Material Safety Data Sheet

TACROLIMUS CAPSULES 0.5 mg, 1 mg & 5 mg

SECTION 1 - PRODUCT

Tacrolimus Capsules 0.5 mg, 1 mg & 5 mg

SECTION 2 – COMPOSITION/INFORMATION ON INGREDIENTS

Active: Tacrolimus

Inactive: lactose monohydrate, hypromellose E5, croscarmellose sodium, and magnesium stearate

Capsule shell:
gelatin, titanium dioxide and sodium lauryl sulfate (in 0.5/1/5 mg)
iron oxide yellow (in 0.5 mg)
iron oxide red (in 5 mg).

SECTION 3 - HAZARDS IDENTIFICATION

Emergency Overview – Toxic. Irritant.

Form: capsules

Adverse Effects: Adverse effects may include nausea; diarrhea; muscle or joint pain; dizziness; difficulty sleeping; flushing; itching or rash; trembling; headache; tingling, prickling, or numbness of skin; high blood pressure; kidney problems; and seizures. Possible allergic reaction to material if inhaled, ingested or in contact with skin.

Overdose Effects: Overdose effects may include coma and delirium.

Acute: Eye, skin, gastrointestinal and/or respiratory tract irritation.

Chronic: Possible hypersensitization.

Medical Conditions Aggravated by Exposure: Hypersensitivity to material, Netherton's syndrome, and impaired liver or kidney function.

Target Organs: Immune system

SECTION 4 - EMERGENCY & FIRST AID MEASURES

Inhalation: May cause irritation. Remove to fresh air.

Eye: Causes irritation. Avoid contact. Flush with copious quantities of water for at least 15 minutes.

Skin: May cause irritation. Flush with copious quantities of water.

Ingestion: May cause irritation. Flush out mouth with water. This material is incompletely and variably absorbed from the gastrointestinal tract.

General First Aid Procedures: Remove from exposure. Remove contaminated clothing. Persons developing serious hypersensitivity (anaphylactic) reactions must receive immediate medical attention. If person is not breathing give artificial respiration. If breathing is difficult give oxygen. Obtain medical attention.

Note to Physicians

Overdose Treatment:

Treatment of overdose should be symptomatic and supportive and may include the following:

1. Do NOT induce vomiting.
2. Administer activated charcoal as a slurry.
3. Perform gastric lavage soon after ingestion (within one hour). Protect airway by placement in Trendelenburg and left lateral decubitus position or by endotracheal intubation. Control any seizures first.
4. Correct magnesium deficits.
5. For seizures, administer intravenous diazepam or lorazepam. If seizures recur, consider phenobarbital or propofol. Monitor for hypotension, dysrhythmias, respiratory depression, and need for endotracheal intubation. Evaluate for hypoflycemia, electrolyte disturbances, and hypoxia.
6. For hypertension and tachycardia in agitated patients, sedate with benzodiazepines. For severe hypertension, administer nitroprusside or labetalol, nitroglycerin, or phentolamine as alternatives.
7. Dialysis will not enhance clearance of tacrolimus. [Meditext 2008 and USP DI 2008]

SECTION 5 - FIRE FIGHTING MEASURES

Extinguishing Media: Water spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and materials.

Fire and Explosion Hazards: This material is assumed to be combustible. As with all dry

powders it is advisable to ground mechanical equipment in contact with dry material to dissipate the potential buildup of static electricity.

Fire fighting Procedures: As with all fires, evacuate personnel to a safe area. Fire fighters should use self-contained breathing equipment and protective clothing.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Spill Response:
Wear approved respiratory protection, chemically compatible gloves and protective clothing. Wipe up spillage or collect spillage using a high efficiency vacuum cleaner. Avoid breathing dust. Place spillage in appropriately-labelled container for disposal. Wash spill site.

SECTION 7 - HANDLING AND STORAGE

Handling: As a general rule, when handling avoids all contact and inhalation of dust, mists, and/or vapors associated with the material. Wash thoroughly after handling.

Storage: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Engineering Controls: Engineering controls such as exhaust ventilation are recommended.

Respiratory Protection: Use a NIOSH-approved respirator, if it is determined to be necessary by an industrial hygiene survey involving air monitoring. In the event that a respirator is not required, an approved dust mask should be used.

Gloves: Chemically compatible

Eye Protection: Safety glasses or goggles

Protective Clothing: Protect exposed skin.

Exposure Limits: Industry: 0.2 micrograms/m^3

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Physical state/Appearance: Solid / Hard gelatin capsule containing white to off granular powder.

Solubility (API): Soluble in Acetone, chloroform and ethyl acetate. Insoluble in water.

SECTION 10 - STABILITY AND REACTIVITY

Stability: The product is stable.

Conditions to avoid: Avoid exposure to light and heat

Incompatibilities: Strong oxidizing agents

Decomposition Products: When heated to decomposition, material emits toxic fumes of NOx. Emits toxic fumes under fire conditions.

Hazardous Polymerization: Will not occur.

SECTION 11 - TOXICOLOGY INFORMATION

Oral Rat: LD50: 134 mg/kg

Oral Mouse: LD50: 134 mg/kg (male); 194 mg/kg (female)

Irritancy Data: Rabbit/skin: not irritating; Rabbit/eye: irritant

Sensitization Data: Antigenicity tests in mice and guinea pigs were negative.

Other Carcinogenicity Data: Rare cases of skin malignancy and lymphoma have been reported in patients treated with topical calcineurin inhibitors, including tacrolimus.
In a 104-week dermal carcinogenicity study performed in mice with tacrolimus ointment (0.03% - 3%) equivalent to tacrolimus doses of 1.1-118 mg/kg/day, a statistically significant elevation in the incidence of pleomorphic lymphoma occurred in high dose males and females, and an increased incidence of undifferentiated lymphoma occurred in high dose females. In the study, the incidence of skin tumors was minimal and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment).

In a 80-week mouse study and a 104-week rat study, no relationship between tumor incidence and tacrolimus dosage was found at daily doses up to 3 mg/kg and 5 mg/kg, respectively.
In a 52-week photocarcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical application of tacrolimus ointment (greater than or equal to 0.1%) with concurrent exposure to UV radiation for 40 weeks.

Mutagenicity Data: No evidence of genotoxicity was seen in bacterial (Salmonella and E. coli) or mammalian (Chinese hamster lungderived cells) in vitro assays of mutagenicity, the in vitro CHO/HGPRT assay of mutagenicity, or in vivo clastogenicity assays performed in mice. Tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.

Reproductive and Developmental Effects: Maternal toxicity and an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability occurred in rats given tacrolimus during pregnancy at oral doses of 3.2 mg/kg. Tacrolimus administered to pregnant rabbits at oral doses of 0.32 and 1.0 mg/kg was associated with maternal toxicity, as well as, an increased incidence of abortions. At the higher dose only, an increased incidence of malformations and developmental variations was also seen. Reduced pup weights occurred in the offspring of pregnant rats given tacrolimus after organogenesis and during lactation at oral doses of 1.0 and 3.2 mg/kg.

SECTION 12 - ECOLOGICAL INFORMATION

Not found

SECTION 13 - DISPOSAL INFORMATION

Waste must be disposed of in accordance with state, local and other environmental control regulations.

SECTION 14 - TRANSPORTATION INFORMATION

Not found

SECTION 15 - REGULATORY INFORMATION

Not found

SECTION 16 - OTHER INFORMATION

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