

# ASTAGRAF XL™

(tacrolimus extended-release capsules)

## Safety Data Sheet

### 1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Product name	Astagraf XL (tacrolimus extended-release capsules)
Material Name	Tacrolimus, FK506
Chemical formula of active ingredient	C <sub>44</sub> H <sub>69</sub> NO <sub>12</sub> •H <sub>2</sub> O
CAS number	104987-11-3
Chemical name of active ingredient	[3S[3R*[E(1S*,3S*,4S*)], 4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,-26aR*]-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-methoxycyclo-hexyl)-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
Use	Pharmaceutical research and manufacturing, and clinical use.
Supplier of Data	Astellas Research Institute of America LLC 1 Astellas Way Northbrook, IL 60062
For emergency or product information, call	(800) 727-7003

### 2. HAZARDS IDENTIFICATION

Emergency Overview	Astagraf XL is a calcineurin inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in patients receiving kidney transplants. <b>EXERCISE CARE TO PREVENT CONTACT OR EXPOSURE.</b> See sections 11 for effects in animals.
Routes of Absorption	Inhalation, ingestion, eye and skin.
Acute effects	<b>Inhalation:</b> Inhalation of tacrolimus can irritate the respiratory tract. <b>Ingestion:</b> Swallowing small amounts is not likely to produce harmful effects. Ingestion of larger amounts may produce abdominal pain and diarrhea <b>Eye Contact:</b> Irritant. <b>Skin Contact:</b> Irritant. Not known sensitizer. See section 11 for effects in animals.
Target Organs/systemic toxicity	None reported. See section 11 for effects in animals.
Reproductive/developmental toxicity	There are no adequate and well-controlled studies in pregnant women.
Mutagenicity and carcinogenicity	None reported. See section 11 for effects in animals.
Occupational exposure limit	None by OSHA, ACGIH, or NIOSH; internally derived by drug substance OEL: 0.2µg/m <sup>3</sup> 8 hour TWA
Medical conditions aggravated by exposure	No data available.
Symptoms of Exposure	Prolonged or repeated skin contact may produce irritation or dermatitis.

### 3. COMPOSITION/INFORMATION ON INGREDIENTS

Specific chemical identity	[3S[3R*[E(1S*,3S*,4S*)], 4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]-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-methoxycyclo-hexyl)-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
OSHA PEL	No data available.
ACGIH TLV	No data available.
Inactive ingredients include ethylcellulose NF, hypromellose USP, magnesium stearate NF and lactose monohydrate NF. The ingredients are directly proportional across all capsule strengths. The capsule shell contains gelatin NF, titanium dioxide USP, ferric oxide NF, and sodium lauryl sulfate.	

### 4. FIRST AID MEASURES

Eye contact	Immediately flush with water for at least 15 minutes.
Skin contact	Remove contaminated clothing immediately. Flush area with water for at least 15 minutes. Seek medical attention.
Inhalation	Move person to fresh air immediately. Give artificial respiration and cardiopulmonary resuscitation (CPR) if required. Seek medical attention.
Ingestion	If swallowed, vomiting may occur spontaneously, but DO NOT INDUCE. If vomiting occurs, keep head below hips to prevent aspiration into lungs. Never give anything by mouth to an unconscious person. Seek medical attention immediately.

For Adverse Reaction Reporting, call 800-727-7003, Monday through Friday 8:00 AM to 4:30 PM CST, or email: [safety-us@astellas.com](mailto:safety-us@astellas.com).

### 5. FIRE-FIGHTING MEASURES

Extinguishing media	Water spray, dry chemical, carbon dioxide or foam as appropriate.
Special fire-fighting procedures	When heated to decomposition it emits toxic fumes. Burns with an almost non-luminous flame which is difficult to detect in strong light.

### 6. ACCIDENTAL RELEASE MEASURES

In case of spill or release	If a capsule is accidentally crushed, using gloves, immediately wipe up the materials using a wet cloth or paper towel and discard. If capsule intact, pick up capsules – no special handling required.
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## 7. HANDLING AND STORAGE

Special precautions – Storage	Avoid breaking or crushing capsules. Wash hands thoroughly after handling. Store in a cool, dry well-ventilated location, away from any area where the fire hazard may be acute.  Store at 15°C-30°C (59°F-86°F).
Label precautionary statement	Material intended for pharmaceutical research, manufacturing, and clinical use.

## 8. EXPOSURE CONTROL / PERSONAL PROTECTION

Occupational exposure band / handling category	Category 4 (See section 3 OEL).
Protective clothing and equipment	Protective clothing is normally not required when handling encapsulated form. If for any reason the capsule is damaged wear impervious protective clothing, including boots, gloves, lab coat, apron or coveralls as appropriate, to prevent skin contact. Eye protection is not normally required when handling encapsulated form. If for any reason the capsule is damaged use chemical safety glasses, goggles and/or a full face shield where contact is possible. Maintain eye wash fountain and quick-drench facilities in work area.
Respiratory protection	Respirators are not normally required unless there is reason to believe that tacrolimus can become airborne.
Skin protection	Same as Protective Clothing and Equipment.
Ventilation	Under indicated use general room ventilation is usually satisfactory. Use local exhaust ventilation when necessary.
Comments	None

## 9. PHYSICAL AND CHEMICAL PROPERTIES

Physical state	Capsule
Color	<b>0.5 mg:</b> hard gelatin capsule with a light yellow cap and orange body branded with red "647" on the capsule body and "0.5 mg" on the capsule cap. <b>1 mg:</b> hard gelatin capsule with a white cap and orange body branded with red "677" on the capsule body and "1 mg" on the capsule cap. <b>5 mg:</b> hard gelatin capsule with a grayish-red cap and orange body branded with red "687" on the capsule body and "5 mg" on the capsule cap.
Odor	No data available.
Boiling point	No data available.
Melting point	No data available.
Freezing point	No data available.
Percent volatility	No data available.
Specific gravity (H <sub>2</sub> O=1)	No data available.
Molecular weight of active ingredient	822.03 g/mol
Solubility of active ingredient	Insoluble in water, freely soluble in ethanol, and very soluble in methanol, and chloroform.
Vapor pressure (mmHg)	No data available.
Vapor density (Air = 1)	No data available.
Evaporation rate (Butyl acetate = 1)	No data available.
pH	No data available.

## 10. STABILITY AND REACTIVITY

Stability	Astagraf XL is stable if stored as directed.
Incompatibility	None known.

## 11. TOXICOLOGICAL INFORMATION

Acute toxicity	In single dose rat studies, the LD <sub>50</sub> for male and female rats following oral administration was 134 and 194 mg/kg, respectively. In single dose intravenous studies, the LD <sub>50</sub> for male and female rats were 57 and 23.6 mg/kg, respectively.
Repeated dose toxicity	The primary target organs of tacrolimus toxicity in rats and baboons were the pancreas, thymus, lymph nodes and spleen; in rats, the kidneys were also affected. In 52-week repeated dose oral toxicity studies, the NOAEL for rats was 0.15 mg/kg/day, while for baboons the NOAEL was 1.0 mg/kg/day.
Carcinogenicity	<p>Carcinogenicity studies were carried out 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. The highest doses used in the mouse and rat studies were 0.8 – 2.5 times (mice) and 3.5 – 7.1 times (rats) the recommended clinical dose range of 0.1 – 0.2 mg/kg/day when corrected for body surface area.</p> <p>In a 104 week dermal carcinogenicity study, topical application of 0.1% tacrolimus increased the incidence of pleomorphic and undifferentiated lymphoma.</p>
Genotoxicity	No evidence of genotoxicity was seen in bacterial ( <i>Salmonella</i> and <i>E. coli</i> ) 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.
Teratogenicity/ Reprotoxicity	<p>Tacrolimus given orally at 1.0 mg/kg (0.8 times the maximum clinical dose based on body surface area) to rats, prior to and during mating was associated with a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (2.6 times the maximum clinical dose based on body surface area), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.</p> <p>In pregnant rabbits, tacrolimus at oral doses of 0.32 and 1.0 mg/kg (0.5 and 1.6 times the maximum clinical dose based on body surface area, respectively) was associated with maternal toxicity as well as an increased incidence of abortions. At the 1 mg/kg dose, fetal rabbits showed an increased incidence of malformations (ventricular hypoplasia, interventricular septal defect, bulbous aortic arch, stenosis of ductus arteriosus, interrupted ossification of vertebral arch, vertebral and rib malformations, omphalocele, and gallbladder agenesis) and developmental variations. In pregnant rats, tacrolimus at oral doses of 3.2 mg/kg (2.6 times the maximum clinical dose) was associated with maternal toxicity, an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally to pregnant rats after organogenesis and during lactation at 1.0 and 3.2 mg/kg (0.8 and 2.6 times the maximum recommended clinical dose, respectively) was associated with reduced pup weights and pup viability (3.2 mg/kg only); among the high dose pups that died early, an increased incidence of kidney hydronephrosis was observed.</p>
Local irritation	No data available.

## 12. ECOLOGICAL INFORMATION

**Environmental Fate:** When released into the soil, this material is expected to readily biodegrade. When released into the soil, this material is expected to leach into groundwater. When released into water, this material is expected to readily biodegrade. This material is not expected to significantly bioaccumulate. When released into the air, this material is not expected to precipitate to ground.

**Environmental Toxicity:** This material was tested for acute toxicity to Rainbow Trout (*Oncorhynchus mykiss*) according to method described in the OECD guidelines for Testing of Chemicals (1992) No. 203, "Fish acute Toxicity Test" referenced as Method C1 of Commission Directive 92/69/EEC. The 96-hour LC<sub>50</sub> was greater than 100% v/v saturated solution (equivalent to 4.8 mg test material and correspondingly the No Observed Effect Concentration was 100% v/v saturated solution.

This material was tested for acute toxicity to *Daphnia Magna* according to method described in the OECD guidelines for Testing of Chemicals (1984) No. 202, "Daphni Sp, Acute Immobilisation Test and Reproduction test" referenced as Method C2 of Commission Directive 92/69/EEC. The 48-hour EC<sub>50</sub> was based on nominal test concentrations greater than 64% v/v saturated solution (equivalent to 3.8 mg test material with 95% confidence limits of 43-120% v/v saturated solution (equivalent to 2.5 - 7.1 mg test material/1. The No Observed Effect Concentration was 5.6% v/v saturated solution (equivalent to 0.33 test material).

## 13. DISPOSAL CONSIDERATIONS

Spills	Collect material in suitable receptacles and wash contaminated area with aqueous alkaline solution more than pH 12 and dispose in waste water treatment.
Waste disposal	This should be handled as hazardous waste and sent to a RCRA or similar approved incinerator or disposed in a RCRA approved waste facility. Processing, use or contamination of this product may change the waste management options. Dispose of container and unused contents in accordance with all applicable federal, state and local laws.

## 14. TRANSPORTATION INFORMATION

DOT shipping name	No data available.
DOT hazard class/ division	No data available.
DOT #	No data available.
Packaging authorization	No data available.
Non-bulk packaging	No data available.
Quantity limits	No data available.
DOT packaging group	No data available.
DOT labels	No data available.
Vessel stowage	No data available.

## 15. REGULATORY INFORMATION

US TSCA	No data available.
SARA	No data available.
EU risk and safety phrases	<b>Risk Phases:</b> R20 Harmful by inhalation R22 Harmful if swallowed R40 Possible risk of irreversible effects R 63 Possible risk of harm to unborn child  <b>Safety Phases:</b> S25 Avoid contact with eyes

**16. OTHER INFORMATION**

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None

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**ABBREVIATIONS**

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CAS: Chemical Abstract Service

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DOT: Department of Transportation

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N/A: Not Applicable

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OEL: Occupational Exposure Limit

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PEL: Permissible Exposure Limit

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RCRA: Resource Conservation and Recovery Act

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SARA: Superfund Amendments and Reauthorization Act

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TLV: Threshold Limit Value

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TSCA: Toxic Substance Control Act

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TWA: Time-Weighted Average

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CAS: Chemical Abstract Service

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