NON-INTERVENTIONAL (NI)/LOW-INTERVENTIONAL STUDY TYPE 1 (LIS1) STUDY REPORT

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
Version identifier of the study report	1.0
Date	20 June 2025
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 (i.e., HCP Checklist, HCP Q&A Brochure and Patient Alert Card). 2- Assess HCPs' utilization of the RM tools (i.e., 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.

Country(-ies) of study	Kingdom of Saudi Arabia.
Author	Redacted

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Not applicable

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Not applicable

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
aRMMs	Additional Risk Minimisation Measures
HCP	Healthcare Professionals
SCC	Squamous Cell Carcinoma
SPC	Summary of Product Characteristics
RM	Risk Minimisation
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
IEC	Independent Ethics Committees
IRB	Institutional Review Board
PASS	Post Authorization Safety Studies
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CI	Confidence Interval
LFTs	Liver Function Tests
VFEND	Voriconazole (medication name)

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Redacted		
		Reda t d

4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
Redacted	

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	15 November 2024	11 November 2024	-
End of data collection	15 February 2025	26 December 2024	-
Registration in the HMA-EMA Catalogues of RWD Studies	10 November 2024	24 October 2024	-
Final report of study results.	30 June 2025	20 June 2025	-

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 *Candida krusei*), and serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. for which voriconazole is authorised for use in 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 will be described in the next local RMP submission, since during the Vfend aRMMs implementation, no local RMP was submitted. 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

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 was designated as a post-authorization safety study (PASS) and is a commitment to the Redacted.

7. RESEARCH QUESTION AND OBJECTIVES

The overall objective of the study was 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 were to:

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

2. Assess HCPs' utilization of the RM tools (i.e., 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 were in accordance with voriconazole SPC (1)

8. AMENDMENTS AND UPDATES

None

9. RESEARCH METHODS

This section presents methods that were employed to evaluate the effectiveness of the aRMMs in Saudi Arabia based on the final protocol (Appendix 2).

9.1. Study design

This was a non-interventional, cross-sectional study to evaluate the effectiveness of RM tools for voriconazole. The study objectives were 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 aimed to obtain completed surveys from 10 HCPs. Data were collected until 10 completed surveys were obtained or up to a data collection period of 60 to 90 days as a maximum. The data from the HCPs were 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 assessed behaviours, including a set of hypothetical scenarios for HCPs. The survey was not intended to be a mechanism for collecting adverse events (AEs), nor was it intended to result in minimizing the numbers of AEs reported. HCPs were invited by e-mail to participate in the survey and were asked to complete the online questionnaire.

Endpoints included:

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

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

3. The proportion of targeted HCPs who responded 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 behaviour with regard to strategies to mitigate the risks.

9.2. Setting

The target population included 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 (distribution list shared

with Saudi Food and Drug Authority [SFDA]) and Redacted of these targeted to receive the RM tools in-person, per Pfizer Inc.'s Distribution List. The selection of targeted HCPs was based on the availability of Vfend® brand at hospitals. Given this relatively small pool of HCPs, an empirical sample size of 10 HCPs was proposed.

HCPs recruitment and survey were conducted by the following process:

- HCPs were invited to participate in the survey by email and/or phone. An email invitation included a web link directing to a webtool named 'Decipher', where the survey questionnaire was available. In the invitation, the survey background and objectives and the contact information for questions were explained to the HCPs. Instructions detailing the survey requirements were displayed at the start of the survey.

- If the HCPs agreed to participate in the survey, they were able access the survey and the instructions for the web questionnaire by clicking on the email link.

- If the questionnaire was not completed in the first attempt, HCPs received a reminder email and/or phone (first reminder) 1 week after the initial invitation.

- If the web questionnaire remained incomplete, a second reminder was sent about 2 weeks after the initial invitation.

- If the questionnaire remained incomplete, a third (and final) reminder was sent 3 weeks after the initial invitation.

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

9.3. Subjects

Inclusion criteria

Participants/ HCPs had to 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.

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

Exclusion criteria

Participants/ HCPs meeting any of the following criteria were excluded from participation in the survey:

1. Employed in full-time research or hospital administration (i.e., non-practicing physicians).

2. Employment by Pfizer Inc or any research organization/vendor contracted by Pfizer to administer the survey.

9.4. 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

9.5. 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) was 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 the evaluation of the effectiveness of the aRMMs.

The questionnaire began 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 was immediately notified with a “thank you” message that survey participation had ended. If eligible, the respondent was 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-month period preceding the survey. Q13

Data pertaining to evaluation of the effectiveness of the aRMMs:

The questionnaire included questions/statements that assess the risk knowledge of the HCPs. The knowledge level analysed using descriptive statistics and confidence intervals (CIs), showcased as the effectiveness of the aRMMs: No formal statistical test was conducted to test 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 behaviour 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 was used for evaluation of the HCP's knowledge.

9.6. Bias

Please refer to section 11.2.

9.7. Study Size

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 were invited to participate in the survey. Given this relatively small pool of HCPs, an empirical sample size of 10 HCPs was proposed. Data were collected until 10 completed surveys were 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 depended on HCPs' willingness to participate in the survey.

9.8. Data transformation

Detailed methodology for data transformations, particularly complex transformations (eg, many raw variables used to derive an analytic variable), are documented in the statistical analysis plan (SAP), which is dated, filed and maintained by the sponsor (Appendix 4).

9.9. Statistical methods

9.9.1. Main summary measures

Detailed methodology for summary and statistical analyses of data collected in this study were documented in the statistical analysis plan (SAP), which was dated, filed and maintained by the sponsor (Appendix 4). Data collected from the survey was reported as descriptive statistics. Frequency distributions with 95% CIs were calculated for HCPs' responses to all questions that address the survey objectives. Confidence intervals were calculated using Clopper-Pearson method.

9.9.2. Main statistical methods

Endpoints

1. Assess HCPs' awareness of the RM tools (i.e., 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 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 was evaluated by estimating the proportion of targeted HCPs whose responses to the practice related questions are consistent with the SPC (1) 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 was considered to assess the success.

An a priori threshold of 80% correct responses per risk question was used to define the success of the program. However, this criterion was 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.

The questions considered complementary were not included in the assessment of success. The details of the assessment of the success for each survey and each objective were 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, SFDA, the percentage of participants responding correctly to the knowledge questions were analysed and discussed (2). The minimum acceptable threshold of knowledge was defined at 80% correct response rate per risk questions.

The distribution of the responses to questions assessing all study objectives were presented in the study report. It is to be noted that the selection of this threshold for success was 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 were contextualized within the context of other available information.

The following were reported as part of the analysis:

<u>Survey administration</u>

- The number of HCPs by selected medical specialties (i.e., infectious disease physicians, pharmacists, as applicable).

- The number of survey invitations issued by strata (i.e., by specialty).

- The number of survey invitations returned due to the incorrect email address of HCPs invited to participate in the survey.

<u>Demographic characteristics of participants</u>

- 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. **HCPs' 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 were distinguished:

- HCPs who did not participate (R): HCPs who did not respond or that explicitly indicated their refusal to participate.
- HCPs with partially answered questionnaires (P): HCPs who clicked on the link provided in the invitation email, and who began answering the questionnaire but never submitted it.

- Failed screening (F): HCPs who were not eligible for the survey (HCPs who didn't meet all inclusion criteria and/or who met any of the exclusion criteria).

- HCPs with completed questionnaire (C): HCPs who completed the entire questionnaire and submitted it.

- Contacted HCPs: HCPs who were contacted by phone or who received a web link to the online survey via email = C+P+R+F.

- HCPs who agreed 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 was examined as follows:

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

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

9.9.3. Missing values

None.

9.9.4. Sensitivity analyses

None.

9.9.5. Amendments to the statistical analysis plan

None.

9.10. Quality control

All surveys were programmed internally using Redac Decipher system, a secure online data collection software. Redac 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. Redac utilized a rigorous quality assurance process which included the following:

- Programmer and researcher manual testing: Manual testing process which included 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 was tested on a stimulator associated with the web browsers.

- Random Data Generation (RDG) and Data Check Edits (DCE): Once testing was completed by both the Redac operations and research teams, a member of the operations team ran a set of randomly generated data ("dummy" data) to fill all possible paths and quotas, then wrote a programmatic check designed to test

the validity of the survey. Each question was tested for the correct number and coding of responses, that respondents answering the questions met the base criteria as well as duplicate any calculated or algorithmic variables and compared for accuracy. An independent member of the operations team then wrote the DCE. The data were 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 was approved, Redacted began fielding with a limited amount of sample designed to recruit 10% of the total quota. The soft launch data was then thoroughly checked utilizing the DCE to ensure programming accuracy.

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

    - Length of survey – survey length was 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 included 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 helped to evaluate a respondent’s level of attention to the survey.

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

9.11. Protection of human subjects

Subject information and consent

Participants needed to go to the survey website to complete the survey. While consent was implied by these actions, the respondent was asked at the beginning of the survey if he/she agrees to take part in the survey. If yes, the respondent continued with the survey questions. If no, the survey was terminated.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

Not applicable.

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 Guideline on GVP Version 3.1 30-January-2023 - Drug Sector, SFDA.

10. RESULTS

10.1. Participants

The study aimed to collect 10 fully completed surveys from healthcare professionals (HCPs) involved in the treatment of patients with Voriconazole. HCP recruitment was conducted competitively, with invitations sent via email and/or phone to HCPs identified as potential prescribers based on Pfizer's distribution list. To be eligible, participants had to have prescribed or managed at least one patient on Voriconazole within the past 12 months and consent to participate. Screening was embedded within the survey to confirm eligibility, and those not meeting inclusion criteria were automatically excluded. Survey invitations contained a web link to the Redacted Decipher platform, where participants could access the questionnaire. Non-responders received up to three reminders at one-week intervals, after which they were considered unreachable. The survey remained open for a maximum of 60–90 days or until 10 fully completed surveys were obtained, per the predefined study stopping criteria.

All responses included in the analysis were complete, and no participants failed screening. Due to the competitive recruitment strategy, the response rate reflects targeted enrolment rather than overall participation among invited HCPs. Table 1

Table 1: Overall Summary of HCP Disposition

Variable descriptions	Overall
Contacted HCPs, n	10
HCPs who agree to participate, n (%)	10 (100)
P: HCPs with partially answered questionnaires, n (%)	0
C: HCPs who completed questionnaire, n (%)	10 (100)
R: HCPs who do not agree to participate, n (%)	0
F: Failed screening, n (%)	0
Response rate	1
Refusal rate	0

HCP = Healthcare Professionals.

Percentages are calculated by using the denominator as number of HCPs contacted.

Response rate = C/(C+P+R); Refusal rate = R/(C+P+R).

10.2. Descriptive data

Among the 10 participating HCPs, 60% (n=6) were based in Jeddah, while the remaining participants were located in Madinah (10%, n=1), Makkah (10%, n=1), Riyadh (10%, n=1), and Tabuk (10%, n=1). Regarding medical specialty, 60% (n=6) were clinical pharmacists, 30% (n=3) specialized in infectious diseases, and 10% (n=1) belonged to another medical specialty. 50% (n=5) of respondents had 6–15 years of experience, while 50% (n=5) had more than 15 years. The number of patients treated with Voriconazole in the past 12 months varied among respondents, with 50% (n=5) treating 1–5 patients, 20% (n=2) treating 6–10 patients, 20% (n=2) treating 11–20 patients, and 10% (n=1) treating more than 20 patients. Table 2

Table 2: HCP's Demographics and Characteristics – Enrolled set

Variable descriptions	Overall (N=10)
HCP's Location, n (%)	
Dahran	0
Dammam	0
Hail	0
Jeddah	6 (60.0)
Jubail	0
Khamis Mushait	0
Khobar	0
Madinah	1 (10.0)
Makkah	1 (10.0)
Najran	0
Qurayat	0
Riyadh	1 (10.0)
Tabuk	1 (10.0)
Taif	0
Other: (Specify)	0
Missing	0
HCP medical specialty type, n (%)	
Critical Care	0
Haematology	0
Infectious diseases	3 (30.0)
Intensive Care	0
Microbiology	0
Oncology	0
Solid Organ Transplant	0
Clinical pharmacist	6 (60.0)
Non-clinical pharmacist	0
Other Subspecialty: (Specify):	1 (10.0)
Other (Specify):	0
Missing	0
How long have you been practicing as an HCP, n (%)	
≤5 years	0
6-15 years	5 (50.0)
>15 years	5 (50.0)
Missing	0

Number of patients that HCP treated with VFEND in past 12 months, n (%)	
1–5	5 (50.0)
6–10	2 (20.0)
11–20	2 (20.0)
>20	1 (10.0)
Missing	0

HCP = Healthcare Professionals.

Percentages are calculated by using the denominator as number of patients with available data.

10.3. Outcome data

The distribution of healthcare professionals (HCPs) across the study outcomes, including awareness of risk minimisation (RM) tools, utilization of these materials in clinical practice, understanding of Voriconazole-associated risks, and self-reported risk mitigation behaviors, is summarized in Tables 3–6. The number of respondents in each category, along with proportions and confidence intervals, are detailed in the respective tables. A comprehensive analysis and interpretation of these findings are provided in Section 10.4 (Main Results).

10.4. Main results

Awareness and Receipt of Risk Minimisation (RM) Tools

Awareness of RM tools varied among respondents. Half of the HCPs (50.0%, n=5, 95% CI: 18.71–81.29) recalled receiving the HCP Q&A Brochure, while 30.0% (n=3, 95% CI: 6.67–65.25) did not receive it, and 20.0% (n=2, 95% CI: 2.52–55.61) could not recall receiving it. Among those who received the brochure, 20.0% (n=1, 95% CI: 0.51–71.64) reported reading it in full, 40.0% (n=2, 95% CI: 5.27–85.34) read part of it, and 40.0% (n=2, 95% CI: 5.27–85.34) could not recall reading it. None of the respondents who received the brochure reported not reading it at all.

The HCP Checklist was received by 20.0% (n=2, 95% CI: 2.52–55.61) of respondents, while 40.0% (n=4, 95% CI: 12.16–73.76) did not receive it, and 40.0% (n=4, 95% CI: 12.16–73.76) could not recall receiving it. Among those who received the checklist, 100.0% (n=2, 95% CI: 15.81–100) read at least part of it, while none reported reading it in full or being unable to recall reading it.

The Patient Alert Card was received by 30.0% (n=3, 95% CI: 6.67–65.25) of HCPs, while 50.0% (n=5, 95% CI: 18.71–81.29) did not receive it, and 20.0% (n=2, 95% CI: 2.52–55.61) could not recall receiving it. Among those who received the Patient Alert Card, 33.3% (n=1, 95% CI: 0.84–90.57) reported reading it in full, while 66.7% (n=2, 95% CI: 9.43–99.16) read part of it. None of the respondents reported not reading the Patient Alert Card or being unable to recall reading it.

Regarding the accessibility of RM tools, 10.0% (n=1, 95% CI: 0.25–44.50) reported obtaining them by downloading from a website, while 90.0% (n=9, 95% CI: 55.50–99.75) did not. No

participants requested additional copies of the RM tools (0%, n=0, 95% CI: 0–30.85). The overall success rate for awareness and receipt of RM tools was 60%. Table 3

Table 3: HCPs' Awareness of the RM tools – Enrolled set

Variable descriptions	Overall (N=10)	Proportion (95% CI)
Did the HCPs receive the VFEND HCP Q&A Brochure, n (%)		
Yes*	5	50.0 (18.71; 81.29)
No	3	30.0 (6.67; 65.25)
Can't remember receiving	2	20.0 (2.52; 55.61)
Did the HCPs read the VFEND HCP Q&A Brochure, n (%)		
Yes, all of it*	1	20.0 (0.51; 71.64)
Yes, some of it*	2	40.0 (5.27; 85.34)
No, did not read	0	0 (0; 52.18)
Can't remember reading	2	40.0 (5.27; 85.34)
Not Applicable	5	
Number of HCPs receiving the VFEND HCP Checklist, n (%)		
Yes*	2	20.0 (2.52; 55.61)
No	4	40.0 (12.16; 73.76)
Can't remember receiving	4	40.0 (12.16; 73.76)
Number of HCPs who read the VFEND HCP Checklist, n (%)		
Yes, all of it*	0	0 (0; 84.19)
Yes, some of it*	2	100 (15.81; 100)
No, did not read	0	0 (0; 84.19)
Can't remember reading	0	0 (0; 84.19)
Not Applicable	8	
Number of HCPs receiving the VFEND Patient Alert Card? n (%)		
Yes*	3	30.0 (6.67; 65.25)
No	5	50.0 (18.71; 81.29)
Can't remember receiving	2	20.0 (2.52; 55.61)
Number of HCPs who read the VFEND Patient Alert Card, n (%)		
Yes, all of it*	1	33.3 (0.84; 90.57)
Yes, some of it*	2	66.7 (9.43; 99.16)
No, did not read	0	0 (0; 70.76)
Can't remember reading	0	0 (0; 70.76)
Not Applicable	7	
Obtained RM tools by downloading from a website, n (%)		
Yes	1	10.0 (0.25; 44.50)
No	9	90.0 (55.50; 99.75)

Requesting additional copies of the VFEND (voriconazole) RM tools, n (%)		
Yes	0	0 (0; 30.85)
No	10	100 (69.15; 100)
Overall success rate	60	

HCP = Healthcare Professionals; CI = Confidence Interval; RM = Risk Minimisation.
Proportions are calculated by using the denominator as number of patients with applicable data.

Confidence interval is calculated using Clopper-Pearson method.
* represents the desired answer for the question asked.
The 'Not Applicable' category is included to show the number of participants for whom the question does not apply.
The overall success rate is the average success rate of the proportion of desired answers for each question in the table.

HCPs' Utilization of the RM tools

The HCP Checklist was reported as always used by 33.3% (n=1) of respondents, while 66.7% (n=2) reported using it sometimes in clinical practice. None of the participants indicated that they never used the checklist. The HCP Q&A Brochure was used sometimes by 60% (n=3) of respondents, whereas 40% (n=2) reported never using it. For utilization of the Patient Alert, 50% (n=2) of those who received it reported using it sometimes, while the remaining 50% (n=2) reported never using it.

Assessment of the perceived usefulness of RM tools showed variations across the different materials. The HCP Checklist was considered very useful by 66.7% (n=2) and somewhat useful by 33.3% (n=1). The HCP Q&A Brochure was rated as very useful by 40% (n=2), somewhat useful by 20% (n=1), and neutral by 40% (n=2). The Patient Alert Card was rated as very useful by 75% (n=3) and somewhat useful by 25% (n=1). The overall success rate for RM tool utilization was 70%. Table 4

Table 4: HCPs' Utilization of the RM tools

Variable descriptions	**Overall (N=10)**	**Proportion (95% CI)**
When treating patients for last 12 months, how often did the HCP used the VFEND HCP Checklist?		
Always*	1	33.3 (0.84; 90.57)
Sometimes*	2	66.7 (9.43; 99.16)
Never	0	0 (0; 70.76)
Not Applicable	7	
When treating patients for last 12 months, how often did the HCP used the VFEND HCP Q&A Brochure?		
Always*	0	0 (0; 52.18)
Sometimes*	3	60.0 (14.66; 94.73)
Never	2	40.0 (5.27; 85.34)

Not Applicable	5	
When treating patients for last 12 months, how often did the HCP distributed and filled the Patient Alert Card?		
Always*	0	0 (0; 60.24)
Sometimes*	2	50.0 (6.76; 93.24)
Never	2	50.0 (6.76; 93.24)
Not Applicable	6	
Use of RM tools		
HCP Checklist		
Not useful	0	0 (0; 70.76)
Somewhat useful	1	33.3 (0.84; 90.57)
No opinion/not sure	0	0 (0; 70.76)
Very useful	2	66.7 (9.43; 99.16)
Extremely useful	0	0 (0; 70.76)
Not Applicable	7	
HCP Q&A Brochure		
Not useful	0	0 (0; 52.18)
Somewhat useful	1	20.0 (0.51; 71.64)
No opinion/not sure	2	40.0 (5.27; 85.34)
Very useful	2	40.0 (5.27; 85.34)
Extremely useful	0	0 (0; 52.18)
Not Applicable	5	
Patient Alert Card		
Not useful	0	0 (0; 60.24)
Somewhat useful	1	25.0 (0.63; 80.59)
No opinion/not sure	0	0 (0; 60.24)
Very useful	3	75.0 (19.41; 99.37)
Extremely useful	0	0 (0; 60.24)
Not Applicable	6	
Overall success rate	70	

HCP = Healthcare Professionals; CI = Confidence Interval; RM = Risk Minimisation.
Proportions are calculated by using the denominator as number of patients with applicable data.
Confidence interval is calculated using Clopper-Pearson method.
* Represents the desired answer to the question asked.
The 'Not Applicable' category is included to show the number of participants for whom the question does not apply.
The overall success rate is the average success rate of the proportion of desired answers for each question in the table.

HCPs' Understanding of Voriconazole-Associated Risks

HCP knowledge of the risks associated with Voriconazole varied across different safety concerns. Phototoxicity was the most recognized risk, with 90.0% (n=9, 95% CI: 55.50–99.75) correctly identifying it, while 10.0% (n=1, 95% CI: 0.25–44.50) were unsure. Hepatic toxicity

was also well recognized, with 80.0% (n=8, 95% CI: 44.39–97.48) correctly identifying it, and 20.0% (n=2, 95% CI: 2.52–55.61) selecting "I don't know." Table 5

Recognition of SCC of the skin as a risk was lower, with only 50.0% (n=5, 95% CI: 18.71–81.29) identifying it correctly, while 30.0% (n=3, 95% CI: 6.67–65.25) stated "No", and 20.0% (n=2, 95% CI: 2.52–55.61) were uncertain. Other conditions, including intestinal perforation, cardiomyopathy, and asthma, were less frequently recognized as incorrect risks, with 20.0% (n=2, 95% CI: 2.52–55.61) identifying intestinal perforation as a risk, 30.0% (n=3, 95% CI: 6.67–65.25) selecting cardiomyopathy, and 0% (n=0) selecting asthma. Table 5

HCP's Knowledge of Voriconazole Treatment and Management Guidelines

All respondents (100%, n=10, 95% CI: 69.15–100) correctly agreed that long-term treatment with Voriconazole (>6 months) should only be considered if the benefits outweigh the risks. Similarly, all HCPs (100%, n=10, 95% CI: 69.15–100) correctly acknowledged that patients experiencing phototoxic reactions should be referred to a dermatologist and multidisciplinary advice should be sought. Table 5

Regarding discontinuation criteria, 80.0% (n=8, 95% CI: 44.39–97.48) correctly stated that Voriconazole should be discontinued if premalignant skin lesions or SCC are identified, while 10.0% (n=1, 95% CI: 0.25–44.50) incorrectly believed it should not be discontinued, and 10.0% (n=1, 95% CI: 0.25–44.50) were unsure. Table 5

All HCPs (100%, n=10, 95% CI: 69.15–100) correctly indicated that hepatic function (AST and ALT) should be evaluated at initiation and during the first month of treatment. Additionally, all respondents (100%, n=10, 95% CI: 69.15–100) agreed that if liver function tests become markedly elevated, Voriconazole should be discontinued unless continued use is justified based on clinical judgment. Table 5

The overall success rate for HCP knowledge of Voriconazole-associated risks and management was 76.4%. Table 5

Table 5: HCPs' Understanding of the risks of phototoxicity, SCC of the skin and hepatic toxicity – Enrolled set

Variable descriptions	Overall (N=10)	Proportion (95% CI)
HCP's answers to the known risks for VFEND as per SPC/PI		
Phototoxicity		
Yes*	9	90.0 (55.50; 99.75)
No	0	0 (0; 30.85)
I Don't Know	1	10.0 (0.25; 44.50)
Intestinal perforation		

Yes	2	20.0 (2.52; 55.61)
No*	5	50.0 (18.71; 81.29)
I Don't Know	3	30.0 (6.67; 65.25)
Squamous cell carcinoma (SCC) of the skin		
Yes*	5	50.0 (18.71; 81.29)
No	3	30.0 (6.67; 65.25)
I Don't Know	2	20.0 (2.52; 55.61)
Asthma		
Yes	0	0 (0; 30.85)
No*	5	50.0 (18.71; 81.29)
I Don't Know	5	50.0 (18.71; 81.29)
Hepatic toxicity		
Yes*	8	80.0 (44.39; 97.48)
No	0	0 (0; 30.85)
I Don't Know	2	20.0 (2.52; 55.61)
Cardiomyopathy		
Yes	3	30.0 (6.67; 65.25)
No*	4	40.0 (12.16; 73.76)
I Don't Know	3	30.0 (6.67; 65.25)
Response given by HCPs for the statements about VFEND Long term treatment (>6 months) with VFEND (voriconazole) should be considered only if the benefits outweigh the potential risks		
True*	10	100 (69.15; 100)
FALSE	0	0 (0; 30.85)
I Don't Know	0	0 (0; 30.85)
If phototoxic reactions occur, multidisciplinary advice should be sought, and the patient should be referred to a dermatologist		
True*	10	100 (69.15; 100)
FALSE	0	0 (0; 30.85)
I Don't Know	0	0 (0; 30.85)
VFEND (voriconazole) should not be discontinued if premalignant skin lesions or skin SCC are identified		
TRUE	1	10.0 (0.25; 44.50)
False*	8	80.0 (44.39; 97.48)
I Don't Know	1	10.0 (0.25; 44.50)

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	0 (0; 30.85)
False*	10	100 (69.15; 100)
I Don't Know	0	0 (0; 30.85)
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*	10	100 (69.15; 100)
FALSE	0	0 (0; 30.85)
I Don't Know	0	0 (0; 30.85)
Overall success rate	76.4	

HCP = Healthcare Professionals; CI = Confidence Interval.
Proportions are calculated by using the denominator as number of patients with applicable data.

Confidence interval is calculated using Clopper-Pearson method.
* represents the desired answer for the question asked.
The overall success rate is the average success rate of the proportion of desired answers for each question in the table.

HCPs' Self-reported practices regarding strategies to mitigate the risks

HCP-reported implementation of precautionary measures for Voriconazole (VFEND) patients varied across different safety domains. Table 6

Precautionary Measures Communicated to Patients Prescribed VFEND

Avoiding exposure to direct sunlight was communicated by 90.0% (n=9, 95% CI: 55.50–99.75) of HCPs, along with the importance of detecting signs and symptoms of phototoxicity (90.0%, n=9, 95% CI: 55.50–99.75). Additional protective measures included covering sun-exposed areas of skin, which was advised by 60.0% (n=6, 95% CI: 26.24–87.84), and using sufficient sunscreen with a high sun protection factor (SPF), communicated by 50.0% (n=5, 95% CI: 18.71–81.29). Regular dermatologic evaluation on a systematic and regular basis was also recommended by 50.0% (n=5, 95% CI: 18.71–81.29).

Monitoring for clinical signs of liver damage, such as jaundice, was communicated by 90.0% (n=9, 95% CI: 55.50–99.75). Other precautionary measures were less frequently communicated. Use with caution in patients with a previous history of intestinal ulceration or

diverticulitis was recommended by 30.0% (n=3, 95% CI: 6.67–65.25). Intensified monitoring of blood glucose levels was advised by only 10.0% (n=1, 95% CI: 0.25–44.50).

Certain precautionary measures were largely overlooked. Regular monitoring of the International Normalized Ratio (INR) was not communicated by any HCPs (0%, n=0, 95% CI: 0–30.85), and 100% (n=10, 95% CI: 69.15–100) did not advise avoiding invasive dental procedures. Table 6

Frequency of HCPs Performing Activities when Initiating Treatment with VFEND

Discussing the contents of the Patient Alert Card was performed by 50.0% (n=2, 95% CI: 6.76–93.24) of HCPs, while the same proportion (50.0%, n=2, 95% CI: 6.76–93.24) did not discuss it. This activity was not applicable to 60.0% (n=6) of HCPs. Advising patients to avoid exposure to direct sunlight and/or use protective measures such as clothing and sunscreen was done by 80.0% (n=8, 95% CI: 44.39–97.48), while 20.0% (n=2, 95% CI: 2.52–55.61) did not provide this advice.

The discussion of specific risks associated with VFEND was less frequent. The risk of lymphoma was not discussed by any of the HCPs (100.0%; n=10, 95% CI: 69.15–100). Similarly, the risk of gastric perforation was discussed by only 20.0% (n=2, 95% CI: 2.52–55.61). Likewise, the risk of amyloidosis was not discussed by any of the HCPs (100.0%; n=10, 95% CI: 69.15–100).

The importance of monitoring risks associated with VFEND use and recognizing serious signs and symptoms warranting immediate medical attention was emphasized by 90.0% (n=9, 95% CI: 55.50–99.75) of HCPs. Table 6

Frequency of Performing Liver Function Tests (LFTs)

At the initiation of VFEND treatment and weekly thereafter for one month, liver function tests were performed by 50.0% (n=5, 95% CI: 18.71–81.29) of HCPs. Meanwhile, 10.0% (n=1, 95% CI: 0.25–44.50) performed LFTs at every contact, 30.0% (n=3, 95% CI: 6.67–65.25) performed them monthly, and 10.0% (n=1, 95% CI: 0.25–44.50) followed other unspecified monitoring schedules. No HCPs indicated that they were unaware of the recommended frequency (0%, n=0, 95% CI: 0–30.85).

If there were no changes in LFTs after one month of VFEND initiation, 70.0% (n=7, 95% CI: 34.75–93.33) of HCPs continued monitoring on a monthly basis, while 30.0% (n=3, 95% CI: 6.67–65.25) followed other monitoring schedules. None of the HCPs monitored LFTs weekly (0%, n=0, 95% CI: 0–30.85), and none reported being uncertain about the frequency (0%, n=0, 95% CI: 0–30.85). Table 6

Frequency of Performing Dermatologic Evaluations

Among HCPs managing patients who continue VFEND despite phototoxicity-related lesions, 20.0% (n=2, 95% CI: 2.52–55.61) performed dermatologic evaluations on a systemic and regular basis, 20.0% (n=2, 95% CI: 2.52–55.61) conducted evaluations monthly, and 10.0% (n=1, 95% CI: 0.25–44.50) performed evaluations every two months. However, half of the

HCPs (50.0%, n=5, 95% CI: 18.71–81.29) reported that they did not know how often dermatologic evaluations should be conducted. None of the HCPs performed these evaluations weekly (0%, n=0, 95% CI: 0–30.85). Table 6

Conditions Leading to Discontinuation of VFEND (Voriconazole) by HCPs

HCPs most frequently chose to discontinue VFEND in patients who developed any of the following conditions: phototoxicity, SCC, and premalignant lesions. This was reported by 80.0% (n=8, 95% CI: 44.39–97.48) of HCPs. Discontinuation due to SCC only was reported by 10.0% (n=1, 95% CI: 0.25–44.50), while another 10.0% (n=1, 95% CI: 0.25–44.50) of HCPs chose to discontinue VFEND only due to premalignant lesions alone. Table 6

Overall Success Rate

The reported overall success rate of VFEND treatment, considering both safety and effectiveness, was 75.5%.Table 6

Table 6: HCPs' Self-reported practices regarding strategies to mitigate the risks

Variable descriptions	Overall (N=10)	Proportion (95% CI)
Precautionary measures communicated to the patients for whom the HCP have prescribed VFEND		
Avoiding exposure to direct sunlight		
Checked*	9	90.0 (55.50; 99.75)
Unchecked	1	10.0 (0.25; 44.50)
Detecting signs and symptoms of phototoxicity		
Checked*	9	90.0 (55.50; 99.75)
Unchecked	1	10.0 (0.25; 44.50)
Use with caution in patients with previous history of intestinal ulceration or diverticulitis		
Checked	3	30.0 (6.67; 65.25)
Unchecked*	7	70.0 (34.75; 93.33)
Dermatologic evaluation should be performed on a systematic and regular basis		
Checked*	5	50.0 (18.71; 81.29)
Unchecked	5	50.0 (18.71; 81.29)
Intensified monitoring of blood glucose level		
Checked	1	10.0 (0.25; 44.50)
Unchecked*	9	90.0 (55.50; 99.75)
Covering sun exposed areas of skin		

Checked*	6	60.0 (26.24; 87.84)
Unchecked	4	40.0 (12.16; 73.76)
Use sufficient sunscreen with high sun protection factor (SPF)		
Checked*	5	50.0 (18.71; 81.29)
Unchecked	5	50.0 (18.71; 81.29)
Clinical signs of liver damage, such as jaundice that warrant contacting the doctor immediately		
Checked*	9	90.0 (55.50; 99.75)
Unchecked	1	10.0 (0.25; 44.50)
International Normalized Ratio regular monitoring		
Checked	0	0 (0; 30.85)
Unchecked*	10	100 (69.15; 100)
Avoid invasive dental procedures		
Checked	0	0 (0; 30.85)
Unchecked*	10	100 (69.15; 100)
Frequency of HCP performing activities when initiating treatment with VFEND		
Discuss contents of the Patient Alert Card		
Yes*	2	50.0 (6.76; 93.24)
No	2	50.0 (6.76; 93.24)
Not Applicable	6	
Advise patient to avoid exposure to direct sunlight and/or to use measures such as protective clothing and sunscreen		
Yes*	8	80.0 (44.39; 97.48)
No	2	20.0 (2.52; 55.61)
Not Applicable	0	
Discuss risk of lymphoma		
Yes	0	0 (0; 30.85)
No*	10	100 (69.15; 100)
Not Applicable	0	
Discuss risk of gastric perforation		
Yes	2	20.0 (2.52; 55.61)
No*	8	80.0 (44.39; 97.48)
Not Applicable	0	

Advise patient of importance of monitoring risks of VFEND (voriconazole) use and signs and symptoms of serious risks that warrant contacting doctor immediately		
Yes*	9	90.0 (55.50; 99.75)
No	1	10.0 (0.25; 44.50)
Not Applicable	0	
Discuss risk of amyloidosis		
Yes	0	0 (0; 30.85)
No*	10	100 (69.15; 100)
Not Applicable	0	
Frequency of performing Liver Function Tests		
At VFEND (voriconazole) treatment initiation and weekly thereafter for one month*	5	50.0 (18.71; 81.29)
At every contact	1	10.0 (0.25; 44.50)
Monthly	3	30.0 (6.67; 65.25)
Other (Specify):	1	10.0 (0.25; 44.50)
I do not know	0	0 (0; 30.85)
If there are no changes in Liver Function Tests (LFTs) after one month of initiation of VFEND (voriconazole), how often does the HCP monitor liver function during VFEND treatment maintenance		
Weekly	0	0 (0; 30.85)
Monthly*	7	70.0 (34.75; 93.33)
Other (Specify):	3	30.0 (6.67; 65.25)
I do not know	0	0 (0; 30.85)
How often does the HCP perform a dermatologic evaluation when VFEND (voriconazole) is continuously used despite the occurrence of phototoxicity related lesions		
Weekly	0	0 (0; 30.85)
Monthly	2	20.0 (2.52; 55.61)
Every two months	1	10.0 (0.25; 44.50)
On systemic and regular basis*	2	20.0 (2.52; 55.61)
I do not know	5	50.0 (18.71; 81.29)
The condition HCP choose to discontinue VFEND (voriconazole) in a patient		
Phototoxicity	0	0 (0; 30.85)
Squamous Cell Carcinoma (SCC)	1	10.0 (0.25; 44.50)
Premalignant lesions	1	10.0 (0.25; 44.50)

All of the above*	8	80.0 (44.39; 97.48)
Overall success rate	75.5	

HCP = Healthcare Professionals; CI = Confidence Interval.

Proportions are calculated by using the denominator as number of patients with applicable data.

Confidence interval is calculated using Clopper-Pearson method.

* Represents the desired answer for the question asked.

The 'Not Applicable' category is included to show the number of participants for whom the question does not apply.

The overall success rate is the average success rate of the proportion of desired answers for each question in the table.

10.5. Other analyses

None.

10.6. Adverse events/adverse reactions

None.

11. DISCUSSION

11.1. Key results

Awareness and Receipt of Risk Minimisation (RM) Tools

Only 50.0% (n=5, 95% CI: 18.71–81.29) of HCPs received the HCP Q&A Brochure, 30.0% (n=3, 95% CI: 6.67–65.25) did not, and 20.0% (n=2, 95% CI: 2.52–55.61) could not recall receiving it. The HCP Checklist was received by only 20.0% (n=2, 95% CI: 2.52–55.61), while 40.0% (n=4, 95% CI: 12.16–73.76) either did not receive or could not recall receiving it. Similarly, 30.0% (n=3, 95% CI: 6.67–65.25) of HCPs received the Patient Alert Card, while 50.0% (n=5, 95% CI: 18.71–81.29) did not. Most HCPs (90.0%, n=9, 95% CI: 55.50–99.75) did not download RM tools from a website, and none requested additional copies. These findings indicate limited dissemination and accessibility of RM tools, which may impact their integration into clinical practice.

Utilization of RM Tools

The extent to which RM tools were utilized in clinical practice varied. The HCP Checklist was always used by 33.3% (n=1) of HCPs and sometimes used by 66.7% (n=2), while none reported never using it. The HCP Q&A Brochure was sometimes used by 60.0% (n=3, 95% CI: 14.66–94.73), while 40.0% (n=2, 95% CI: 5.27–85.34) never used it. Similarly, the Patient Alert Card was used sometimes by 50.0% (n=2, 95% CI: 6.76–93.24) and never used by the remaining 50.0% (n=2, 95% CI: 6.76–93.24). These results highlight gaps in RM tool utilization, suggesting that even when tools were received, they were not consistently incorporated into practice.

HCP Knowledge of VFEND-Associated Risks

HCPs demonstrated high awareness of phototoxicity (90.0%, n=9, 95% CI: 55.50–99.75) and hepatic toxicity (80.0%, n=8, 95% CI: 44.39–97.48). However, awareness of SCC was lower (50.0%, n=5, 95% CI: 18.71–81.29), with 30.0% (n=3, 95% CI: 6.67–65.25) responding incorrectly and 20.0% (n=2, 95% CI: 2.52–55.61) uncertain. Other potential risks, including intestinal perforation (20.0%), cardiomyopathy (30.0%), and asthma (0.0%), were infrequently recognized. These findings highlight a gap in SCC awareness and underscore the need for enhanced education and risk communication strategies.

HCP-Reported Risk Mitigation Practices

Photoprotection measures were commonly advised. 90.0% (n=9, 95% CI: 55.50–99.75) of HCPs recommended avoiding direct sunlight and monitoring for phototoxicity symptoms. Additional protective measures, such as covering sun-exposed areas and using high-SPF sunscreen, were recommended by 60.0% (n=6, 95% CI: 26.24–87.84) and 50.0% (n=5, 95% CI: 18.71–81.29), respectively. Liver function monitoring was advised by 90.0% (n=9, 95% CI: 55.50–99.75). However, only 30.0% (n=3, 95% CI: 6.67–65.25) advised caution in patients with prior gastrointestinal conditions, and none regularly monitored INR or advised avoiding invasive dental procedures. These findings suggest strong emphasis on photoprotection and hepatic monitoring but inadequate attention to other potential risks.

VFEND Discontinuation Criteria

Treatment discontinuation was reported to be done due to multiple risk factors. 80.0% (n=8, 95% CI: 44.39–97.48) of HCPs discontinued VFEND when either phototoxicity, SCC, or premalignant lesions were present. 10.0% (n=1, 95% CI: 0.25–44.50) chose SCC only, and another 10.0% (n=1, 95% CI: 0.25–44.50) chose only premalignant lesions as a reason for discontinuation.

Overall Success Rate and Implications

The overall success rate for risk minimisation practices was 75.5%, reflecting good awareness of key risks but gaps in SCC recognition, RM tool utilization, and discontinuation criteria. Future strategies should focus on improving RM tool dissemination and use, increasing SCC-related education, and reinforcing specific monitoring recommendations (e.g., INR, gastrointestinal risks) to enhance patient safety and optimize VFEND’s risk-benefit balance.

11.2. Strengths and limitations of the research methods

This study provides valuable insights into the effectiveness of additional risk minimisation measures (aRMMs) for voriconazole; however, several limitations must be acknowledged when interpreting the findings.

Selection Bias

Selection bias was a key limitation, as participation in the survey was voluntary. HCPs with greater awareness of voriconazole-associated risks may have been more likely to respond, potentially leading to an overestimation of overall knowledge and engagement with risk minimisation measures. Additionally, non-response bias may have occurred due to factors

such as email filtering that blocked unsolicited messages, multiple email addresses where the invitation may not have reached the primary inbox, or infrequent email checking, causing some HCPs to miss the survey during the recruitment period. There is also a possibility that some targeted HCPs did not receive the mailed survey invitations, further limiting participation. The limited sample size reduced the ability to capture a more representative assessment of risk awareness (3).

Information Bias

Information biases, particularly recall bias and social desirability bias, may have influenced the study findings. Recall bias could have led to underreporting awareness and engagement with aRMMs, as participants may not have accurately remembered receiving or reading risk minimisation materials. To mitigate this, only HCPs who prescribed or dispensed voriconazole in the past 12 months were included in the study.

Social desirability bias was also a concern, as respondents may have provided answers, they believed were expected rather than reflecting their actual knowledge or behavior. This issue is particularly relevant in web-based surveys, where HCPs could have searched for answers or copied information from external sources instead of relying on their existing knowledge (4–6).

To minimize these biases, the study used prepopulated questionnaire items and strict access control measures, ensuring that only invited participants could complete the survey once. A traceability system was also implemented to prevent multiple responses from the same individual or external stakeholders attempting to influence the results.

Lack of Baseline (Pre-aRMM) Data

Another major limitation is the absence of baseline (pre-aRMM) data, preventing a direct comparison of HCP knowledge and behaviors before and after the implementation of risk minimisation measures. Without a pre-intervention reference point, it is difficult to quantify the direct impact of aRMMs. A pre-post study design or longitudinal assessment would have strengthened the ability to draw conclusions regarding aRMM effectiveness (7).

Threshold for Success

The study defined success as achieving 80% correct responses per risk question; however, this threshold was not based on established scientific evidence or validated risk communication literature. As acknowledged by the European Medicines Agency (EMA), there is no universal standard for defining success in aRMM evaluations, and knowledge levels may vary depending on the complexity of the risk message, the clinical setting, and HCP specialty. A review of similar aRMM evaluation surveys in the EU PAS Register found that only 2 of 11 cross-sectional surveys applied an 80% success benchmark, suggesting that success criteria should be more rigorously defined and evidence-based (3,8).

Lack of Direct Assessment of Patient Outcomes

While the study measured HCP awareness and self-reported practices, it did not assess whether these efforts translated into improved patient safety. The effectiveness of aRMMs should ideally be evaluated by tracking real-world patient outcomes, such as monitoring adherence to liver function testing, dermatologic evaluations, and sun protection recommendations. Without these data, it remains unclear whether increased HCP awareness leads to meaningful risk reduction for patients.

Need for Alternative Methodologies and Real-World Data Integration

Survey-based evaluations, while valuable for assessing knowledge and engagement, have inherent limitations in measuring actual behavior change. Real-world data sources should be leveraged to provide more objective measures of aRMM effectiveness. Electronic health record (EHR) audits could determine whether HCPs are adhering to risk minimisation recommendations, such as ordering liver function tests or referring patients for dermatologic evaluations. Prescription data analysis could assess whether prescribers are making risk-based dose adjustments for voriconazole, while observational studies tracking patient safety outcomes would help determine whether risk minimisation efforts lead to tangible improvements in clinical care (9–11).

The study results must be interpreted in the light of the limitations described above including variability and uncertainty of the data and methods.

11.3. Interpretation

Utilization and Engagement with aRMMs

In our study, 50% of HCPs reported receiving the Q&A Brochure, but only 20% read it fully. Similarly, 33.3% of HCPs consistently used the HCP Checklist. Additionally, engagement with RM tools was also limited, with only 33.3% of HCPs consistently using the HCP Checklist and 50% utilizing the Patient Alert Card on an occasional basis. These findings raise critical concerns regarding the effectiveness of current risk communication strategies and highlight persistent gaps in the implementation of safety measures.

The findings from this study align with those from the EU evaluation of voriconazole aRMMs, which reported low engagement with RM tools (12). In the EU study A1501103(EU PAS registration number: EUPAS12624), only 19.6% of HCPs recalled receiving the Q&A Brochure, and 22.6% recalled receiving the Checklist, suggesting that a large proportion of prescribers either never received these materials or did not recognize their significance. Although our study reported a slightly higher rate of recall and utilization compared to the EU study, the rates remain insufficient to ensure consistent risk communication. A common finding across both studies is that awareness of RM tools does not necessarily translate to their active use.

Multiple factors may have contributed to the limited use of aRMMs. Time constraints and competing clinical priorities are key challenges, as HCPs often prioritize urgent patient care over reviewing additional RM materials (13). This issue is exacerbated by the perception that many of these materials provide redundant information already covered in SmPCs and clinical guidelines or their perception as promotional material which leads to them being deprioritized

(14). Additionally, the passive distribution of RM tools without structured engagement strategies reduces their perceived relevance and likelihood of utilization (7).

The limited engagement with aRMMs is not unique to voriconazole, as similar trends have been observed with other pharmacological agents, including apixaban and aripiprazole. Despite moderate awareness of these risk minimisation tools, their implementation in clinical practice remains inconsistent. For instance, studies on apixaban have demonstrated that while HCPs who received the Prescriber Guide generally acknowledged its utility, a substantial proportion reported not receiving or actively utilizing the material (15). Similarly, evaluations of aripiprazole's aRMMs indicate that although many HCPs were aware of the available resources, their integration into routine patient management was suboptimal (16). These findings highlight a persistent gap between awareness and practical application, underscoring the need for more effective dissemination strategies and structured engagement initiatives to enhance the utilization of aRMMs in clinical settings.

Effectiveness of aRMMs

Among surveyed healthcare professionals, awareness of phototoxicity (90%) and hepatotoxicity (80%) remained high despite limited receipt of aRMM tools. However, knowledge of the risk of SCC was substantially lower (50%), indicating a gap in risk awareness. This mirrors findings from the evaluations of voriconazole's aRMMs in the EU, where SCC awareness was also disproportionately low (44.3%) compared to other adverse effects (12). This suggests that SCC remains underrecognized across different healthcare settings, possibly due to its delayed onset relative to more immediate adverse effects like phototoxicity and hepatic toxicity. Unlike phototoxicity, which can manifest within weeks of voriconazole exposure, SCC may take months or years to develop, leading to a lower perceived urgency among prescribers (17). Additionally, SCC was incorporated into the SmPC at a later stage than other adverse effects, potentially contributing to its reduced emphasis in prescriber education.

The effectiveness of aRMMs in enhancing HCPs' knowledge and behavior has been evaluated in various studies. A review of Post-Authorization Safety Studies (PASS) indicated that 62.4% aimed to measure HCPs' awareness, knowledge, and behavior regarding risk minimisation measures. However, nearly 40% of these studies did not render a conclusion on the effectiveness of the risk minimisation measures, suggesting a need for more robust assessment methods (3). These findings underscore the necessity for improved dissemination strategies and structured engagement initiatives to enhance the utilization of aRMMs in clinical settings. Emphasizing early counseling, regular dermatologic evaluations, and providing clear guidance on preventive measures -such as sun protection and routine skin checks- are critical steps to mitigate the risk of SCC associated with voriconazole therapy.

Strengthening Risk Minimisation Strategies

Given these challenges, future risk minimisation efforts should prioritize proactive, integrated, and data-driven approaches. Digital integration of RM tools into clinical workflows is a promising strategy. Embedding risk reminders into electronic prescribing (e-prescribing) systems and clinical decision support alerts could enhance engagement by ensuring that safety information is encountered at the point of care. Such integration has been shown to improve adherence to safety protocols in other therapeutic areas.

Mandatory continuing medical education (CME) programs should incorporate risk minimisation training to ensure that prescribers receive structured, up-to-date education on voriconazole-associated risks. Traditional printed brochures may not be the most effective means of risk communication, as our study found that only 20% of HCPs fully read the voriconazole Q&A Brochure. More concise and targeted communication strategies should be explored, such as one-page summaries, infographics, video-based educational content, and interactive case studies, which are more likely to engage HCPs effectively.

Addressing the SCC awareness gap is particularly crucial. SCC remains an underrecognized adverse effect of voriconazole, and efforts should be made to emphasize SCC risk and the importance of dermatologic monitoring. Routine dermatologic evaluations should be recommended, particularly for long-term voriconazole users. In addition, patient-facing educational materials should be improved to provide clearer guidance on sun protection measures, early SCC detection, and when to seek medical attention.

Given these challenges, future risk minimisation efforts should prioritize proactive, integrated, and data-driven approaches. Integrating risk minimisation tools into clinical workflows, such as embedding risk reminders into electronic prescribing (e-prescribing) systems and clinical decision support alerts, can enhance engagement by ensuring that safety information is encountered at the point of care (18). This integration has been shown to improve adherence to safety protocols in other therapeutic areas.

Continuing medical education (CME) programs should incorporate risk minimisation training to provide prescribers with structured, up-to-date education on voriconazole-associated risks. More concise and targeted communication strategies, such as one-page summaries, infographics, video-based educational content, and interactive case studies, may be more likely to engage healthcare professionals effectively.

11.4. Generalizability

The generalizability of this study is limited to HCPs who were reachable, willing to participate, and met the inclusion criteria. Since participation was voluntary, the study population may not fully represent all HCPs prescribing or dispensing voriconazole, potentially overestimating awareness levels. Inclusion was restricted to HCPs who prescribed or dispensed voriconazole in the past 12 months, ensuring recent experience but excluding those who used it outside this timeframe or influenced prescribing decisions indirectly. The online format also limited participation to those with digital access. Differences in knowledge levels between participants and non-participants could have introduced further bias, and the small sample size limited the ability to conduct meaningful subgroup or stratified analyses. Variability in knowledge across HCP specialties, clinical practices, and key risk messages may not have been fully captured due to these sample size constraints.

These factors may have affected external validity, as differences in knowledge across specialties, regions, and practice settings may not have been fully captured. The study's conclusions should be interpreted with these constraints in mind.

12. OTHER INFORMATION

Not Applicable

13. CONCLUSIONS

This study evaluated the effectiveness of additional risk-minimization measures (aRMMs) for Voriconazole (VFEND®) in Saudi Arabia. While awareness of phototoxicity (90%) and hepatic toxicity (80%) was high among healthcare professionals (HCPs), recognition of squamous cell carcinoma (SCC) of the skin as a risk was notably lower (50%), mirroring findings from the EU study A1501103 (EUPAS12624). Moreover, although 60% of HCPs confirmed receipt of the aRMM toolkit, actual utilization of the HCP Checklist, Q&A Brochure, and Patient Alert Card was suboptimal, and patient counselling did not fully align with guideline recommendations.

In Europe, the EMA's PASS programs (A1501102 and A1501103) assessed downstream safety outcomes and found no clear, attributable benefit from continued HCP-focused materials; prompting removal of the Checklist and Brochure, and retention of only the Patient Alert Card in EU RMP v6.3 (Part V.2, approved 28 September 2023). However, our Saudi study addresses the critical upstream issue of tool uptake and risk awareness where significant gaps persist, and which may mask any downstream impact on adverse event rates. Accordingly, we recommend that Saudi regulators maintain all three aRMM components in active circulation while piloting simple digital reminders and periodic, case-based audits to reinforce core safety messages and drive consistent tool uptake. Such targeted interventions could help close knowledge gaps; especially around SCC; and achieve regional benchmarks of HCP awareness and consistent utilization, after which a phased alignment with the EMA's streamlined EU approach may be appropriate. Moving forward, structured educational programs, tighter integration of risk-minimization materials into clinical workflows, and more streamlined communication channels should be prioritized to sustain HCP engagement and ensure the safe, effective use of voriconazole in routine practice.

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15. LIST OF SOURCE TABLES AND FIGURES

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