Protopic® (Tacrolimus) Ointment

Safety Data Sheet

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Revision Date: 05/13/2015 Date of issue: 05/13/2015 Supersedes Date: 06/05/2012 Version: 1.0

SECTION 1: IDENTIFICATION

1.1. Product Identifier

Product Form: Mixture

Product Name: Protopic® (Tacrolimus) Ointment

Material Name: Tacrolimus, FK506

CAS No: 109581-93-3

Chemical Name of Active Ingredient: [3*S*-[3*R**[*E*(1*S**,3*S**,4*S**)], 4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**,18*S**,19*S**,-26a*R**]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate

Chemical Formula of Active Ingredient: $C_{44}H_{69}NO_{12} \bullet H_2O$

1.2. Intended Use of the Product

Use of the substance/mixture: Topical dermatologic use only. For professional use only.

1.3. Name, Address, and Telephone of the Responsible Party

Company

Astellas US LLC
1 Astellas Way
Northbrook, IL 60062
Tel.: 800-888-7704
www.us.astellas.com

1.4. Emergency Telephone Number

Emergency Number : 800-727-7003 Medical Communications

SECTION 2: HAZARDS IDENTIFICATION

2.1. Classification of the Substance or Mixture

Classification (GHS-US)

Eye Irrit. 2A	H319
Carc. 2	H351
Repr. 2	H361
Asp. Tox. 1	H304

Full text of H-phrases: see section 16

2.2. Label Elements

GHS-US Labeling

Hazard Pictograms (GHS-US) :

GHS07 GHS08

Signal Word (GHS-US) : Danger

Hazard Statements (GHS-US) : H304 - May be fatal if swallowed and enters airways.
H319 - Causes serious eye irritation.
H351 - Suspected of causing cancer.
H361 - Suspected of damaging the unborn child.

Precautionary Statements (GHS-US) : P201 - Obtain special instructions before use.
P202 - Do not handle until all safety precautions have been read and understood.
P264 - Wash hands, forearms, and other exposed areas thoroughly after handling.
P280 - Wear protective gloves, protective clothing, and eye protection.
P301+P310 - IF SWALLOWED: Immediately call a poison center or doctor.
P305+P351+P338 - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P308+P313 - If exposed or concerned: Get medical advice/attention.
P331 - Do NOT induce vomiting.
P337+P313 - If eye irritation persists: Get medical advice/attention.
P405 - Store locked up.
P501 - Dispose of contents/container in accordance with local, regional, national, and international regulations.

2.3. Other Hazards

Exposure may aggravate those with pre-existing eye, skin, or respiratory conditions.

2.4. Unknown Acute Toxicity (GHS-US)

No data available

SECTION 3: COMPOSITION/INFORMATION ON INGREDIENTS

3.1. Substance

Not applicable

3.2. Mixture

Name	Product Identifier	%	Classification (GHS-US)
Petrolatum	(CAS No) 8009-03-8	> 60	Not classified
Paraffin oils	(CAS No) 8012-95-1	< 15	Carc. 1A, H350* Asp. Tox. 1, H304 Aquatic Chronic 4, H413
Propylene carbonate	(CAS No) 108-32-7	< 10	Eye Irrit. 2A, H319
Paraffin waxes and Hydrocarbon waxes	(CAS No) 8002-74-2	< 5	Comb. Dust
Beeswax	(CAS No) 8012-89-3	< 5	Not classified
Tacrolimus	(CAS No) 109581-93-3	< 1	Acute Tox. 3 (Oral), H301 Skin Irrit. 2, H315 Eye Irrit. 2A, H319 Carc. 2, H351 Repr. 2, H361 STOT SE 3, H335 STOT RE 1, H372

*Evidence indicates that unrefined paraffin oils are carcinogenic to humans. Because this is a pharmaceutical product, it is unlikely that unrefined oils used in the formulation, therefore the Carc. 1A hazard does not apply to the overall product.

Full text of H-phrases: see section 16

SECTION 4: FIRST AID MEASURES

4.1. Description of First Aid Measures

First-aid Measures General: Never give anything by mouth to an unconscious person. If you feel unwell, seek medical advice (show the label if possible).

First-aid Measures After Inhalation: Remove to fresh air and keep at rest in a position comfortable for breathing. Obtain medical attention if breathing difficulty persists.

First-aid Measures After Skin Contact: Remove contaminated clothing. Drench affected area with water or soap and water for at least 15 minutes. Wash contaminated clothing before reuse. Obtain medical attention if irritation develops or persists.

First-aid Measures After Eye Contact: Rinse cautiously with water for at least 15 minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Obtain medical attention.

First-aid Measures After Ingestion: Do NOT induce vomiting. Rinse mouth. Immediately call a POISON CENTER or doctor/physician.

4.2. Most important symptoms and effects, both acute and delayed

Symptoms/Injuries: Pharmaceutical. When handling in workplace settings, in quantities that are most likely above the therapeutic dose, this product may be harmful if absorbed through the eyes, skin, or respiratory tract.

Symptoms/Injuries After Inhalation: May cause respiratory irritation.

Symptoms/Injuries After Skin Contact: May cause skin irritation.

Symptoms/Injuries After Eye Contact: Redness, pain, swelling, itching, burning, tearing, and blurred vision.

Symptoms/Injuries After Ingestion: The major health threat of ingestion occurs from the danger of aspiration (breathing) of liquid drops into the lungs, particularly from vomiting. Aspiration may result in chemical pneumonia (fluid in the lungs), severe lung damage, respiratory failure and even death.

Chronic Symptoms: Suspected of causing cancer (dermal). Suspected of damaging the unborn child.

4.3. Indication of Any Immediate Medical Attention and Special Treatment Needed

If you feel unwell, seek medical advice (show the label where possible).

SECTION 5: FIRE-FIGHTING MEASURES

5.1. Extinguishing Media

Suitable Extinguishing Media: Use extinguishing media appropriate for surrounding fire.

Unsuitable Extinguishing Media: Do not use a heavy water stream. Use of heavy stream of water may spread fire.

5.2. Special Hazards Arising From the Substance or Mixture

Fire Hazard: Not considered flammable but may burn at high temperatures.

Explosion Hazard: Product is not explosive.

Reactivity: Hazardous reactions will not occur under normal conditions.

5.3. Advice for Firefighters

Precautionary Measures Fire: Exercise caution when fighting any chemical fire.

Firefighting Instructions: Use water spray or fog for cooling exposed containers.

Protection During Firefighting: Do not enter fire area without proper protective equipment, including respiratory protection.

Other Information: Refer to Section 9 for flammability properties.

SECTION 6: ACCIDENTAL RELEASE MEASURES

6.1. Personal Precautions, Protective Equipment and Emergency Procedures

General Measures: Use only as directed. Avoid unnecessary contact with skin, eyes, or clothing. Avoid breathing (vapor, mist, spray).

6.1.1. For Non-emergency Personnel

Protective Equipment: Use appropriate personal protection equipment (PPE).

Emergency Procedures: Evacuate unnecessary personnel.

6.1.2. For Emergency Responders

Protective Equipment: Equip cleanup crew with proper protection.

Emergency Procedures: Upon arrival at the scene, a first responder is expected to recognize the presence of dangerous goods, protect oneself and the public, secure the area, and call for the assistance of trained personnel as soon as conditions permit.

6.2. Environmental Precautions

Prevent entry to sewers and public waters. Notify authorities if liquid enters sewers or public waters.

6.3. Methods and Material for Containment and Cleaning Up

For Containment: Contain any spills with dikes or absorbents to prevent migration and entry into sewers or streams.

Methods for Cleaning Up: Clean up spills immediately and dispose of waste safely. Spills should be contained with mechanical barriers. Transfer spilled material to a suitable container for disposal. Contact competent authorities after a spill.

6.4. Reference to Other Sections

See Heading 8. Exposure controls and personal protection. For further information refer to section 13.

SECTION 7: HANDLING AND STORAGE

7.1. Precautions for Safe Handling

Hygiene Measures: Handle in accordance with good industrial hygiene and safety procedures. Wash hands and other exposed areas with mild soap and water before eating, drinking or smoking and when leaving work.

7.2. Conditions for Safe Storage, Including Any Incompatibilities

Technical Measures: Comply with applicable regulations.

Storage Conditions: Store in a dry, cool and well-ventilated place. Keep container closed when not in use. Keep/Store away from direct sunlight, extremely high or low temperatures and incompatible materials.

Incompatible Products: Strong acids. Strong bases. Strong oxidizers.

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

7.3. Specific End Use(s)

Topical dermatologic use only. For professional use only.

SECTION 8: EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1. Control Parameters

For substances listed in section 3 that are not listed here, there are no established exposure limits from the manufacturer, supplier, importer, or the appropriate advisory agency including: ACGIH (TLV), NIOSH (REL), or OSHA (PEL).

Paraffin oils (8012-95-1)		
USA ACGIH	ACGIH TWA (mg/m³)	5 mg/m³ (excluding metal working fluids, highly & severely refined-inhalable fraction)
USA ACGIH	ACGIH chemical category	Not Classifiable as a Human Carcinogen highly and severely refined,Suspected Human Carcinogen highly and severely refined
USA NIOSH	NIOSH REL (TWA) (mg/m³)	5 mg/m³
USA NIOSH	NIOSH REL (STEL) (mg/m³)	10 mg/m³
USA IDLH	US IDLH (mg/m³)	2500 mg/m³
USA OSHA	OSHA PEL (TWA) (mg/m³)	5 mg/m³

Paraffin waxes and Hydrocarbon waxes (8002-74-2)		
USA ACGIH	ACGIH TWA (mg/m³)	2 mg/m³ (fume)

USA NIOSH	NIOSH REL (TWA) (mg/m³)	2 mg/m³ (fume)

8.2. Exposure Controls

Appropriate Engineering Controls : Ensure adequate ventilation, especially in confined areas. Emergency eye wash fountains and safety showers should be available in the immediate vicinity of any potential exposure. Ensure all national/local regulations are observed.

Personal Protective Equipment : Protective goggles. Gloves. Protective clothing.

Materials for Protective Clothing : Chemically resistant materials and fabrics.

Hand Protection : Wear chemically resistant protective gloves.

Eye Protection : Chemical safety goggles.

Skin and Body Protection : Wear suitable protective clothing.

Respiratory Protection : If exposure limits are exceeded or irritation is experienced, approved respiratory protection should be worn.

Environmental Exposure Controls : Do not allow the product to be released into the environment.

Consumer Exposure Controls : Do not eat, drink or smoke during use.

SECTION 9: PHYSICAL AND CHEMICAL PROPERTIES

9.1. Information on Basic Physical and Chemical Properties

Physical State	: Liquid
Appearance	: White ointment
Odor	: No data available
Odor Threshold	: No data available
pH	: No data available
Evaporation Rate	: No data available
Melting Point	: 123.6 - 131.9 °C (254.48 - 269.42 °F)
Freezing Point	: No data available
Boiling Point	: No data available
Flash Point	: No data available
Auto-ignition Temperature	: No data available
Decomposition Temperature	: No data available
Flammability (solid, gas)	: No data available
Vapor Pressure	: No data available
Relative Vapor Density at 20 °C	: No data available
Relative Density	: No data available
Solubility	: Insoluble in water, freely soluble in ethanol, and very soluble in methanol, DMSO and chloroform
Partition Coefficient: N-Octanol/Water	: No data available
Viscosity	: No data available
Molecular Weight Of Active Ingredient	: 822.03

9.2. Other Information No additional information available.

SECTION 10: STABILITY AND REACTIVITY

10.1. Reactivity: Hazardous reactions will not occur under normal conditions.

10.2. Chemical Stability: Stable under recommended handling and storage conditions (see section 7).

10.3. Possibility of Hazardous Reactions: Hazardous polymerization will not occur.

10.4. Conditions to Avoid: Direct sunlight. Extremely high or low temperatures. Ignition sources. Incompatible materials.

10.5. Incompatible Materials: Strong acids. Strong bases. Strong oxidizers.

10.6. Hazardous Decomposition Products: Carbon oxides (CO, CO_2). Nitrogen oxides. Thermal decomposition generates toxic vapors.

SECTION 11: TOXICOLOGICAL INFORMATION

11.1. Information On Toxicological Effects

Acute Toxicity: Not classified

Tacrolimus (109581-93-3)	
LD50 Oral Rat	134 - 194 mg/kg
LD50 I.V. Rat	23.6 - 57 mg/kg

Paraffin oils (8012-95-1)	
LC50 Inhalation Rat	2062 ppm/4h

Paraffin waxes and Hydrocarbon waxes (8002-74-2)	
LD50 Oral Rat	> 3750 mg/kg
LD50 Dermal Rabbit	> 3600 mg/kg

Propylene carbonate (108-32-7)	
LD50 Oral Rat	29000 mg/kg
LD50 Dermal Rabbit	> 20 ml/kg

Petrolatum (8009-03-8)	
LD50 Dermal Rabbit	3600 mg/kg

Skin Corrosion/Irritation: Not classified

Serious Eye Damage/Irritation: Causes serious eye irritation.

Respiratory or Skin Sensitization: Not classified

Germ Cell Mutagenicity: Not classified

Tacrolimus (109581-93-3)	
Additional information	No evidence of genotoxicity was seen in bacterial (Salmonella and E. coli) or mammalian (Chinese hamster lung-derived 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.

Carcinogenicity: Suspected of causing cancer.

Tacrolimus (109581-93-3)	
Additional information	Oral (feed) carcinogenicity studies have been carried out with systemically administered tacrolimus in male and female rats and mice. In the 80-week mouse study and in the 104-week rat study no relationship of tumor incidence to tacrolimus dosage was found at daily doses up to 3 mg/kg [9X the Maximum Recommended Human Dose (MRHD) based on AUC comparisons] and 5 mg/kg (3X the MRHD based on AUC comparisons), respectively. A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03% - 3%), equivalent to tacrolimus doses of 1.1-118 mg/kg/day or 3.3-354 mg/m2/day. 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. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high dose female animals (13/50) was noted in the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment) (26X MRHD based on AUC comparisons). No drug-related tumors were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1 mg/kg (0.03% tacrolimus ointment) (10X MRHD based on AUC comparisons). In a 52-week photocarcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing with concurrent exposure to UV radiation (40 weeks of treatment followed by 12 weeks of observation) with tacrolimus ointment at ≥ 0.1% tacrolimus.

Paraffin oils (8012-95-1)	
IARC group	1

Reproductive Toxicity: Suspected of damaging the unborn child.

Tacrolimus (109581-93-3)	
Additional information	Reproduction studies were carried out with systemically administered tacrolimus in rats and rabbits. Adverse effects on the fetus were observed mainly at oral dose levels that were toxic to dams. Tacrolimus at oral doses of 0.32 and 1.0 mg/kg (0.04X-0.12X MRHD based on BSA) during organogenesis in rabbits was associated with maternal toxicity as well as an increase in incidence of abortions. At the higher dose only, an increased incidence of malformations and developmental variations was also seen. Tacrolimus, at oral doses of 3.2 mg/kg during organogenesis in rats, was associated with maternal toxicity and caused an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally at 1.0 and 3.2 mg/kg (0.04X-0.12X MRHD based on BSA) to pregnant rats after organogenesis and during lactation, was associated with reduced pup weights. No reduction in male or female fertility was evident.

Specific Target Organ Toxicity (Single Exposure): Not classified

Specific Target Organ Toxicity (Repeated Exposure): Not classified

Aspiration Hazard: May be fatal if swallowed and enters airways.

Symptoms/Injuries After Inhalation: May cause respiratory irritation.

Symptoms/Injuries After Skin Contact: May cause skin irritation.

Symptoms/Injuries After Eye Contact: Redness, pain, swelling, itching, burning, tearing, and blurred vision.

Symptoms/Injuries After Ingestion: The major health threat of ingestion occurs from the danger of aspiration (breathing) of liquid drops into the lungs, particularly from vomiting. Aspiration may result in chemical pneumonia (fluid in the lungs), severe lung damage, respiratory failure and even death.

Chronic Symptoms: Suspected of causing cancer (dermal). Suspected of damaging the unborn child.

SECTION 12: ECOLOGICAL INFORMATION

12.1. Toxicity

Propylene carbonate (108-32-7)	
LC50 Fish 1	> 1000 mg/l (Exposure time: 96 h - Species: Cyprinus carpio [semi-static])
EC50 Daphnia 1	> 500 mg/l (Exposure time: 48 h - Species: Daphnia magna)

12.2. Persistence and Degradability

No additional information available.

12.3. Bioaccumulative Potential

Propylene carbonate (108-32-7)	
Log Pow	0.48 (at 25 °C)

12.4. Mobility in Soil

No additional information available.

12.5. Other Adverse Effects

Other Information : Avoid release to the environment.

SECTION 13: DISPOSAL CONSIDERATIONS

13.1. Waste treatment methods

Waste Disposal Recommendations: Dispose of waste material in accordance with all local, regional, national, and international regulations.

Ecology – Waste Materials: Avoid release to the environment.

SECTION 14: TRANSPORT INFORMATION

14.1. In Accordance with DOT Not regulated for transport.

14.2. In Accordance with IMDG Not regulated for transport.

14.3. In Accordance with IATA Not regulated for transport.

SECTION 15: REGULATORY INFORMATION

15.1 US Federal Regulations

Protopic® (Tacrolimus) Ointment (109581-93-3)	
SARA Section 311/312 Hazard Classes	Delayed (chronic) health hazard Immediate (acute) health hazard

Paraffin oils (8012-95-1)
Listed on the United States TSCA (Toxic Substances Control Act) inventory

Paraffin waxes and Hydrocarbon waxes (8002-74-2)
Listed on the United States TSCA (Toxic Substances Control Act) inventory

Propylene carbonate (108-32-7)
Listed on the United States TSCA (Toxic Substances Control Act) inventory

Petrolatum (8009-03-8)
Listed on the United States TSCA (Toxic Substances Control Act) inventory

Beeswax (8012-89-3)
Listed on the United States TSCA (Toxic Substances Control Act) inventory

15.2 US State Regulations

Paraffin oils (8012-95-1)
U.S. - Massachusetts - Right To Know List
U.S. - New Jersey - Right to Know Hazardous Substance List
U.S. - Pennsylvania - RTK (Right to Know) List

Paraffin waxes and Hydrocarbon waxes (8002-74-2)
U.S. - Massachusetts - Right To Know List
U.S. - New Jersey - Right to Know Hazardous Substance List
U.S. - Pennsylvania - RTK (Right to Know) List

SECTION 16: OTHER INFORMATION, INCLUDING DATE OF PREPARATION OR LAST REVISION

Revision Date : 05/13/2015

Other Information : This document has been prepared in accordance with the SDS requirements of the OSHA Hazard Communication Standard 29 CFR 1910.1200.

GHS Full Text Phrases:

Acute Tox. 3 (Oral)	Acute toxicity (oral) Category 3
Aquatic Chronic 4	Hazardous to the aquatic environment - Chronic Hazard Category 4
Asp. Tox. 1	Aspiration hazard Category 1
Carc. 1A	Carcinogenicity Category 1A
Carc. 2	Carcinogenicity Category 2
Comb. Dust	May form combustible dust concentrations in air
Eye Irrit. 2A	Serious eye damage/eye irritation Category 2A
Repr. 2	Reproductive toxicity Category 2
Skin Irrit. 2	Skin corrosion/irritation Category 2
STOT RE 1	Specific target organ toxicity (repeated exposure) Category 1
STOT SE 3	Specific target organ toxicity (single exposure) Category 3
H301	Toxic if swallowed
H304	May be fatal if swallowed and enters airways
H315	Causes skin irritation
H319	Causes serious eye irritation
H335	May cause respiratory irritation
H350	May cause cancer
H351	Suspected of causing cancer
H361	Suspected of damaging the unborn child
H372	Causes damage to organs through prolonged or repeated exposure
H413	May cause long lasting harmful effects to aquatic life

We believe that the information contained herein is current as of the date of this Safety Data Sheet, and is offered in good faith. Since the use of this information and of these opinions and the conditions of the use of the product are not within the control of NuSil Technology, it is the user's obligation to determine the conditions of safe use of the product.

SDS US (GHS HazCom)