NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study 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 Saudi Arabia.
Protocol number	A1501110
Protocol version identifier	1.0
Date	16 August 2024
EU Post Authorization Study (PAS) register number	EUPAS1000000266
Active substance	Voriconazole; Triazole and tetrazole derivatives ATC code: J02AC03
Medicinal product	Vfend® (Voriconazole)
Research question and objectives	The overall objective of the study is to evaluate the effectiveness of the additional risk minimisation measures (aRMMs) being implemented across Saudi Arabia to mitigate the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity with the use of voriconazole. Specifically, the objectives of this research are to: 1 Assess HCPs' awareness of the RM tools (ie, HCP Checklist, HCP Q&A Brochure and Patient Alert Card). 2 Assess HCPs' utilization of the RM tools (ie, HCP Checklist, HCP Q&A Brochure and Patient Alert Card).` 3 Assess HCPs' knowledge of the risks of phototoxicity, SCC of the skin, and hepatic toxicity with voriconazole. 4 Assess whether HCPs' self-reported practices with respect to minimising the risks of phototoxicity, SCC of the skin, and hepatic toxicity are in accordance with voriconazole SPC.[1]
Country of study	Kingdom of Saudi Arabia

Author	Redacted

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
CIs	Confidence Intervals
DCT	Data Collection Tools
DCE	Data Check Edits
DSU	Data Safety Unit
EMA	European Medicines Agency
HMA-EMA	Heads of Medicines Agencies - European Medicines Agency
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCPs	Healthcare Professionals
HSCT	Hematopoietic stem cell transplant
IA	Invasive Aspergillosis
IEA	International Epidemiological Association
IEC	Independent Ethics Committees
ID	Identifier
IRB	Institutional Review Board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISPE	International Society for Pharmacoepidemiology
IT	Information Technology
LFTs	Liver Function Tests
MAH	Marketing Authorization Holder
NIS	Non-Interventional Study

Abbreviation	Definition
PASS	Post-Authorisation Safety Studies
PRAC	Pharmacovigilance Risk Assessment Committee
Q&A	Question & Answer
RDG	Random Data Generation
RM	Risk Minimisation
RMP	Risk Management Plan
aRMM	Additional Risk Minimisation
aRMMs	Additional Risk Minimisation Measures
SAP	Statistical Analysis Plan
SCC	Squamous Cell Carcinoma
SFDA	Saudi Food and Drug Authority
SPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SPF	Sun Protection Factor
URL	Uniform Resource Locator
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
Redacted	[redacted]	[redacted]	[redacted]
Redacted	[redacted]	Redacted	Redacted [redacted]

4. ABSTRACT

Refer to ANNEX 1.1 Abstract.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	15 November 2024
End of data collection	15 February 2025
Registration in the HMA-EMA Catalogues of RWD Studies	10 November 2024
Final study report	30 June 2025

7. 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 *Candida krusei*), and serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. for which voriconazole is authorised for use in the Saudi Arabia. Voriconazole is also indicated in Saudi Arabia for the prophylaxis of invasive fungal infections 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 (SPC).[1] To ensure that these risks are adequately managed, additional risk minimisation measures (aRMMs) across Saudi Arabia have been implemented in February 2023. These included updating the voriconazole SPC[1] with revisions to information on hepatotoxicity, phototoxicity, and SCC of the skin (routine risk minimisation activity), and developing a comprehensive educational programme at the point of patient care, intended to educate/remind healthcare professionals (HCPs) about the risks and how to manage them. These aRMMs target specialty care physicians who prescribe voriconazole (i.e., infectious disease physicians), and clinical pharmacists who manage the drug and its interactions (hereafter referred to as "HCPs"). The details of the Risk Minimisation (RM) tools for the education programme and how these tools are being implemented in Saudi Arabia are described in the RMP. The three components of the RM tools are the HCP Checklist, HCP Question & Answer (Q&A) Brochure, and Patient Alert Card. A brief description of each follows:

- **HCP Checklist for the risks of phototoxicity, SCC of the skin and hepatic toxicity:** This is the core RM tool that reminds HCPs about: i) the risks of phototoxicity, SCC of the skin, and hepatic toxicity with the use of voriconazole, ii) the appropriate use of voriconazole and management of patients with underlying hepatic impairment and those developing hepatic injury during voriconazole therapy as described in the SPC,[1] iii) the dermatological examination and liver function monitoring required per the SPC,[1] iv) discussing the importance of monitoring these risks with patients, and, v) providing the Patient Alert Card (described below) to each patient prescribed voriconazole. The HCPs have been instructed to complete the HCP Checklist for all new patients receiving voriconazole and retain it in the patient's medical record.

- **HCP Q&A Brochure for the risks of phototoxicity, SCC of the skin and hepatic toxicity:** This brochure in Q&A format provides detailed information to HCPs about: i) the risks of phototoxicity, ii) counselling patients regarding the risks of hepatotoxicity and SCC of the skin, iii) alerting patients/caregivers to the signs and symptoms that warrant contacting the doctor immediately, iv) regular dermatological examination and liver function monitoring as described in the SPC,[1] v) discontinuing voriconazole if premalignant lesions or SCC are identified; and, vi) providing the Patient Alert Card to patients prescribed voriconazole. This brochure also provides information about the HCP Checklist and Patient Alert Card and instructs HCPs how to use these tools when managing patients receiving voriconazole.

- **Patient Alert Card for the risks of phototoxicity and SCC of the skin:** The purpose of this wallet-sized folded card is to help remind patients about the need for dermatological evaluations on a regular basis (if phototoxic reactions occur). It also prompts the patient to report phototoxic symptoms that increase the risk of SCC of the skin. Furthermore, patients are reminded to avoid exposure to sunlight, to use protective clothing and sunscreen with high sun protective factor (SPF), and to inform their physicians if they develop sunburn or severe skin reactions or skin abnormalities. The HCPs were instructed to fill in their contact details on the card and give a card to each patient undergoing treatment with voriconazole.

This non-interventional study is designated as a post-authorization safety study (PASS) and is a commitment to Redacted

8. RESEARCH QUESTION AND OBJECTIVES

The overall objective of the study is to evaluate the effectiveness of the aRMMs being implemented across Saudi Arabia to mitigate the risks of phototoxicity, SCC of the skin, and hepatic toxicity with the use of voriconazole.

Specifically, the objectives of this research are to:

1 Assess HCPs' awareness of the RM tools (ie, HCP Checklist, HCP Q&A Brochure and Patient Alert Card).

2 Assess HCPs' utilization of the RM tools (ie, HCP Checklist, HCP Q&A Brochure and Patient Alert Card).`

3 Assess HCPs' knowledge of the risks of phototoxicity, SCC of the skin, and hepatic toxicity with voriconazole.

4 Assess whether HCPs' self-reported practices with respect to minimising the risks of phototoxicity, SCC of the skin, and hepatic toxicity are in accordance with voriconazole SPC.[1]

9. RESEARCH METHODS

This section presents methods that will be employed to evaluate the effectiveness of the aRMMs in Saudi Arabia.

9.1. Study design

This is a non-interventional, cross-sectional study to evaluate the effectiveness of RM tools for voriconazole. The study objectives will be accomplished by means of a cross-sectional, web-based survey of all HCPs who were targeted to receive the aRMMs and self-report as prescribers of voriconazole within 12 months preceding the survey in Saudi Arabia (Central, East and North regions). The study aims to obtain completed surveys from 10 HCPs. Data will be collected until 10 completed surveys are obtained or up to a data collection period of 60 to 90 days as a maximum. The data from the HCPs will be collected using a structured self-administered questionnaire to gather evaluation metrics related to the utilization and understanding of RM tool content and messages. In addition, the survey will assess behaviors, including a set of hypothetical scenarios for HCPs. The survey is not intended to be a mechanism for collecting adverse events (AEs), nor is it intended to result in minimizing the numbers of AEs reported. HCPs will be invited by e-mail to participate in the survey and asked to complete the online questionnaire.

9.1.1. Endpoints

1 The proportion of targeted HCPs who acknowledge receiving each of the RM tools.

2 The proportion of targeted HCPs who acknowledge reading and utilizing the tools.

3 The proportion of targeted HCPs who responds to correctly to questions about the risks of phototoxicity, SCC of the skin, and hepatic toxicity.

4 The proportion of targeted HCPs who provided desirable responses to the practice-related questions and self-declared behavior with regard to strategies to mitigate the risks.

9.2. Setting

The target population will include all HCPs who were targeted to receive Vfend® aRMM materials within 12 months preceding the survey.

At the time of protocol writing, approximately Redacted HCPs were prescribing/dispensing voriconazole in Saudi Arabia and around Redacted of these targeted to receive the RM tools in-person, per Pfizer Inc.'s Distribution List. Given this relatively small pool of HCPs, an empirical sample size of 10 HCPs is proposed.

HCPs recruitment and survey will be conducted by the following process:

- HCPs will be invited to participate in the survey by email and/or phone. An email invitation will include a web link directing to a webtool named 'Decipher', where the survey questionnaire will be available. In the invitation, the survey background and objectives, the contact information for questions will be explained to the HCPs. Instructions detailing the survey requirements will be displayed at the start of the survey.
- If the HCPs agree to participate in the survey, they can access the survey and the instructions for the web questionnaire by clicking on the email link.
- If the questionnaire is not completed in the first attempt, HCPs will receive a reminder email and/or phone (first reminder) 1 week after the initial invitation.
- If the web questionnare remains incomplete, a second reminder will be sent about 2 weeks after the initial invitation.
- If the questionnaire still remains incomplete, a third (and final) reminder will be sent 3 weeks after the initial invitation.

An HCP will be considered unreachable if he/she has been contacted up to 3 times without an answer. For each recruited HCP, the number of times the HCP is contacted, as well as the date and time when he/she completes the web questionnaire, will be recorded. HCP recruitment will be competitive.

9.2.1. Inclusion criteria

Participants/ HCPs must meet all of the following criteria to be eligible for inclusion in the survey:

1. Willing/consent to participate in this self-administered survey.
2. Involved in the treatment of at least 1 patient with voriconazole within the last 12 months.

Evidence of an electronically signed and dated informed consent document indicating that the participant/ HCP has been informed of all pertinent aspects of the study.

9.2.2. Exclusion criteria

Participants/ HCPs meeting any of the following criteria will not be included in the survey:

1. Employed in full-time research or hospital administration (i.e., non-practising physicians).
2. Employment by Pfizer Inc or any research organization/vendor contracted by Pfizer to administer the survey.

9.3. Variables

Screening questions

- Consent to participate.
- Whether the HCP managed patient(s) treated with voriconazole during the last 12 months period preceding the survey.
- Employment by Pfizer or any research organization/vendor contracted by Pfizer to administer the survey.
- Participation in qualitative research of the VFEND (voriconazole) Risk Minimisation materials.

HCP demographics and medical background

1. Location
2. Primary medical specialty
3. Length of professional practice as a HCP

HCP knowledge on voriconazole toxicities:

1. Knowledge testing for specific risks associated with voriconazole treatment
2. Knowledge of treatment discontinuation recommendations and dealing with toxicities

RM tools receipt

1. Acknowledge receiving Q&A brochure
2. Acknowledge receiving HCP checklist
3. Acknowledge receiving Patient alert card

RM tools reading

1. Acknowledge reading Q&A brochure
2. Acknowledge reading HCP checklist
3. Acknowledge reading Patient alert card

RM tools utilization

1. Frequency of using HCP checklist, Q&A brochure, and Patient alert card
2. Ranking the usefulness of each RM tool

Practice-related questions and, Self-declared behavior

1. Patient counseling
2. Discussing risks with patients
3. Liver function monitoring
4. Dermatological evaluation
5. Treatment discontinuation recommendations

Other variables

1. Requesting extra RM tools
2. Number of patients treated with voriconazole in the past 12 months
3. Downloading the tools from website

9.4. Data Sources

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) will be used to collect the survey data. The questionnaire will collect data on HCP characteristics and their responses to the risk knowledge questions. The data collected from the surveys will be used to inform the evaluation of the effectiveness of the aRMMs.

The questionnaire will begin with a screening module with questions to confirm eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a “thank you” message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

Screening questions for the HCPs:

- Consent to participate. Q1
- Whether the HCP managed patient(s) treated with voriconazole during the last 12 months period preceding the survey. Q2
- Employment by Pfizer or any research organization/vendor contracted by Pfizer to administer the survey. Q3
- Participation in qualitative research of the VFEND (voriconazole) RM materials. Q4

Data on HCP demographic characteristics:

- Location (city). Q5a
- HCP medical specialty type (eg, infectious disease physician, pharmacist). Q5
- Number of years practicing medicine. Q6
- Number of self-reported voriconazole-treated patients the HCP managed in the last 12-months period preceding the survey. Q13

Data pertaining to evaluation of the effectiveness of the aRMMs:

The questionnaire includes questions/statements that will assess the risk knowledge of the HCPs. The knowledge level analysed using descriptive statistics and confidence intervals (CIs), will be showcased as the effectiveness of the aRMMs: No formal statistical test will be conducted to test the effectiveness.

- Awareness of each of the RM tools among the HCPs:
  - Receipt of each of the RM tools. Q9, Q10, Q11
  - Review (read) each of the RM tools. Q9.1, Q10.1, Q11.1
- Downloading the tools from website. Q12 (complementary question)
- Requesting additional copies of the VFEND (voriconazole) RM tools. Q23 (complementary question)
- Utilization of the tools in clinical practice. Q14, Q15 and Q16
- Assessing the usefulness of each tool Q17 (complementary question)
- Knowledge/ comprehension of the risks of phototoxicity, SCC of the skin and hepatic toxicity. Q7 and Q8

- Practice-related questions and self-declared behavior with respect to mitigating the risks, as described in the SPC.[1] Q18, Q18a, Q19, Q20 , Q21, and Q22

The key messages informing HCPs about the risks of phototoxicity, SCC of the skin and hepatic toxicity with voriconazole, and instructions on how to manage these risks when treating patients with voriconazole have been identified from the most current version of the SPC[1] and will be used for evaluation of the HCP's knowledge.

9.4.1. Data Collection Process

Eligible HCPs (those HCPs to whom the RM tools were distributed by hand) will receive a letter by E-mail inviting them to participate in the survey. The invitation letter will include: 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). The survey data collection will be open until 10 completed surveys are received, up to 60-90 days. The survey start date begins within 12-18 months after initiation of distribution (05 February 2023) of the aRMMs tools in the Saudi Arabia.

9.4.2. Follow-up reminder process

The HCP database will be routinely updated with responders and, will be cross-checked with any correspondence that had an invalid address, bounced back or had incorrect contact details.

If no response was received, additional mailings will be sent, with up to a total of three invitations within the 60-90 days data collection period to participate in the web-based survey.

9.5. Study Size

At the time of protocol writing, a total of Redacted HCPs (distribution list shared with Saudi Food and Drug Authority [SFDA]) are expected to initiate or manage patients on Vfend®. All HCPs who were targeted to receive the RM tools (per Pfizer Inc.'s Distribution List.) within the 12 months preceding the initiation of the survey will be invited to participate in the survey. Given this relatively small pool of HCPs, an empirical sample size of 10 HCPs is proposed. Data will be collected until 10 completed surveys are obtained or up to a data collection period of 60 to 90 days as a maximum. It is important to note that the final survey sample size will depend on HCPs' willingness to participate in the survey.

An a priori threshold of 80% correct responses per risk question will be used to define the success of the program. However, this criterion will not be used for formal statistical testing. The selection of this threshold for success was regarded as being subjective and not based on prior knowledge, experience, or established scientific criteria.

9.6. Data management

All data collected during the survey will be held confidentially by the vendor. The data collection tool (DCT) [Decipher] used for data collection encrypts all identifiable information, and respondents' IDs are stored separately from the survey responses.

Skip logic for certain questions as well as the ability to mark only one response or multiple responses are part of the programming for the survey administration, which minimises the occurrence of data entry errors. There will be no queries to respondents for this project.

9.6.1. Data collection tools (DCTs)

All surveys are programmed internally using Redacted Decipher system, a secure online data collection software. Redacted guarantees senior-level programming support on all research engagements, with programmers who have been trained using a stringent quality control process to ensure that the surveys are programmed error-free. Redacted utilizes a rigorous quality assurance process which includes the following:

- Programmer and researcher manual testing: Manual testing process which includes several members of the research and programming team (Operations) testing each survey path thoroughly to ensure accuracy in both the text and all survey logic (skip and jump patterns). Each survey is tested on stimulator associated with the web browsers.
- Random Data Generation (RDG) and Data Check Edits (DCE): Once testing is completed by both the Redacted operations and research teams, a member of the operations team runs a set of randomly generated data ("dummy" data) to fill all possible paths and quotas, then writes a programmatic check designed to test the validity of the survey. Each question is tested for the correct number and coding of responses, that respondents answering the questions meet the base criteria as well as duplicate any calculated or algorithmic variables and compared for accuracy. An independent member of the operations team then writes the DCE. The data is also run through the DCE one again with soft launch data, full field data (data from the day after full fielding has begun) and the final data set.

As used in this protocol, the term DCTs should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study. A completed DCT is required for each included participant. The completed original DCTs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. Redacted shall ensure that the DCTs are securely stored in Decipher in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

Redacted has ultimate responsibility for the collection and reporting of all data entered on the DCTs as required and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCT serves as the source document.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Redacted agrees to keep all study-related records. The records should be retained by Redacted according to local regulations or for the period specified by the sponsor, whichever is longer. Redacted must ensure that the records continue to be stored securely for so long as they are retained.

If Redacted becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Redacted and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations. Redacted must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Data collected from the survey will be reported as descriptive statistics. Frequency distributions with 95% CIs will be calculated for HCPs' responses to all questions that address the survey objectives.

Endpoints

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

2. Assess HCPs' utilization of the RM tools (ie, HCP Checklist, HCP Q&A Brochure and Patient Alert Card) by estimating the proportion of targeted HCPs who acknowledge reading and utilizing the tools.

3. Assess HCPs' knowledge of the risks of phototoxicity, SCC of the skin and hepatic toxicity with voriconazole by estimating the proportion of targeted HCPs with correct responses to risk knowledge questions.

4. Assess whether HCPs' self reported behaviour/practices with respect to minimizing the risks of phototoxicity, SCC of the skin and hepatic toxicity are in accordance with the voriconazole SPC.1 This will be evaluated by estimating the proportion of targeted HCPs whose responses to the practice related questions are consistent with the SPC's1 prescribing information.

In the survey, the proportion of correct or desirable responses across all questions related to the evaluation of the objectives of the surveys will be considered to assess the success.

The questions considered as complementary will not be included in the assessment of success. The details of the assessment of the success for each survey and each objective are described in the "Assessment of Success" document.

As described in the Guideline on Good Pharmacovigilance Practices (GVP) Version 3.1 30 January 2023 - Drug Sector, Redacted [1] the percentage of participants responding correctly to the knowledge questions will be analysed and discussed. The minimum acceptable threshold of knowledge will be defined at 80% correct response rate per risk questions.

The distribution of the responses to questions assessing all study objectives will be presented in the study report. It is to be noted that the selection of this threshold for success is subjective and not based on a priori knowledge, experience, or established scientific criteria in the education or risk communication or evaluation literature. Therefore, the results will be contextualized within the context of other available information.

The following will be reported as part of the analysis:

- Survey administration
  - The number of HCPs by select medical specialty (ie, infectious disease physicians, pharmacists, as applicable).
  - The number of survey invitations issued by strata (ie, by speciality).
  - The number of survey invitations returned due to incorrect E-mail address of HCPs invited to participate in the survey.
- Demographic characteristics of participants
  - Distribution of participants by region.
  - Distribution by medical specialty.
  - Distribution of participants by years in medical practice.
  - Distribution of participants by number of patients treated with voriconazole in the past 12 months.
- HCP responses to questions pertaining to the survey objectives:

1. Awareness of the RM tools.

- The number and percentage of HCPs who acknowledged receiving each of the tools.

2. Utilization of the RM tools

- The number and percentage of HCPs indicating which tools they utilized when treating patients with voriconazole.
- The number and percentage of HCPs indicating they read tools.

3. HCP's knowledge/understanding of the risks

- The number and percentage of HCPs who correctly responded to each question/item about the risks of phototoxicity, SCC of the skin and hepatic toxicity with voriconazole.

4. HCPs' self-reported practices

- The number and proportion of HCPs whose responses to each behavior/practice related questions are consistent with the SPC[1] prescribing information.

Analysis of participation rate

The following different cases will be distinguished:

- HCPs who do not participate (R): HCPs who do not respond or that explicitly indicate their refusal to participate.
- HCPs with partially answered questionnaires (P): HCPs click on the link provided in the invitation email, and who begin answering the questionnaire but never submit it.
- Failed screening (F): HCPs who will not be eligible for the survey (HCPs who will not meet inclusion criteria and/or who will meet any of the exclusion criteria).
- HCPs with completed questionnaire (C): HCPs who complete the entire questionnaire and submit it.
- Contacted HCPs: HCPs who are contacted by phone or who receive a web link to the online survey via email = C+P+R+F.
- HCPs who agree to participate: HCPs willing to participate in the survey (e.g., by clicking on the link provided in the invitation email) = P+C.
- The HCPs participation in the survey will be examined as follows:

Response rate $= \frac{C}{C+P+R}$

Refusal rate $= \frac{R}{C+P+R}$

The details of analysis will be provided in the SAP.

9.8. Quality control

All surveys are programmed internally using Redacted Decipher system, a secure online data collection software. Redacted guarantees senior-level programming support on all research engagements, with programmers who have been trained using a stringent quality control

process to ensure that the surveys are programmed error-free. Redacted utilizes a rigorous quality assurance process which includes the following:

- Programmer and researcher manual testing: Manual testing process which includes several members of the research and programming team (Operations) testing each survey path thoroughly to ensure accuracy in both the text and all survey logic (skip and jump patterns). Each survey is tested on stimulator associated with the web browsers.

- Random Data Generation (RDG) and Data Check Edits (DCE): Once testing is completed by both the Redacted operations and research teams, a member of the operations team runs a set of randomly generated data ("dummy" data) to fill all possible paths and quotas, then writes a programmatic check designed to test the validity of the survey. Each question is tested for the correct number and coding of responses, that respondents answering the questions meet the base criteria as well as duplicate any calculated or algorithmic variables and compared for accuracy. An independent member of the operations team then writes the DCE. The data is also run through the DCE one again with soft launch data, full field data (data from the day after full fielding has begun) and the final data set.

- Soft launching: Once the DCE is approved, Redacted begins fielding with a limited amount of sample designed to recruit 10% of the total quota. The soft launch data is then thoroughly checked utilizing the DCE to ensure programming accuracy.

- In-field data checks: A core member of the Redacted research team monitors the data at regular intervals (e.g., 10%, 25%, 50%, 75% of data collection). The data is examined for the following, and considered together to identify and exclude respondents for whom the data is suspect/of poor quality:

    - Length of survey – survey length is estimated prior to fielding; any surveys completed substantially below a lower threshold are flagged with the help of hidden variables.

    - Quality control questions – each survey includes a few questions for the sole purpose of being a quality control check (e.g., "For quality control purposes, please select No" with response options of "Yes, No, Maybe"). These questions help to evaluate a respondent's level of attention to the survey.

Standard organizational procedures will be followed to ensure data quality and integrity, including data collection, archiving of statistical programs, appropriate documentation of data cleaning, validity for variables and description of data.

9.9. Strengths and Limitations of the Research Methods

9.9.1. Strengths

1. Web-based surveys

Web-based surveys have been selected as the preferred research approach because:

- The HCP survey includes behavioral scenario-based questions that might be difficult to implement using other approaches.

- Web-based surveys can be answered at the participant's convenience so that an interview does not need arranging – this can increase a participant's motivation to do the survey (improving response rates), thus resulting in more consistent completion of surveys.

- Web-based surveys are programmed to ask standardized questions and should elicit more consistent and reliable results than questions asked by telephone interviewers.

- Web-based techniques allow for a degree of interactivity to be introduced into the survey (e.g., logic to ask follow-on questions or not ask irrelevant questions), which strengthens the validity of the behavioral scenarios.

2. Questionnaire design and testing

- The web questionnaires include general questions followed by specific ones. They include both open and closed questions. As the HCPs may understand the right answer in subsequent questions, it will not be possible to go back in the questionnaire and edit answers in former questions.

- The questionnaires will be tested for their clarity. It will also be checked whether there are questions which would suggest a specific answer for any reason.

3. Experience in drug safety and the evaluation of RM measures

The study will be conducted by an experienced team specialized in the design and conduct of such surveys. It follows Redacted SOPs, as well as the methodological guidelines from SFDA Guideline on GVP.

4. Quality control and compliance

Quality controls are implemented on a regular basis by our teams.

9.9.2. Limitations

1. Bias

Selection bias

a) HCPs survey

The potential for selection bias of HCPs participating in a survey is an inherent limitation to any study based on volunteer participation. For instance, it is possible that HCPs willing to

participate in the study will have the highest awareness of risks associated with use of voriconazole.

Non-response bias may also be introduced into the study if targeted HCPs have activated filters in their mailbox that block spam and unsolicited emails. If a very strict degree of message filtering is set, they may not even see the invitation to participate in the survey. Having multiple email addresses could also be a critical situation. If the one used is not the primary address or if the HCPs do not check their emails frequently, they will not receive the invitation during the recruitment period. Some HCPs who are sent a letter may not receive it. This is one of the reasons why the HCPs will also be contacted by phone.

Selection and non-response bias will be assessed by comparing select characteristics between survey non-responders and responders using descriptive statistics, and will be included in the final study report.

Information bias

Recall bias may lead to an underestimation of the HCP recalling having received aRMMs. To mitigate the risk of recall bias for HCPs, they will be recruited in the survey if they have provided (prescribed or dispensed) voriconazole in the past 12 months.

Moreover, web surveys may promote social desirability bias, which refers to the tendency of HCP to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behavior, e.g., physicians can copy-paste information gathered online instead of giving their own opinions. Social desirability can affect the validity of survey research findings, but the use of prepopulated items in the questionnaire could/tends to reduce this bias. The access to the web questionnaire interface will be strictly limited to the invited participants, with the possibility to participate only once, and a traceability system. Thus, stakeholder bias (multiple answers of people who have a personal interest in survey results and/or who incite peers to fulfill the survey in order to influence the results) or unverified respondents (when it is not possible to verify who responds) are not applicable.

All questions must be answered in order to complete the survey. In each survey, response options presented in a list will be presented in random order (where appropriate) to minimise positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

2. Generalization of the survey results to the overall target population

In such surveys, the generalization and external validity of the results is restricted to HCPs who can be reached and are willing (and able) to answer a questionnaire online questionnaire. These HCPs may not be fully representative of the whole target population.

The study report will discuss the results in the light of the limitations described above including variability and uncertainty of the data and methods.

Finally, the marketing authorization holder (MAH) acknowledges that an a priori threshold of 80% correct per risk questions will be used to define the success of the program. However as acknowledged by EMA, the selection of this threshold for success is subjective (7 May 2015 PRAC Rapporteur PASS Protocol Assessment Report; Procedure no.: EMEA/H/C/000387/MEA 087.2) and not based on a prior knowledge, experience, or established scientific criteria in the education or risk communication literature. The MAH expects that the knowledge may differ by key risk message, clinical practice, & HCP specialties. Moreover, sample size may not be sufficient to conduct subgroup or stratified analyses.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Study Participant information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant personal data. Such measures will include omitting participant /HCP names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Participant/ HCP personal data will be stored at a secure online data collection software in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. Redacted will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, Redacted shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any HCP names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, participant-specific code. Redacted will maintain a confidential list of HCPs who participated in the study, linking each HCP's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the research agreement and applicable privacy laws.

10.2. Study Participant consent

Due to the nature of the study, informed consent is not required. Participants need to go to the survey website in order to complete the survey. Consent is implied by these actions. Additionally, at the beginning of the survey, the respondent is asked if he/she agrees to take part in the survey. If yes, the respondent continues with the survey questions. If no, the survey is terminated.

10.3. Participant withdrawal

Any participant who will not complete all survey questions will be considered as withdrawal from the study.

10.4. Institutional review board (IRB)/Independent ethics committee (IEC)

Not applicable.

10.5. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guideline on GVP Version 3.1 30-January-2023 - Drug Sector, SFDA.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study does not involve data collection on individual patients by their treating HCPs and the DCT used in this study does not intend to identify product safety information. The DCT for this study will be completed online via a secure website. The DCT does not provide a free text field where study participants could specify information that may constitute product safety information. Further, routine communication with study participants via email or phone with Redacted is not expected during the conduct of the study. However, it is possible that a study participant may volunteer product safety information to Redacted while in conversation about the DCT for any other reason (e.g., seeking information about the purpose of the study); this information must be reported as described below.

The following safety events must be reported on the NIS AEM Report Form: serious and non-serious AEs when associated with the use of the Pfizer product, and scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure (all reportable, regardless of whether associated with an AE), when associated with the use of a Pfizer product.

For exposure during pregnancy in studies of pregnant women, data on the exposure to Vfend® (voriconazole) during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

In the event that a study participant volunteers product safety information, Redacted team must complete the NIS AEM Report Form and submit to Pfizer DSU within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form is the study participant's contact information; complete contact information should be obtained so that, once the NIS AEM Report Form is sent to Pfizer, the NIS AEM Report Form can be assessed and processed according to Pfizer's standard operating procedures, including requests for follow-up to the study participant.

Redacted team who will serve to be available to study participants to answer questions during study participant completion of the data collection tool, address any query from participants about the study must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) with Supplemental Topics".*

These trainings must be completed by Redacted team prior to the start of data collection. All trainings include a "Confirmation of Training Statement" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. The study vendor will also provide copies of all signed training statements to Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report describing the survey objectives, detailed methods, results, discussion, and conclusions will be developed at the end of the survey for submission to SFDA within the timeframe specified in Section 6 'MILESTONES'.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if Redacted is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, Redacted will inform Pfizer immediately of any urgent safety measures taken by the Redacted to protect the study participant against any immediate hazard, and of any serious breaches of this NI study protocol that Redacted becomes aware of.

13. REFERENCES

1. Vfend SUMMARY OF PRODUCT CHARACTERISTICS (Saudi Arabia), June 2023

2. Guideline on Good Pharmacovigilance Practices (GVP) Version 3.1 30-January-2023 - Drug Sector, Saudi Food & Drug Authority (SFDA).

3. Prieto L, Spooner A, Hidalgo-Simon A, Rubino A, Kurz X, Arlett P. Evaluation of the effectiveness of risk minimisation measures. Pharmacoepidemiol Drug Saf. 2012 Aug;21(8):896-9. Doi: 10.1002/pds.3305. Epub 2012 Jun 22.

4. Guidelines for Good Pharmacoepidemiology Practices (GPP). International Society for Pharmacoepidmiology (ISPE). Pharmacoepidemiology and Drug Safety 2008; 17:200-208.

5. Good Outcomes Research Practices. International Society for Pharmacoeconomic and Outcomes Research (ISPOR). http://www.ispor.org/research_initiatives/hs_initiatives.asp

6. International Ethical Guidelines for Epidemiological Studies, issued by the Council for International Organizations of Medical Sciences (CIOMS), World Health Organization (WHO) Press, Geneva Switzerland. April 2009.

7. Guide on Methodological Standard in Pharmacoepidemiology. European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology (ENCePP); June 2013. (http://www.encepp.eu/standards_and_guidances).

8. Food and Drug Administration. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment US Dept of Health and Human Services. Food and Drug Administration. Rockville, Maryland. March 2005.

14. LIST OF TABLES

Not applicable.

15. LIST OF FIGURES

Not applicable.

16. ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1.1		16 August 2024	Abstract
1.2		16 August 2024	HCP Questionnaire
1.3		16 August 2024	Invitation letter
1.4		16 August 2024	Follow up letter
1.5		16 August 2024	Assessment of success

Annex 1.1. Abstract

Title

Evaluation of the effectiveness of additional risk minimisation measures (aRMMs) that aim to reduce the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients receiving voriconazole in the Saudi Arabia.

Protocol version and date

Version 1.0 16 August 2024

Name and affiliation of main author

Redacted

Rationale and Background

Pfizer Saudi Limited will conduct a non-interventional, cross-sectional survey of healthcare professionals (HCPs) to evaluate the effectiveness of the aRMMs being implemented across Saudi Arabia to mitigate the risks of phototoxicity, SCC of the skin and hepatic toxicity in patients prescribed voriconazole (Vfend®), a broad spectrum triazole antifungal agent used to treat or prevent a range of serious fungal infections in both inpatient and outpatient settings.

To ensure that the risks are adequately managed, aRMMs in Saudi Arabia have been implemented since February 2023. The aRMM material distribution has been started on 05-February-2023 and continued until 05-February-2024 to the relevant HCPs who may initiate or manage patients on Vfend®. These include an updated voriconazole Summary of Product Characteristics (SPC)[1] (routine) and a new comprehensive education programme at the point of patient care that will educate/remind HCPs about the risks of phototoxicity, SCC of the skin and hepatic toxicity and how to manage them. The details of the Risk Minimisation (RM) tools for the educational programme and how these tools will be implemented across Saudi Arabia are described in the Risk Management Plan (RMP). The RM tools are the HCP Checklist, HCP Question & Answer (Q&A) Brochure and Patient Alert Card. HCPs who the materials are targeting will be invited to participate in the survey. The start of the data collection is intended to be within 18-24 months period from the launch of Vfend® in Saudi Arabia to allow physicians time for familiarity and use of the materials before evaluating the effectiveness of Vfend® aRMM.

Research Question and Objectives

The overall objective is to evaluate the effectiveness of the aRMMs to mitigate the risks of phototoxicity, SCC of the skin and hepatic toxicity in patients using voriconazole. The

evaluation is being conducted in Saudi Arabia where RM tools are being implemented. Specifically, the objectives of the study are to:

4. Assess HCPs' awareness of the RM tools (i.e., HCP Checklist, HCP Q&A Brochure and Patient Alert Card).

5. Assess HCPs' utilization of the RM tools (i.e., HCP Checklist, HCP Q&A Brochure and Patient Alert Card)

6. Assess HCPs' knowledge of the risks of phototoxicity, SCC of the skin, and hepatic toxicity with voriconazole.

7. Assess whether HCPs' self-reported behaviour/practices with respect to minimizing the risks of phototoxicity, SCC of the skin, and hepatic toxicity are in accordance with the voriconazole SPC.[1]

Study Design

This is a non-interventional, cross-sectional study to evaluate the effectiveness of RM tools for voriconazole. The study objectives will be accomplished by means of a cross-sectional, web-based survey of all HCPs who were targeted to receive the aRMMs and self-report as prescribers of voriconazole within 12 months preceding the survey in Saudi Arabia (Central, East and North regions). The study aims to obtain completed surveys from 10 HCPs. Data will be collected until 10 completed surveys are obtained or up to a data collection period of 60 to 90 days as a maximum. The data from the HCPs will be collected using a structured self-administered questionnaire to gather evaluation metrics related to the utilization and understanding of RM tool content and messages. In addition, the survey will assess behaviors, including a set of hypothetical scenarios for HCPs. The survey is not intended to be a mechanism for collecting adverse events (AEs), nor is it intended to result in minimizing the numbers of AEs reported. HCPs will be invited by e-mail to participate in the survey and asked to complete the online questionnaire.

Population

The target polulation will include all HCPs who were targeted to receive Vfend® aRMM materials within 12 months preceding the survey.

Inclusion criteria

1. Willing/consent to participate in this self-administered survey.

2. Involved in the treatment of at least one patient with voriconazole within the last 12 months.

Exclusion criteria

The HCPs meeting any of the following criteria will not be included in the survey:

1. Employed in full-time research or hospital administration (i.e., non-practising physicians).
2. Employment by Pfizer Inc or any research organization/vendor contracted by Pfizer to administer the survey.

Variables

Screening questions

- Consent to participate.
- Whether the HCP managed patient(s) treated with voriconazole during the last 12 months period preceding the survey.
- Employment by Pfizer or any research organization/vendor contracted by Pfizer to administer the survey.
- Participation in qualitative research of the VFEND (voriconazole) Risk Minimisation materials

The following variables will be collected through the HCP survey:

HCP demographics and medical mackground

1. Location
2. Primary medical specialty
3. Length of professional practice as a HCP

HCP knowledge on voriconazole toxicities:

1. Knowledge testing for specific risks associated with voriconazole treatment
2. Knowledge of treatment discontinuation recommendations and dealing with toxicities

RM tools receipt

1. Acknowledge receiving Q&A brochure
2. Acknowledge receiving HCP checklist
3. Acknowledge receiving Patient alert card

RM tools reading

1. Acknowledge reading Q&A brochure
2. Acknowledge reading HCP checklist
3. Acknowledge reading Patient alert card

RM tools utilization

1. Frequency of using HCP checklist, Q&A brochure, and Patient alert card
2. Ranking the usefulness of each RM tool

Self-declared behavior/practice

1. Patient counseling
2. Discussing risks with patients
3. Liver function monitoring
4. Dermatological evaluation
5. Treatment discontinuation recommendations

Other variables

1. Requesting extra RM tools
2. Number of patients treated with voriconazole in the past 12 months
3. Downloading the tools from website

Endpoints

1. The proportion of targeted HCPs who acknowledge receiving each of the RM tools (i.e., HCP Checklist, HCP Q&A Brochure and Patient Alert Card).
2. The proportion of targeted HCPs who acknowledge reading and utilizing the tools.
3. The proportion of targeted HCPs' who respond correctly to questiontions about the risks of phototoxicity, SCC of the skin, and hepatic toxicity.
4. The proportion of targeted HCPs who respond correctly to the practice-related questions and self-declared behavior with regard to strategies to mitigate the risks.

Data Sources (Survey)

A structured self-administered questionnaire comprised of closed-ended questions or statements with multiple response choices (i.e., questions or statements asking the HCPs to choose from a predefined list of responses) will be used to collect the survey data. The questionnaire will collect data on HCP characteristics in addition to their responses pertaining to the effectiveness of the aRMMs. It is estimated to take 20 to 25 minutes to complete the HCP questionnaire.

Study Size

At the time of protocol writing, a total of around Redacted HCPs (distribution list shared with the Saudi Food and Drug Authority [SFDA]) are expected to initiate or manage patients on Vfend®. All HCPs who were targeted to receive the RM tools (per Pfizer Inc.'s Distribution List.) within the 12 months preceding the initiation of the survey will be invited to participate in the survey. Given this relatively small pool of HCPs, an empirical sample size of 10 HCPs is proposed. Data will be collected until 10 completed surveys are obtained or up to a data collection period of 60 to 90 days as a maximum. It is important to note that the final survey sample size will depend on HCPs' willingness to participate in the survey.

An a priori threshold of 80% correct responses per risk question will be used to define the success of the program. However, this criterion will not be used for formal statistical testing. The selection of this threshold for success was regarded as being subjective and not based on prior knowledge, experience, or established scientific criteria.

Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Data collected from the survey will be reported as descriptive statistics. Frequency distributions with 95% confidence intervals (CIs) will be calculated for HCPs' responses to all questions that address the survey objectives.

Milestones

In accordance with the SFDA Guideline on Good Pharmacovigilance Practices Module XVI (Risk minimisation measure: selection of tools and effectiveness indicators 30 January 2023)[1], data collection will begin after initial implementation of a RM programme in Saudi Arabia in February 2023 within 18-24 months), in order to allow the possibility of necessary amendments following the initial distribution of the approved RM tools in Saudi Arabia. This period will allow for the time required for utilization of the tools in Saudi Arabia health care

system. The planned timeline is contingent upon the date of the finalization and distribution of the RM tools within Saudi Arabia and the protocol endorsement by the SFDA.

Annex 1.2. HCP Survey Questionnaire

SURVEY LEGEND

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

- **[BEGIN SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer.

  Thank you for your time today. Based on your answer, you are not eligible to take part in this survey.

- **[GO TO Qx]** (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

- **[FREE TEXT]** indicates to the programmer that one line should be provided for data entry.

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines).

[PREAMBLE 1]

Disclaimer

This research is sponsored by Pfizer Inc. The aim of this research is to assess knowledge about the prescribing information for VFEND® (voriconazole). Taking part in this survey is voluntary; you are under no obligation to participate. You may refuse to take the survey or stop taking the survey at any time.

How We Use Your Information

Your answers to the survey questions will be combined with those from other respondents and reported in an anonymous form to Pfizer Saudi Arabia and SFDA. Your name will not be used in any report. If you are eligible to take the questionnaire, complete all the questions, and provide your contact information, you will receive compensation based on your local rules and regulations. This compensation represents the fair value for your time in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you. Your name and address will only be used to send you the honorarium after you complete the survey.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. All the information you provide will be kept strictly confidential. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the SFDA or local country Ethics Committees. Your choice to allow Pfizer to use your information is entirely voluntary but necessary to take part in this survey.

How to Learn More about the Online Survey

If you have questions about or problems with the survey, please contact the Help Desk at: XXXXXXXXXXX and your questions will be answered.

[PREAMBLE 2]

VFEND® (voriconazole) Healthcare Professional (HCP) Survey

Please provide a response to all questions and statements.

1. Do you agree to take part in this survey?

   ☐ Yes

☐ No **[TERMINATE]**

2. Have you managed patient(s) treated with VFEND (voriconazole) within the past 12 months?

   ☐ Yes

   ☐ No **[TERMINATE]**

3. Are you currently employed by Pfizer Saudi Limited or United BioSource Corporation?

   ☐ Yes **[TERMINATE]**

   ☐ No

4. Have you ever participated in qualitative research of the VFEND (voriconazole) Risk Minimisation materials?

   ☐ Yes **[TERMINATE]**

   ☐ No

5. What is your primary medical specialty?

   ☐ Critical Care

   ☐ Haematology

   ☐ Infectious diseases

   ☐ Intensive Care

   ☐ Microbiology

   ☐ Oncology

   ☐ Solid Organ Transplant

   ☐ Clinical pharmacist

   ☐ Non-clinical pharmacist

   ☐ Other Subspecialty: (Specify) **[FREE TEXT]**

☐ Other: (Specify) **[FREE TEXT]**

5a. Where do you practice as an HCP?

☐ Dahran
☐ Dammam
☐ Hail
☐ Jeddah
☐ Jubail
☐ Khamis Mushait
☐ Khobar
☐ Madinah
☐ Makkah
☐ Najran
☐ Qurayat
☐ Riyadh
☐ Tabuk
☐ Taif
☐ Other: (Specify) **[FREE TEXT]**

6. For how long have you been practicing as an HCP?

☐ ≤5 years
☐ 6-15 years
☐ >15 years

7. According to the SPC/PI, the known risks for VFEND (voriconazole) are as follows: **(**Please select only <u>one</u> response for <u>each</u> of the risks listed in the table below.)

	Yes	No	I Don't Know
Phototoxicity (eg, skin rash)	☐	☐	☐
Intestinal perforation	☐	☐	☐
Squamous cell carcinoma (SCC) of the skin	☐	☐	☐
Asthma	☐	☐	☐
Hepatic toxicity	☐	☐	☐
Cardiomyopathy	☐	☐	☐

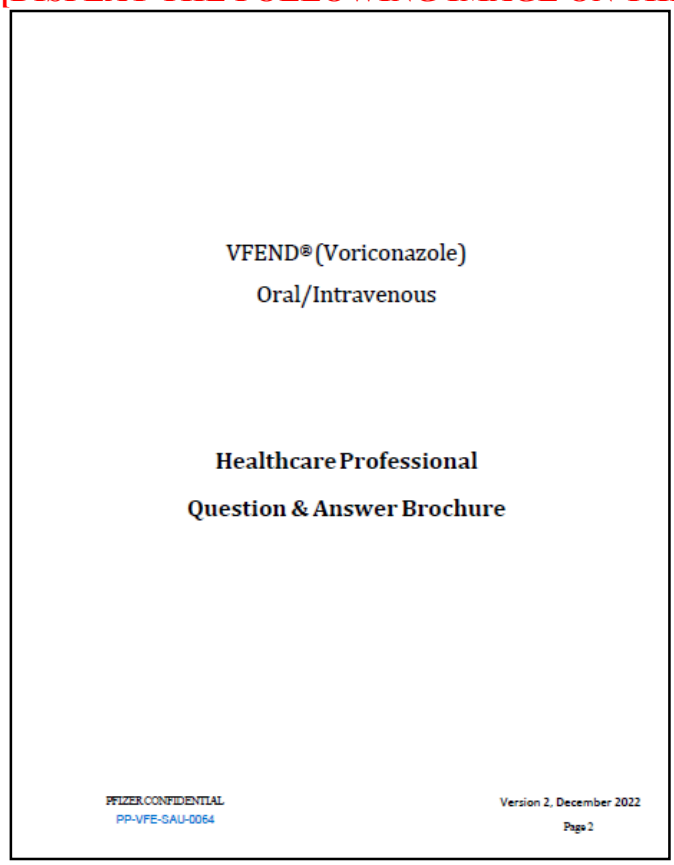
8. Please select only one response for <u>each</u> statement about VFEND (voriconazole) below:

	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	☐	☐	☐
If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist	☐	☐	☐
VFEND (voriconazole) ***should not be discontinued*** if premalignant skin lesions or skin Squamous Cell Carcinoma are identified	☐	☐	☐
Laboratory evaluation of hepatic function (specifically AST and ALT) at initiation and during the first month of treatment with VFEND (voriconazole) ***is not necessary***	☐	☐	☐
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	☐	☐	☐

9. Did you or your hospital receive the VFEND (voriconazole) Healthcare Professional (HCP) Q&A Brochure?

- ☐ Yes
- ☐ No **[GO TO Q10]**
- ☐ I don't remember receiving it **[GO TO Q10]**

[DISPLAY THE FOLLOWING IMAGE ON THE SAME PAGE NEXT TO Q9]



9.1. Did you read the VFEND (voriconazole) **HCP Q&A Brochure**?

- ☐ Yes, all of it
- ☐ Yes, some of it
- ☐ No, I did not read it
- ☐ I don't remember reading it

10. Did you or your hospital receive copies of the VFEND (voriconazole) **Healthcare Professional (HCP) Checklist?**

- ☐ Yes
- ☐ No [**GO TO Q11**]
- ☐ I don't remember receiving it **[GO TO Q11]**

[DISPLAY THE FOLLOWING IMAGE ON THE SAME PAGE NEXT TO Q10

VFEND® (Voriconazole) Healthcare Professional Checklist

Please complete this Checklist at each visit with your patient being treated with VFEND® (Voriconazole). Each of the three sections includes important risk information followed by a series of check boxes to help in the management of your patient for whom you prescribed VFEND.

A) Minimizing the Risk of Phototoxicity and Skin Squamous Cell Carcinoma

- VFEND has been associated with phototoxicity and pseudoporphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during VFEND treatment and use measures such as protective clothing and sufficient sunscreen with high sun protection factor (SPF).
- The frequency of phototoxicity reactions is higher in the paediatric population. As an evolution towards SCC has been reported, stringent measures for the photoprotection are warranted in this population of patients. In children experiencing photoaging injuries such as lentigines or ephelides, sun avoidance and dermatologic follow-up are recommended even after treatment discontinuation.
- Squamous cell carcinoma (SCC) of the skin has been reported in patients taking VFEND, some of whom have reported prior phototoxic reactions.
- If phototoxic reactions occur, multidisciplinary advice (e.g. a consultation with a dermatologist) should be sought for the patient . VFEND discontinuation and use of alternative antifungal agents should be considered.
- Dermatologic evaluation should be performed on a regular basis whenever VFEND is continued, despite occurrence of phototoxicity-related lesions to allow early detection and management of premalignant lesions.
- VFEND should be discontinued if premalignant skin lesions or skin SCC are identified.
- SCC has been reported in relation with long-term VFEND treatment. Treatment duration should be as short as possible. Long- term exposure (treatment or prophylaxis) greater than 180 days (6 months) requires careful assessment of the benefit risk balance and physicians should therefore consider the need to limit the exposure to VFEND.
- For prophylaxis use, dose adjustments are not recommended in the case of lack of efficacy or treatment-related adverse events. In the case of treatment-related adverse events, discontinuation of VFEND and use of alternative antifungal agents must be considered.

Refer to the Summary of Product Characteristics for full prescribing and adverse event information.

Please review and answer the questions below for each patient receiving VFEND:

△ **Has your patient developed phototoxicity?** YES☐ NO☐
If YES, **please refer to the Summary of Product Characteristics (SmPC) for guidance.**

△ **Have you arranged regular dermatologic evaluation for the patient if he/she presented with phototoxicity?** YES☐ NO☐
If YES, **please refer to the SmPC for further details.**
If NO, **regular dermatologic evaluation should be arranged promptly. Please refer to the SmPC for further details.**

In case of phototoxicity, did you consider discontinuing treatment with VFEND? YES☐ NO☐
If YES, **please refer to the SmPC for further advice.**
If NO. VFEND discontinuation and use of alternative antifungal agents should be considered Please refer to the SmPC for further instruction.

In case of premalignant skin lesions or SSC, did you discontinue treatment with VFEND? YES☐ NO☐
If NO, **VFEND should be discontinued. Please refer to the SmPC for further advice.**

Page 1 of 3 Version 2, December 2022

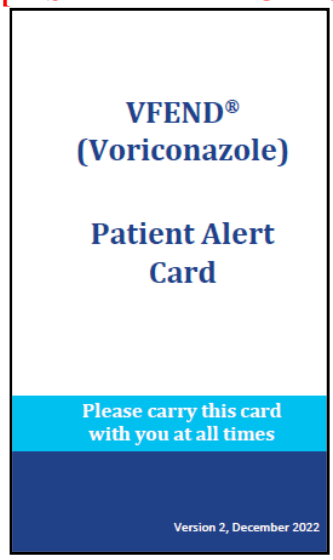
10.1. Did you read the VFEND (voriconazole) **Healthcare Professional (HCP) Checklist?**

- ☐ Yes, all of it
- ☐ Yes, some of it
- ☐ No, I did not read it
- ☐ I don't remember reading it

11. Did you or your hospital receive copies of the VFEND (voriconazole) **Patient Alert Card**?

- ☐ Yes
- ☐ No [**GO TO Q12**]
- ☐ I don't remember receiving them [**GO TO Q12**]

[DISPLAY THE FOLLOWING IMAGE ON THE SAME PAGE NEXT TO Q11]



11.1. Did you read the VFEND (voriconazole) **Patient Alert Card?**

- ☐ Yes, all of it
- ☐ Yes, some of it
- ☐ No, I did not read it
- ☐ I don't remember reading it

12. Did you or another staff member obtain the VFEND (voriconazole) RM tools by downloading them from a website?

- ☐ Yes
- ☐ No

13. Approximately how many patients have you treated with VFEND (voriconazole) in the past 12 months?

- ☐ 1–5
- ☐ 6–10
- ☐ 11–20
- ☐ >20

Programing: if response to Q10 or Q12 is YES, they can continue with Q14

14. When treating patients with VFEND (voriconazole) in the past 12 months, how often did you use the VFEND HCP Checklist?

- ☐ Always
- ☐ Sometimes
- ☐ Never

Programing: if response to Q9 or Q12 is YES, they can continue with Q15

15. When treating patients with VFEND (voriconazole) in the past 12 months, how often did you use the HCP Q&A Brochure?

- ☐ Always
- ☐ Sometimes
- ☐ Never

Programing: if response to Q11 or Q12 is YES, they can continue with Q16

16. When treating patients with VFEND (voriconazole) in the past 12 months, how often did you distribute and fill in the Patient Alert Card?

- ☐ Always
- ☐ Sometimes
- ☐ Never

17 Did you find the VFEND (voriconazole) RM tools to be of use in your clinical practice? Please select only one rank for <u>each</u> RM tool listed below:

Programing Note: if response to Q9 or Q12 is YES, they can continue with Q17.1

	Not useful	Somewhat useful	No opinion/not sure	Very useful	Extremely useful
17.1 HCP Q&A Brochure	☐	☐	☐	☐	☐

Programing Note if response to Q10 or Q12 is YES, they can continue with Q17.2

	Not useful	Somewhat useful	No opinion/not sure	Very useful	Extremely useful
17.2 HCP Checklist	☐	☐	☐	☐	☐

Programing Note: if response to Q11 or Q12 is YES, they can continue with Q17.3

	Not useful	Somewhat useful	No opinion/not sure	Very useful	Extremely useful
17.3 Patient Alert Card	☐	☐	☐	☐	☐

18. Which precautionary measures do you communicate to your patients for whom you prescribe VFEND (voriconazole)? Please check all that apply.

- ☐ Avoiding exposure to direct sunlight
- ☐ Detecting signs and symptoms of phototoxicity
- ☐ Use with caution in patients with previous history of intestinal ulceration or diverticulitis
- ☐ Dermatologic evaluation should be performed on a systematic and regular basis
- ☐ Intensified monitoring of blood glucose level

- ☐ Covering sun exposed areas of skin
- ☐ Use sufficient sunscreen with high sun protection factor (SPF)
- ☐ Clinical signs of liver damage, such as jaundice that warrant contacting the doctor immediately
- ☐ International Normalized Ratio regular monitoring
- ☐ Avoid invasive dental procedures

Programing Note: if response to Q11 or Q12 is YES, they can continue with options *"Discuss contents of the Patient Alert Card"* in Q18a

18a. Do you, or another member of your healthcare team (eg, nurse, pharmacist or other) perform each of these activities when initiating treatment with VFEND (voriconazole)? (Please check one response for each activity below).

	Yes	No
Discuss contents of the Patient Alert Card	☐	☐
Advise patient to avoid exposure to direct sunlight and/or to use measures such as protective clothing and sunscreen	☐	☐
Discuss risk of lymphoma	☐	☐
Discuss risk of gastric perforation	☐	☐
Advise patient of importance of monitoring risks of VFEND (voriconazole) use and signs and symptoms of serious risks that warrant contacting doctor immediately	☐	☐
Discuss risk of amyloidosis	☐	☐

19. How frequently do you perform Liver Function Tests (specifically AST, ALT)?

- ☐ At VFEND (voriconazole) treatment initiation and weekly thereafter for one month
- ☐ At every contact
- ☐ Monthly

- ☐ Other [Free text]
- ☐ I do not know

20. If there are no changes in Liver Function Tests (LFTs) after one month of initiation of VFEND (voriconazole), how often do you monitor liver function during VFEND treatment maintenance?

- ☐ Weekly
- ☐ Monthly
- ☐ Other [Free text]
- ☐ I do not know

21. How often do you perform a dermatologic evaluation when VFEND (voriconazole) is continuously used despite the occurrence of phototoxicity-related lesions?

- ☐ Weekly
- ☐ Monthly
- ☐ Every two months
- ☐ On systemic and regular basis
- ☐ I do not know

22. For which of below condition(s) would you discontinue VFEND (voriconazole) in a patient? (Select the one best response).

- ☐ Phototoxicity
- ☐ Squamous Cell Carcinoma (SCC)
- ☐ Premalignant lesions
- ☐ All of the above

23. Did you or another staff member request additional copies of the VFEND (voriconazole) RM tools?

☐ Yes

☐ No

[CLOSING 1]
[CLOSING 2]

End of Questionnaire

Thank you.

Annex 1.3. Draft Survey Invitation Letter for Healthcare Professionals (HCPs)

[Date]

[Addressee's name] [Title]
[Street address]
[City, State, zip code]
[Country]

Re: Invitation to Participate in VFEND® Survey
Dear Dr. [insert HCP LAST NAME],

On behalf of Pfizer Saudi Limited, we would like to invite you to participate in a voluntary research survey about VFEND (voriconazole). The survey is part of a post-marketing agreement between Pfizer and the Saudi Arabia health authority (SFDA) and should take no more than 20 minutes to complete. If you complete the survey, you will be receiving compensation based on your local rules and regulations to thank you for your time.

You may be eligible to participate if you have prescribed VFEND in the past 12 months and have received a set of risk minimization materials for VFEND. The survey can be completed on or before [END DATE], and for your convenience can be completed online at **[www.surveyURL.com]** at any time.

You will need the following ID code when completing the survey: **[CODE_ID]**.

Participating in this survey is entirely voluntary. All information which is collected during the course of the survey will be kept strictly confidential. Results will be reported in aggregate form only. Your participation in the survey and your answers to the survey questions will not affect your ability to prescribe VFEND. You will not be contacted for marketing purposes. Neither Pfizer, nor its contractors, will sell, transfer, or rent your information. This letter and this survey have been approved by the SFDA.

Thank you in advance for your participation in this important research.

Sincerely,

{Note: Signatory to be determined for each country and customized accordingly}

Annex 1.4. Draft Survey Follow-up Letter for Healthcare Professionals (HCPs)

[Date]

[Addressee's name] [Title]
[Street address]
[City, State, zip code]
[Country]

Re: Reminder - Invitation to Participate in VFEND® Survey
Dear Dr. [insert HCP LAST NAME],

Kind reminder on behalf of Pfizer Saudi Limited, we would like to invite you to participate in a voluntary research survey about VFEND (voriconazole). The survey is part of a post-marketing agreement between Pfizer and the Saudi Arabia health authority (SFDA) and should take no more than 20 minutes to complete. If you complete the survey, you will be receiving compensation based on your local rules and regulations to thank you for your time.

You may be eligible to participate if you have prescribed VFEND in the past 12 months and have received a set of risk minimization materials for VFEND. The survey can be completed on or before [END DATE], and for your convenience can be completed online at **[www.surveyURL.com]** at any time.

You will need the following ID code when completing the survey: **[CODE_ID]**.

Participating in this survey is entirely voluntary. All information which is collected during the course of the survey will be kept strictly confidential. Results will be reported in aggregate form only. Your participation in the survey and your answers to the survey questions will not affect your ability to prescribe VFEND. You will not be contacted for marketing purposes. Neither Pfizer, nor its contractors, will sell, transfer, or rent your information. This letter and this survey have been approved by the SFDA.

Thank you in advance for your participation in this important research.

Sincerely,

{Note: Signatory to be determined for each country and customized accordingly}

Annex 1.5. Assessment of success

Objectives	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of desirably/correctly answered question	Assessment of success
Awareness of the RM tools	Q9. Did you or your hospital receive the VFEND (voriconazole) Healthcare Professional (HCP) Q&A Brochure?	Yes	Question completed desirably (Answer 1 is desirable)	An HCP is considered successful for awareness when he/she acknowledges receiving all RM tools Success for awareness: if ≥80% of HCPs are successful
	Q10. Did you or your hospital receive copies of the VFEND (voriconazole) Healthcare Professional (HCP) Checklist?	Yes	Question completed desirably (Answer 1 is desirable)	
	Q11. Did you or your hospital receive copies of the VFEND (voriconazole) Patient Alert Card?	Yes	Question completed desirably (Answer 1 is desirable)	
	Q12. Did you or another staff member obtain the VFEND (voriconazole) RM tools by downloading them from a website?	No	Complementary question	
Reading and Utilizing the tools.	Q9.1 Did you read the VFEND (voriconazole) HCP Q&A Brochure?	Yes	Question completed desirably (Answers 1 & 2 are desirable)	An HCP is considered successful for utilization when he/she reports reading all/some of all RM tools and always/sometimes using them Success for utilization: if ≥80% of HCPs are successful
	Q10.1 Did you read the VFEND (voriconazole) Healthcare Professional (HCP) Checklist?	Yes	Question completed desirably (Answers 1 & 2 are desirable)	
	Q11.1 Did you read the VFEND (voriconazole) Patient Alert Card?	Yes	Question completed desirably (Answers 1 & 2 are desirable)	
	Q14. When treating patients with VFEND (voriconazole) in the past 12 months, how often did you use the VFEND HCP Checklist?	Yes	Question completed desirably (Answers 1 & 2 are desirable)	
	Q15. When treating patients with VFEND (voriconazole) in the past 12 months, how often did you use the HCP Q&A Brochure?	Yes	Question completed desirably (Answers 1 & 2 are desirable)	

	Q16. When treating patients with VFEND (voriconazole) in the past 12 months, how often did you distribute and fill in the Patient Alert Card?	Yes	Question completed desirably (Answers 1 & 2 are desirable)	
	Q17. 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 (Q17.1, Q17.2 and Q17.3)	No	Complementary question	
Knowledge about the RM tools	Q7. According to the SPC/PI, the known risks for VFEND (voriconazole) are as follows: **(**Please select only <u>one</u> response for <u>each</u> of the risks listed in the table below.)	Yes	Question completed correctly (6 points)	An HCP is considered successful for Knowledge when he/she provides at least 9 out of 11 (~80%) correct/desirable responses. Success for Knowledge: if ≥80% of HCPs are successful
	Q8. Please select only one response for <u>each</u> statement about VFEND (voriconazole) below:	Yes	Question completed correctly (5 points)	
Self-declared behavior/ Practice	Q18. Which precautionary measures do you communicate to your patients for whom you prescribe VFEND (voriconazole)? Please check all that apply.	Yes	Question completed desirably (6 points)	An HCP is considered successful for awareness when he/she provides desirable responses to all sub-questions. Success for self-reported practices if ≥80% of HCPs are successful
	18.a 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 <u>one</u> response for <u>each</u> activity below).	Yes	Question completed desirably (6 points)	
	Q19. How frequently do you perform Liver Function Tests (specifically AST, ALT)?	Yes	Question completed desirably (Answer 1 is desirable)	

	Q20. If there are no changes in Liver Function Tests (LFTs) after one month of initiation of VFEND (voriconazole), how often do you monitor liver function during VFEND treatment maintenance?	Yes	Question completed desirably (Answer 2 is desirable)	
	Q21. How often do you perform a dermatologic evaluation when VFEND (voriconazole) is continuously used despite the occurrence of phototoxicity related lesions?	Yes	Question completed desirably (Answer 4 is desirable)	
	Q22. For which of below condition(s) would you discontinue VFEND (voriconazole) in a patient? (Select the one best response).	Yes	Question completed desirably (Answer 4 is desirable)	

17. ANNEX 3. ADDITIONAL INFORMATION

3.1	HCP Checklist	
3.2	HCP Question & Answer (Q&A) Brochure	
3.3	Patient Alert Card	

Document Approval Record

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Signed By:	Date(GMT)	Signing Capacity
Redacted	[redacted]	[redacted]
Redacted	[redacted]	[redacted]