	1 (6.3)	27 (14.1)	3 (21.4)	1 (4.8)	2 (15.4)
No opinion/not sure	12 (57.1)	19 (45.2)	2 (100.0)	5 (71.4)	4 (80.0)	9 (56.3)	119 (62.3)	6 (42.9)	16 (76.2)	6 (46.2)

Table 7.1: Responses to Other Survey Questions by Country – (Completed Surveys From All Countries Combined)

	Country									
Question	UK N=21 n (%)	F N=42 n (%)	A N=2 n (%)	IRL N=7 n (%)	DK N=5 n (%)	D N=16 n (%)	E N=191 n (%)	I N=14 n (%)	NL N=21 n (%)	H N=13 n (%)
Very useful	1 (4.8)	10 (23.8)	0	2 (28.6)	1 (20.0)	2 (12.5)	32 (16.8)	4 (28.6)	3 (14.3)	1 (7.7)
Extremely useful	0	0	0	0	0	2 (12.5)	3 (1.6)	0	0	3 (23.1)

Abbreviations: UK = United Kingdom; F = France; A = Austria; IRL = Ireland; DK = Denmark; D = Germany; E = Spain; I = Italy; NL = The Netherlands; H = Hungary.

Listing 1: Verbatim Responses to Question 5 (Other primary medical subspecialty) - Completed Surveys from all countries combined

Verbatim Response	English Translation
Dermatoloog	Dermatologist
Gynecologie Obstetrique	Gynecology/Obstetric
Haematology/Oncology	Hematology/Oncology
Infectolog?a pedi?trica	Pediatric Infectious Disease Specialist
Medicina interna	Internal Medicine
Oncohematolog?a pedi?trica	Pediatric Onco-hematology
Pulmonol?gia	Pulmonology
Radioth?rapie	Radiotherapy
Vasculaire Geneeskunde	Vascular Medicine
interne geneeskunde/nierziekten	Internal Medicine/Nephrology
kinderarts hemato-oncologie SCT	Pediatrician Haematology/ Oncology SCT (Stem Cell Transplantation)
nefrologie	Nephrology
oncop?diatrie	Oncopediatrics
pneumologie	Pulmonology
surgery	Surgery

Listing 2: Verbatim Responses to Question 5 (Other primary medical specialty) - Completed Surveys from all countries combined

Verbatim Response	English Translation
Dermatoloog	Dermatologist
Farmacolog?a Clinica	Clinical Pharmacology
PAediatric Oncology	Pediatric Oncology
PNEUMOLOGIE	Pulmonologist
Urol?gia, Onkol?gia	Urology, Oncology
VIH	HIV specialist
gastroent?rologie	Gastroenterology
gyermekonkol?gia	Pediatric Oncology
h?ziorvos	General Practitioner
longarts	Pulmonologist
ziekenhuisapotheker	Hospital Pharmacist
ziekenhuisfarmacie	Hospital Pharmacist

Listing 3: Safety Events - All Surveys from all countries

Safety event (English translation)	Country
No safety events were reported.	

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Sobel, Rachel E	18-May-2016 08:43:00	Final Approval
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