TEVA PHARMACEUTICALS USA

Material Safety Data Sheet

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

TEVA Pharmaceuticals
650 Cathill Rd
PO Box 904
Sellersville, PA 18960
Date Approved:
Date Last Revision:

Telephone Number: 215-591-3000
Emergency Number: 1-888-838-2872

Ketoconazole Cream 2%

Ketoconazole Cream 2% is supplied in 15 gram, 30 gram, and 60 gram tubes

Chemical Name: *cis*-1-Acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine

Intended Use: Imidazole antifungal; topical administration

2. COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS Number
Ketoconazole, USP	65277-42-1
Stearyl Alcohol	112-92-5
Cetyl Alcohol	36653-83-4
Propylene Glycol	55-57-6
Sorbitan Monostearate	1338-41-6
Polysorbate 60	9006-67-8
Isopropyl Myristate	110-27-1

See Section 8 for exposure limits.

According to 29 CFR 1910.1200, no other hazardous ingredients are present at $\geq$ 1%. No carcinogens are present at $\geq$ 0.1%.

3. HAZARDS IDENTIFICATION

Emergency Overview: Because of the risk of hepatitis and hypoadrenalism, ketoconazole should be used with caution in patients with impaired hepatic function or adrenal reserve. Ketoconazole cream 2% contains sodium sulfite anhydrous, a sulfite that may cause allergic type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people.

The health hazards associated with this mixture have not been thoroughly investigated. The signs and symptoms of exposure listed below are based upon potential health effects from the active pharmaceutical ingredient contained in this formula unless otherwise noted.

Routes of Exposure:

Eyes:
Possible irritant. Not for ophthalmic use.

Skin:
Possible mild to moderate irritant. Clinical route.

Ingestion:
For topical use only.

Inhalation:
Not expected

Signs and Symptoms of Over Exposure:
None expected from incidental contact. Allergic reactions such as urticaria and angioedema, and rare cases of anaphylaxis have been reported. Pruritus, rash, alopecia, headache, dizziness, impotence, and somnolence may also occur.

Carcinogenicity:
No evidence of oncogenic activity was observed in animal studies. However, the significance of these studies in humans is not known. Refer to Section 11, Toxicological Information.

NTP:	Not Listed	IARC:	Not Listed
OSHA:	Not Listed	ACGIH:	Not Listed

Teratogenicity/Reproductive Effects:
Some reproductive effects have been observed in animal studies. However, the significance of these studies in humans is not known. Refer to Section 11, Toxicological Information.

Medical Conditions Aggravated By Exposure:
Hypersensitivity to final formulation or any of its ingredients, and concurrent use with astemizole, terfenadine, cisapride, or oral triazolam.

4. FIRST AID MEASURES

Eyes:
Remove from source of exposure. Flush with copious amounts of water. If irritation persists or signs of toxicity occur, seek medical attention.

Skin:
Remove from source of exposure. Flush with copious amounts of water. If irritation persists or signs of toxicity occur, seek medical attention.

Ingestion:
Remove from source of exposure. If signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.

Inhalation:
Remove from source of exposure. If signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.

Note to Physicians:
Ketoconazole interferes with steroid biosynthesis and reported adverse endocrine effects include gynaecomastia, oligospermia, menstrual irregularities, and adrenal cortex suppression, especially at high doses.

5. FIRE-FIGHTING MEASURES

Flashpoint: N/D

Flash point Method: N/D

Fire and explosion hazards: Not expected under normal conditions.

Extinguishing media: Use foam, carbon dioxide, or dry chemical. Use water spray to cool fire-exposed containers and to protect personnel.

Hazardous combustion products: May produce carbon dioxide, carbon monoxide, and other toxic thermal decomposition products.

Fire-fighting instructions: Because fire may produce toxic thermal decomposition products, wear self-contained breathing apparatus and protective clothing. Do not release runoff from fire control methods to sewers or waterways.

6. ACCIDENTAL RELEASE MEASURES

Spills: Scoop or wipe cream with inert dry material and dispose of as pharmaceutical waste. May cause slippery conditions. Keep spills and runoff from entering drains or surface water. In the event of a spill, contact the appropriate authorities as required by Federal, State, and Local regulations.

7. HANDLING AND STORAGE

Handling: Avoid contact with eyes, skin or clothing. Use only with appropriate personal protective equipment, safe work practices, and good hygiene practices. Wash thoroughly after handling and before eating, drinking, smoking, and/or applying cosmetics.

Storage: Store below: 77°F (25°C). Final product is light sensitive. Protect from light. Ensure that finished product packaging lines are protected from light.

8. EXPOSURE CONTROL/ PERSONAL PROTECTION

Exposure Limits:

Ingredient	OSHA PEL	ACGIH TLV	Other
Ketoconazole	Not Established	Not Established	None Identified
Cetyl Alcohol	Not Established	Not Established	None Identified
Stearyl Alcohol	Not Established	Not Established	None Identified
Propylene Glycol	Not Established	Not Established	50 ppm (TWA) 10 mg/m³ (Aerosol)
Sorbitan Monostearate	Not Established	Not Established	None Identified
Polysorbate 60	Not Established	Not Established	None Identified
Isopropyl Myristate	Not Established	Not Established	None Identified

Eye/Skin Protection: Avoid contact with eyes and skin. Wear eye protection and appropriate gloves while handling.

Respiratory Protection: Not required unless misting or aerosolization could occur. Respiratory equipment must be NIOSH-approved and comply with OSHA's Respiratory Protection Standard, 29 CFR 1910.134.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance: White, opaque cream

Vapor Pressure: N/D

Vapor Density: N/D

Specific Gravity: N/D

Solubility: Ketoconazole is insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; soluble in methyl alcohol.

Boiling Point: N/D

pH: N/D

10. STABILITY AND REACTIVITY

Stability: Under normal circumstances, believed to be stable.

Conditions to Avoid: None known

Incompatibility: None known

Hazardous Polymerization: None known

Hazardous Decomposition Products: None known

11. TOXICOLOGICAL INFORMATION

Unless otherwise noted the following pertains to the active pharmaceutical ingredient.

Oral Toxicity:
LD_{50} = N/D

Acute Effects: Adverse effects include allergic reactions such as urticaria and angioedema, and rare cases of anaphylaxis have been reported. Pruritus, rash, alopecia, headache, dizziness, impotence, and somnolence may also occur. Thrombocytopenia, paraesthesia, raised intracranial pressure, and photophobia have been reported rarely.

Effects of Repeated Doses: After topical administration of ketoconazole, irritation, dermatitis, or a burning sensation has occurred.

Skin Irritation: Two dermal studies, a human sensitization test, a phototoxicity study, and a photo allergy study conducted in male and female volunteers showed no sensitazation of the delayed hypersensitivity type, no irritation, no phototoxicity, and no photoallergenic potential due to ketoconazole cream 2%.

Reproductive and Developmental Effects: FDA Pregnancy Category C (Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; however, the benefits may outweigh the risks: or there are no animal studies and no adequate human studies.)

Ketoconazole has been shown to be teratogenic (syndactylia and oligo-dactylia) in the rat when given orally in a diet at 80 mg/day, (10 times the maximum recommended human oral dose). However, these effects may be related to maternal toxicity, which was seen at this and higher dose levels.

There are no adequate and well-controlled studies in pregnant women. Ketoconazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Sensitization: Irritation is not expected from normal clinical use of this product; however, severe cases of irritation, pruritus and stinging have occurred.

Mutagenicity: The Ames *Salmonella* microsomal activator assay was negative.

Carcinogenicity: A long-term feeding study in Swiss Albino mice and in Wistar rats showed no evidence of oncogenic activity. The dominant lethal mutation test in male and female mice revealed that single oral doses of ketoconazole as high as 80 mg/kg produced no mutation in any stage of germ cell development.

National Toxicology Program: Not listed
I.A.R.C. Monographs: Not listed
OSHA: Not listed

12. ECOLOGICAL INFORMATION

Not Determined

13. DISPOSAL CONSIDERATIONS

This product should be disposed of as pharmaceutical waste in accordance with all Federal, State, and Local regulations.

14. TRANSPORTATION INFORMATION

Proper Shipping Name: Ketoconazole Cream 2% is typically supplied 15 gram, 30 gram, and 60 gram tubes. All packaging and transportation must meet the applicable Federal, State, and Local regulations.

15. REGULATORY INFORMATION

The following regulations apply to storage and/or handling. It is the responsibility of the end users to determine the applicability of these regulations at their specific locations.

This product is regulated under the Food, Drug, and Cosmetic Act.

TSCA Status: FDA-regulated material is exempt from TSCA.

EPCRA Section 313 (SARA Title III): Not listed

EPCRA Section 302: Not listed

CERCLA: Not listed

RCRA: Not a RCRA hazardous waste.

DOT: Not applicable.

16. OTHER INFORMATION

N/A = Not Applicable N/D = Not Determined ~ = Approximately Equal To

DISCLAIMER OF EXPRESSED AND IMPLIED WARRANTIES

Although reasonable care has been taken in the preparation of this document, we extend no warranties and make no representations as to the accuracy or completeness of the information contained therein, and assume no responsibility regarding the suitability of this information for the user's intended purposes or for the consequences of its use. Each individual should make a determination as to the suitability of the information for his or her particular purpose(s).