Voriconazole Healthcare Professional Question & Answer Brochure

1. What is the purpose of this brochure?

These questions and answers (Q&A's) are provided by generic medicine manufacturers for prescribers and other healthcare professionals (HCPs) involved in the treatment of patients with Voriconazole.

This document will enable you to:

- Understand what Voriconazole is used for and how it should be used
- Be aware of important identified risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity adverse reactions of Voriconazole and how they should be mitigated and managed
- Understand what other tools are available to communicate and remind patients of these risks
- Provide important safety information to patients

Please also familiarise yourself with the complete Summary of Product Characteristics (SmPC), which can be obtained for each generic company as listed in the accompanying covering letter before prescribing or dispensing Voriconazole.

2. What is Voriconazole?

Voriconazole is a broad spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:

- Treatment of invasive aspergillosis.
- Treatment of candidemia in non-neutropenic patients.
- Treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei).
- Treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp.

Voriconazole should be administered primarily to patients with progressive, possibly life-threatening infections.

Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

3. What should I know about phototoxicity and skin squamous cell carcinoma risk associated with Voriconazole?

Voriconazole has been associated with phototoxicity reactions.
Squamous cell carcinoma of the skin has also been reported in patients receiving Voriconazole, some of whom have reported prior phototoxic reactions.

4. What should I know about patient management to minimise the risk of phototoxicity and squamous cell carcinoma with Voriconazole?

All patients, including children, and their parents or caregivers, should be educated about avoiding exposure to direct sunlight during Voriconazole treatment and using measures such as protective clothing and sufficient sunscreen with high sun protection factor (SPF).

Patients should be asked to inform you immediately of the occurrence of sunburn or severe skin reaction following exposure to light or sun.

If phototoxic reactions occur, multidisciplinary advice (e.g., a consultation with a dermatologist) should be sought for the patient. Voriconazole discontinuation and use of alternative antifungal agents should be considered.

Dermatological evaluation should be performed on a systematic and regular basis, whenever Voriconazole is continued despite the occurrence of phototoxicity-related lesions to allow early detection and management of premalignant lesions. Voriconazole treatment should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified.

Squamous cell carcinoma of the skin has been reported in relation with long-term Voriconazole therapy.

Treatment duration with Voriconazole 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 Voriconazole.

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.

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.

5. What do I need to know about the hepatic risk associated with Voriconazole?

Voriconazole has been associated with hepatic toxicity. In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with voriconazole (including clinical hepatitis, cholestasis, and fulminant hepatic failure including fatalities).

Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly haematological malignancy).

Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors.

Liver dysfunction has usually been reversible on discontinuation of therapy.

6. What are the knowledge and the recommendations regarding patients with hepatic impairment?

There are limited data on the safety of Voriconazole in patients with abnormal liver function tests (LFTs) (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [AP], or total bilirubin >5 times the upper limit of normal [ULN]).

Patients with hepatic impairment must be carefully monitored for drug toxicity. In patients with severe hepatic impairment, Voriconazole must only be used if the benefit outweighs the potential risk.

In patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving Voriconazole, it is recommended that the standard loading dose regimens be used but that the maintenance dose be halved. Voriconazole has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

7. What should I know about safety monitoring to minimise the hepatotoxicity risk of Voriconazole?

Both children and adult patients receiving Voriconazole 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 Voriconazole and at least weekly for the first month of treatment.**

Treatment should be as short as possible. However, if based on the benefit-risk assessment the treatment is continued, and if there are no changes in the LFTs, monitoring frequency can be reduced to monthly.

If the LFTs become markedly elevated, Voriconazole use should be discontinued, unless medical judgment of the risk-benefit of the treatment justifies continued use.

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.

8. What tools are available to help me for the monitoring of my patients?

THE HCP CHECKLIST

The HCP Checklist is a recommended tool. It is designed to help you evaluate and discuss the risks of phototoxicity, SCC of the skin and hepatic toxicity with your patients before prescribing Voriconazole. This will remind you to closely monitor patients who develop phototoxicity and to refer them for regular dermatological consultation to minimise the risk of developing SCC of the skin, as well as to monitor liver function at the initiation of, and on a regular basis during Voriconazole treatment.

The completed checklist can be included within the patient chart to document that the patient has been informed of these risks. If other members of your team, such as junior doctors and specialist nurses, are involved in prophylaxis use or treating patients with severe fungal infections, the checklist is a useful educational aid.

THE PATIENT ALERT CARD

The Patient Alert Card is a card, which helps to remind patients about the need for dermatological evaluations on a regular basis (if phototoxic reactions occur). It also urges the patient to report phototoxic symptoms that increase the risk of SCC of the skin.

Additionally, it reminds patients:

- To avoid exposure to sunlight
- To use protective clothing and sufficient sunscreen with high sun protective factor (SPF)
- To inform their doctor if they develop sunburn or severe skin reactions

You are encouraged to fill in your contact details on the Patient Alert Card and give it to each patient receiving Voriconazole treatment. Patients should be encouraged to carry this card during their daily activities. If you need additional copies of the HCP Checklist or the Patient Alert Card, please contact the generic medicines manufacturers listed in the accompanying covering letter.

9. What should I discuss with my patient?

Your role in educating patients about their treatment and its potential adverse effects is very important.

You will need to inform patients about:

- Important phototoxicity, SCC of the skin, and hepatic risks associated with Voriconazole
- The need for dermatological evaluation in case of phototoxicity and regular follow- up afterwards
- The need for patients (including children) to avoid exposure to direct sunlight during Voriconazole treatment and to use measures such as protective clothing and sufficient sunscreen with high SPF.
- The need for patients to inform you immediately of the occurrence of sunburn or severe skin reaction following exposure to light or sun
- The need for liver function tests on a regular basis
- The need for patients to recognize symptoms and signs of liver toxicity (jaundice, unexplained vomiting, stomach pain, dark urine) and to report to you immediately.

You should give the patient a Voriconazole **Patient Alert Card**, which reinforces the important risk of phototoxicity and skin SCC associated with Voriconazole treatment, and advise the patient to carry this card during their daily activities.

You should also remind the patient about this important safety information regularly during their treatment with Voriconazole.

10. Where can I obtain further information?

For further information please contact the generic medicines manufacturers listed in the accompanying covering letter.

11. How do I report Adverse Reactions/Events?

It is important that you promptly report any adverse reactions associated with Voriconazole to assist in fully characterising the product's safety profile.

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to;
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000
E: postlicensing.medicinesauthority@gov.mt

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported to the Marketing Authorization Holder: Zentiva, k.s. U Kabelovny 130, Dolní Měcholupy,
102 37, Prague 10,
Czech Republic