Appendix 1.4. Health Care Professional Checklist for Phototoxicity, Squamous Cell Carcinoma of the Skin and Hepatic Toxicity

VFEND® (voriconazole) Healthcare Professional Checklist

Please complete this Checklist at each visit with your patient when treatment with VFEND® (voriconazole) is being initiated or reviewed. 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 voriconazole 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?** ***If YES*, please refer to the Summary of Product Characteristics (SmPC) for guidance.**	YES ☐	NO ☐
☐	**Have you arranged regular dermatologic evaluation for the patient if he/she presented with phototoxicity?** ***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.**	YES ☐	NO ☐
☐	**In case of phototoxicity, did you consider discontinuing treatment with VFEND?** ***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.**	YES ☐	NO ☐
☐	**In case of premalignant skin lesions or SSC, did you discontinue treatment with VFEND?** ***If NO*, VFEND should be discontinued. Please refer to the SmPC for further advice.**	YES ☐	NO ☐

B) Important Information Regarding VFEND and Liver Function Monitoring

- Patients receiving VFEND must be carefully monitored for hepatic toxicity.
  - Clinical management should include laboratory evaluation of hepatic function (specifically AST and ALT) at the initiation of treatment with VFEND and at least weekly for the first month of treatment. If there are no changes in these liver function tests (LFTs) after one month, monitoring frequency can be reduced to monthly.
  - If the LFTs become markedly elevated, VFEND should be discontinued, unless the medical judgment of the risk-benefit balance of the treatment for the patient justifies continued use.
  - There are limited data on the safety of VFEND in patients with abnormal LFTs (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [AP], or total bilirubin >5 times the upper limit of normal).
  - VFEND has been associated with elevations in LFTs and clinical signs of liver damage, such as jaundice, and must only be used in patients with severe hepatic impairment if the benefit outweighs the potential risk.
  - It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving VFEND.
  - VFEND has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).
  - 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 voriconazole and use of alternative antifungal agents must be considered.

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

- ☐ **Have you recently checked liver function test (LFT) results for your patient?** YES ☐ NO ☐
  ***If YES*, use these results to closely monitor hepatic drug toxicity. Please refer to the Summary of Product Characteristics (SmPC) for guidance.**
- ☐ **Does your patient have hepatic cirrhosis?** YES ☐ NO ☐
  ***If YES*, dose adjustment is advised. Please refer to the SmPC for details.**
- ☐ **Have you arranged for routine monitoring of LFTs for your patient at least weekly for the first month of treatment while he/she is receiving treatment with VFEND?** YES ☐ NO ☐
  ***If YES*, please refer to the SmPC for further details.**
  ***If NO*, routine monitoring should be arranged promptly. Please refer to the SmPC for further details.**

C) Discussion with Your Patient

Regarding phototoxicity and skin SCC

- ***Have you discussed*** the risks of phototoxicity and skin SCC with VFEND and the need for regular dermatological evaluation (if phototoxicity occurs)? YES ☐ NO ☐
- ***Have you discussed*** the need to avoid sunlight and sun exposure (including use of protective clothing and sufficient sunscreen with high sun protective factor [SPF]) during treatment with VFEND? YES ☐ NO ☐
- ***Have you discussed*** the signs and symptoms of phototoxicity that warrant contacting the doctor immediately? YES ☐ NO ☐
- ***Have you given*** the patient a **Patient Alert Card** that was provided to you in the package? YES ☐ NO ☐
- ***Have you discussed*** with caregivers/parents of your paediatric patients, who experience photoaging injuries, the need to avoid all sun exposure and have follow-up dermatologic evaluations even after VFEND treatment is discontinued? YES ☐ NO ☐

Regarding hepatotoxicity

- ***Have you discussed*** the risk of liver toxicity with VFEND and the need for periodic monitoring of liver function? YES ☐ NO ☐
- ***Have you discussed*** the signs and symptoms of liver injury that warrant contacting the doctor immediately? YES ☐ NO ☐

Please retain the completed checklist in patient's medical record.

Please report any suspected adverse drug reactions related to VFEND in the usual way.

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Appendix 1.5. Patient Alert Card for Phototoxicity and Squamous Cell Carcinoma of the Skin

This card contains **important safety information** you need to be aware of before you are given VFEND for prevention of fungal infections or during treatment with VFEND for your fungal infection.

If you do not understand this information, please ask your doctor to explain it to you.

Show this card to any doctor or healthcare professional involved in your care.

See the VFEND package leaflet for more information.

VFEND®
(voriconazole)

Patient Alert Card

Please carry this card with you at all times

Other information (please complete):

Your name:

Date VFEND first prescribed:

Treating doctor's name:

Treatment centre name:

Treatment centre phone number:

You should avoid exposure to direct sunlight during VFEND treatment. It is important to cover sun- exposed areas of skin and use sufficient sunscreen with high sun protection factor (SPF), as an increased sensitivity of skin to the sun's UV rays can occur. There is a small chance that skin cancer could develop over time.

You should contact your doctor if you experience:
sunburn or severe skin reaction following exposure to light or sun

Please ensure you **undergo all follow-up visits** for blood tests or skin evaluations arranged by your doctor. Please have a list of all your other medicines and medical conditions available at each visit to a healthcare professional.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

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

Study reference number:

Protocol # A1501102

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	11
1.1.2 End of data collection[2]	☒	☐	☐	11
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	11

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1.6 Final report of study results.	☒	☐	☐	11

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8, 14
2.1.2 The objective(s) of the study?	☒	☐	☐	8, 14
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9, 15
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (eg, cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	9, 15
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☒	☐	
3.3 Does the protocol describe the measure(s) of effect? (eg, relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	15-16
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	14
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	15
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	16

Comments:

The study population is healthcare professionals only; no patients.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (eg, operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (eg, precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (eg, current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

This protocol is a HCP survey to evaluate the effectiveness of risk minimisation measures without patient paticipation with no medical intervention.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☒	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (eg, collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (eg, collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	
8.1.2 Endpoints? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
8.1.3 Covariates?	☐	☐	☒	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
8.2.2 Endpoints? (eg, date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	20-
8.2.3 Covariates? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
8.3 Is a coding system described for:				
8.3.1 Diseases? (eg, International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (eg, Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (eg, based on a unique identifier or other)	☒	☐	☐	18

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	19-20

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	21
10.4 Are stratified analyses included?	☒	☐	☐	21
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect				

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
modification?	☐	☐	☒	

Comments:

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.

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	18-19
11.3 Are methods of quality assurance described?	☒	☐	☐	23
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	23

Comments:

For point 11.1, the design of the EDC system is such that respondents must complete each answer before advancing so there should not be missing data.

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	24
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (eg, sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	24
12.3 Does the protocol address other limitations?	☒	☐	☐	23-24

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	25
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	24

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	11

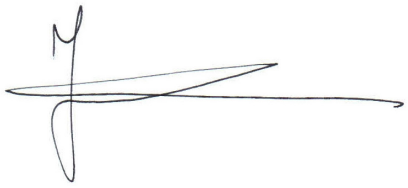
Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	26
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	26

Comments:

Name of the main author of the protocol: __Joanna (Asia) Lem, MPH_____

Date: 08/07/2015

Signature: 

ANNEX 3. ADDITIONAL INFORMATION

Not applicable