**Safety Data Sheet**
**Voriconazole Tablets**

**Strength:** 50/200mg. **Pack Size:** 30/90/100/500/1000 Tablets per bottle for 50/200 mg
Unit-dose blister cartons of 100 (10 x 10) unit-dose tablets for 50/200 mg

**Revision No.:** 00

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**EMERGENCY OVERVIEW**

Each Voriconazole Tablets intended for oral administration contains Voriconazole and excipients generally considered to be non- toxic and non-hazardous in small quantities and under conditions of normal occupational exposure.

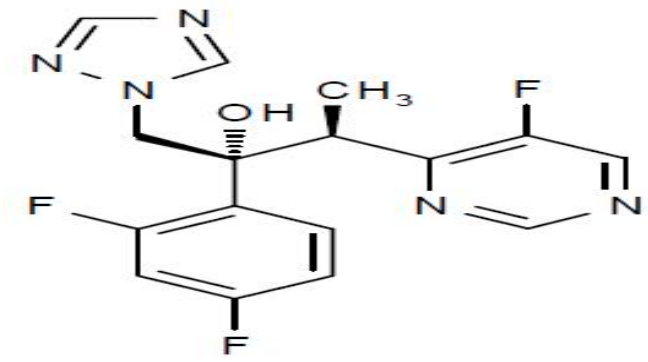
## Section 1. Identification

**Identification of the product**

**Product name:** Voriconazole Tablets

**Formula:** $C_{16}H_{14}F_3N_5O$

**Chemical Name:** (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol.




**Manufacturer / supplier identification**

**Company:** **Cadila Healthcare Ltd. Ahmedabad, India**

**Address:** Cadila Healthcare Ltd
Swaraj Majra, Juddi Kalan,
Post: Baddi, Ta: Nalagarh, Dist: Solan,
State: Himachal Pradesh-173205. India.

**Contact for information:** Tel.: +91 1795 246841 Fax: +91 1795 246842

**Emergency Telephone No.** Tel.: +91 1795 247887

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|---|---|
| **Recommended use / Therapeutic Category** | Treat or prevent Serious Fungal Infections Caused by Scedosporium Apiospermum (Asexual Form of Pseudallescheria boydii) and Fusariumspp, Including Fusarium solani, in Patients Intolerant of, or Refractory to, Other Therapy. Invasive Aspergillosis. |
| **Restriction on Use / Contraindication** | Voriconazole tablets are contraindicated in patients with known hypersensitivity to voriconazole or its excipients. There is no information regarding cross-sensitivity between voriconazole and other azole antifungal agents. Caution should be used when prescribing voriconazole to patients with hypersensitivity to other azoles. This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.<br><br>Coadministration of terfenadine, astemizole, cisapride, pimozide or quinidine with voriconazole is contraindicated because increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of torsade de pointes.<br><br>Coadministration of voriconazole with rifampin, carbamazepine and long-acting barbiturates is contraindicated because these drugs are likely to decrease plasma voriconazole concentrations significantly. |

## Section 2. Hazard(s) Information

**Dose and Administration**

**Instructions for Use in All Patients**
Voriconazole tablets should be taken at least one hour before or after a meal.

**Recommended Dosing in Adults**
Invasive aspergillosis and serious fungal infections due to *Fusarium* spp. and *Scedosporium apiospermum*

Therapy must be initiated with the specified loading dose regimen of intravenous voriconazole on Day 1 followed by the recommended maintenance dose regimen. Intravenous treatment should be continued for at least 7 days. Once the patient has clinically improved and can tolerate medication given by mouth, the oral tablet form or oral suspension form of voriconazole may be utilized. The recommended oral maintenance dose of 200 mg achieves a voriconazole exposure similar to 3 mg/kg IV; a 300 mg oral dose achieves an exposure similar to 4 mg/kg IV.

**Adverse Effects**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most frequently reported adverse events (all causalities) in the therapeutic trials were visual disturbances (18.7%), fever (5.7%), nausea (5.4%), rash (5.3%), vomiting (4.4%), chills (3.7%), headache (3.0%), liver function test increased (2.7%), tachycardia (2.4%), hallucinations (2.4%). The treatment-related adverse events which most often led to discontinuation of voriconazole therapy were elevated liver function tests, rash, and visual disturbances.

**Over Dose Effects**

In clinical trials, there were three cases of accidental overdose. All Occurred in pediatric patients who received up to five times the recommended intravenous dose of voriconazole. A single adverse event of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

Voriconazole is hemodialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 mL/min. In an overdose, hemodialysis may assist in the removal of voriconazole and SBECD from the body.

The minimum lethal oral dose in mice and rats was 300 mg/kg (equivalent to 4 and 7 times the recommended maintenance dose (RMD), based on body surface area). At this dose, clinical signs observed in both mice and rats included salivation, mydriasis, titubation (loss of balance while moving), depressed behavior, prostration, partially closed eyes, and dyspnea. Other signs in mice were convulsions, corneal opacification and swollen abdomen.

**Contraindications**

Voriconazole tablets are contraindicated in patients with known hypersensitivity to voriconazole or its excipients. There is no information regarding cross-sensitivity between voriconazole and other azole antifungal agents. Caution should be used when prescribing voriconazole to patients with hypersensitivity to other azoles. This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

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| **Medical condition** | 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 hematological malignancy). 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.<br>Measure serum transaminase levels and bilirubin at the initiation of voriconazole therapy and monitor at least weekly for the first month of treatment. Monitoring frequency can be reduced to monthly during continued use if no clinically significant changes are noted. If liver function tests become markedly elevated compared to baseline, voriconazole should be discontinued unless the medical judgment of the benefit-risk of the treatment for the patient justifies continued use. |
| **Pregnancy Comments** | If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus.<br>Voriconazole can cause fetal harm when administered to a pregnant woman and should not be taken in pregnancy except in patients where the benefit to the mother clearly outweighs the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women.<br>If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patients should be informed of the potential hazard to the fetus. |
| **Pregnancy Category** | **D** |

## Section 3. Composition / information on ingredient

| **Component** | **Exposure Limit** | **CAS No.** |
|---|---|---|
| **Principle Component :** | | |
| Voriconazole | Not Found | 137234-62-9 |

**Inactive Ingredients :**

| | | |
|---|---|---|
| Croscarmellose sodium | Not Found | 74811-65-7 |
| lactose monohydrate | Not Found | 64044-51-5 |
| Povidone | Not Found | 9003-39-8 |
| Magnesium stearate | Not Found | 557-04-0 |
| Pregelatinized starch | Not Found | 9005-25-8 |
| Opadry II white 33F28398 | Not Found | ---------- |
| Hypromellose | Not Found | ---------- |
| Polyethylene glycol | Not Found | ---------- |
| Talc | Not Found | ---------- |
| Titanium dioxide | Not Found | ---------- |

## Section 4. First - aid measures

**General**

Inhalation

Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Seek medical attention.

Contact with skin

Wash skin with soap and water. Remove contaminated clothing and shoes. If irritation occurs or persists, get medical attention.

Contact with eyes
Immediately flush eyes with water for at least 15 minutes. If irritation occurs or persists, get medical attention.

Ingestion
Get medical attention immediately. Do not induce vomiting unless directed by medical personnel. Never give anything by mouth to an unconscious person.

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| **Overdose Treatment** | In clinical trials, there were three cases of accidental overdose. All occurred in pediatric patients who received up to five times the recommended intravenous dose of voriconazole. A single adverse event of photophobia of 10 minutes duration was reported.<br><br>There is no known antidote to voriconazole.<br><br>Voriconazole is hemodialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 mL/min. In an overdose, hemodialysis may assist in the removal of voriconazole and SBECD from the body. |

## Section 5. Fire - fighting measures

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|---|---|---|---|
| **Flash point** | Not Found | **Upper Flammable Limit:** | Not Found |
| **Auto-Ignition Temperature:** | Not Found | **Lower Flammable Limit:** | Not Found |
| **Extinguishing Media** | Use carbon dioxide, dry chemical, or water spray. Also use alcohol - resistant foam. | **Fire and Explosion Hazard** | No Data available. |
| **Fire Fighting Procedure** | As with all fires, evacuate personnel to a safe area. Fire fighter should use self- contained breathing equipment and protective clothing. | | |

## Section 6. Accidental Release Measures

**Spill Response**

**Health and Safety Precautions:** Personnel involved in clean-up should wear appropriate personal protective equipment.

**Measures for Cleaning / Collecting:** Contain the source of spill if it is safe to do so. Collect spilled material by a method that controls dust generation. A damp cloth or a filtered vacuum should be used to clean spills of dry solids. Clean spill area thoroughly.

**Measures for Environmental Protections:**

Place waste in an appropriately labeled, sealed container for disposal. Care should be taken to avoid environmental release.

**Additional Consideration for Large Spills:**

Non-essential personnel should be evacuated from affected area. Report emergency situations immediately. Clean-up operations should only be undertaken by trained personnel.

## Section 7. Handling and Storage

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| **Storage** | Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP. |
| **Incompatibilities:** | Oxidizing agent. |

## Section 8. Exposure controls / personal protection

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| **Respiratory Protection** | If applicable Occupational Exposure Limit (OEL) is exceeded, wear an appropriate respirator with a protection factor sufficient to control exposures to below the OEL. |
| **Skin Protection** | Impervious protective clothing is recommended if skin contact with drug product is possible and for bulk processing operations. Wear protective clothing when working with large quantities. Individuals with known sensitivity should wear long sleeves to avoid skin contact. Wash hand and arms throughly after handling materials. |
| **Eye protection** | Eye protection is not normally necessary. If concerned wear protective goggles or glasses. Wash hands prior to touching eye and in particular handling contact lenses. |
| **Protective Clothing** | Protective clothing is not normally necessary, however it is good practice to use apron. |
| **Engineering Control** | General room ventilation is adequate unless the process generates dust, mist or fumes. |

## Section 9. Physical and chemical properties

**Appearance**

Voriconazole Tablets, 50 mg are white to off-white, round, biconvex, film-coated tablet debossed with “735” on one side and plain on the other side.

Voriconazole Tablets, 200 mg are white to off-white, oval, biconvex, film-coated tablet debossed with “736” on one side and plain on the other side.

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|---|---|---|---|
| **Solubility in water** | No Data Available | **Odour** | Odourless |
| **Boiling point** | No Data Available | **Melting Point** | No Data Available |
| **Evaporation rate** | No Data Available | **Vapour density** | No Data Available |
| **Reactivity in water** | No Data Available | **Evaporation rate** | No Data Available |
| **% Volatile by volume** | No Data Available | **Specific gravity** | No Data Available |
| | | **Vapour pressure** | No Data Available |

**Other information** Not applicable

## Section 10. Stability and Reactivity

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| **Condition to avoid** | Avoid exposure to extreme heat, light and moisture. | **Stable** | Product is stable under normal condition. |
| **Decomposition Products** | No Data Available | **Hazardous Reaction** | No data available. |
| **Incompatibilities:** | Oxidizing agents. | | |

## Section 11. Toxicological information

**General**

**Nonclinical Toxicology**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Two-year carcinogenicity studies were conducted in rats and mice. Rats were given oral doses of 6, 18 or 50 mg/kg voriconazole, or 0.2, 0.6, or 1.6 times the recommended maintenance dose (RMD) on a mg/m$^2$ basis. Hepatocellular adenomas were detected in females at 50 mg/kg and hepatocellular carcinomas were found in males at 6 and 50 mg/kg. Mice were given oral doses of 10, 30 or 100 mg/kg voriconazole, or 0.1, 0.4, or 1.4 times the RMD on a mg/m$^2$ basis. In mice, hepatocellular adenomas were detected in males and females and hepatocellular carcinomas were detected in males at 1.4 times the RMD of voriconazole.

**Target organ**

Voriconazole demonstrated clastogenic activity (mostly chromosome breaks) in human lymphocyte cultures *in vitro*. Voriconazole was not genotoxic in the Ames assay, CHO assay, the mouse micronucleus assay or the DNA repair test (Unscheduled DNA Synthesis assay).

Voriconazole administration induced no impairment of male or female fertility in rats dosed at 50 mg/kg, or 1.6 times the RMD (recommended maintenance dose).

**Other**

Not applicable

## Section 12. Ecological information

Do not allow product to enter drinking water supplies, waste water or soil.

## Section 13. Disposal Consideration

Dispose the waste in accordance with all applicable Federal, State and Local laws.

## Section 14. Transport Information

The product is not hazardous when shipping via air (IATA), ground (DOT), or sea (IMDG).

## Section 15. Regulatory Information

Generic Medicine. Approved by USFDA & the ANDA Number is 206747

## Section 16. Other information

None

**Date of issue:** 09/05/2016 **Supersedes edition:** New addition