SAFETY DATA SHEET

Prepared to U.S. OSHA, CMA, ANSI, Canadian WHMIS Standards, European Union CLP EC 1272/2008 and the Global Harmonization Standard

1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY UNDERTAKING

PRODUCT IDENTIFIER/TRADE/MATERIAL NAME: AVYCAZ for Injection for Intravenous Use

DESCRIPTION: Ceftazidime Pentahydrate and Avibactam Sodium Lyophilized Powder

CHEMICAL NAME: For Active Ingredients:

Avibactam Sodium: sodium [(2S,5R)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl] sulfate

Ceftazidime Pentahydrate: (6*R*,7*R*,*Z*)-7-(2-(2-aminothiazol-4-yl)-2-(2-carboxypropan-2-yloxyimino)acetamido)-8-oxo-3-(pyridinium-1-ylmethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate pentahydrate

CHEMICAL FAMILY: For Active Ingredients: *Avibactam Sodium:* beta-Lactam; *Ceftazidime Pentahydrate:* Cephalosporin

FORMULA: For Active Ingredients: *Avibactam Sodium:* $C_7H_{10}N_3O_6SNa$; *Ceftazidime Pentahydrate:* $C_{22}H_{32}N_6O_{12}S_2$

OTHER DESIGNATIONS: NDC 0456-2700-01: Single Use Vials; NDC 0456-2700-10: 10 vials in a carbon

RELEVANT USE of the SUBSTANCE: Human Pharmaceutical

USES ADVISED AGAINST: Non-Pharmaceutical Use

HOW SUPPLIED: Single Dose vials 2.635 gm Ceftazidime Pentahydrate and 0.551 gm Avibactam Sodium Lyophilized Powder

SUPPLIER OF THE SAFETY DATA SHEET

RESPONSIBLE PARTY U.S.:	**ACTAVIS, INC.**
U.S. ADDRESS:	400 Interpace Parkway, Morris Corporate Center III Parsippany, NJ 07054, USA
U.S. BUSINESS PHONE/GENERAL SDS INFORMATION	+1-800-272-5525
RESPONSIBLE PARTY EUROPE:	
EUROPEAN ADDRESS:	
EUROPEAN BUSINESS PHONE:	
EMERGENCY PHONE (U.S./NORTH AMERICA):	CHEMTREC: 1-800-424-9300 (24 hours) U.S., Canada, Puerto Rico
EMERGENCY PHONE (OUTSIDE U.S.):	CHEMTREC: +1-703-527-3887 (24 hours) Outside North America
Email:	SDS@Actavis.com

NOTE: ALL United States Occupational Safety and Health Administration Standard (29 CFR 1910.1200), U.S. State equivalent Standards, Canadian WHMIS [Controlled Products Regulations], EU Directives through EC 1907: 2006, and European Union CLP EC 1272/2008, required information is included in appropriate sections based on the U.S. ANSI Z400.1-2010 format. This product has been classified in accordance with the hazard criteria of the countries listed above.

DATE OF PREPARATION: February 28, 2015 **DATE OF REVISION:** New

2. HAZARDS IDENTIFICATION

EU CLP REGULATION (EC) 1272/2008 LABELING AND CLASSIFICATION: According to Article 1, item 5 (a) of CLP Regulation (EC) 1272/2008, medicinal products in the finished state for human use, as defined in 2001/83/EC, are excepted from classification and other criteria of 1272/2008.

EU 67/548/EEC LABELING AND CLASSIFICATION: According to Article 1 of European Union Council Directive 92/32/EEC, medical products in the finished state for human use (as defined by European Union Council Directives 67/548/EEC and 87/21/EEC) are not subject to the regulations and administrative provisions of European Union Council Directive 92/32/EEC.

EMERGENCY OVERVIEW:

Product Description: This product is a white to yellow lyophilized powder.

Health Hazards: May be harmful if swallowed. May cause mechanical eye irritation. May cause skin sensitization. Accidental inhalation may be harmful and may cause serious allergic reactions in susceptible individuals. In therapeutic use the most common adverse effects reported include anxiety, dizziness, abdominal pain, constipation, nausea and vomiting. Significant adverse effects to the central nervous system have occurred. Severe hypersensitivity reactions have been reported from therapeutic use. Chronic exposure can result in *Clostridium difficile*-associated diarrhea (CDAD), which may range in severity from mild diarrhea to fatal colitis. There is a risk of the development of drug-resistant bacteria. These effects may be possible as a result of workplace exposure. Refer to Section 11 (Toxicological Information) for additional information on adverse effects.

Flammability Hazards: The drug product may be combustible and may ignite if subjected to direct flame or if heated to high temperature for a prolonged period. Finely-divided dusts can create a serious hazard of explosion. When involved in a fire, this material may decompose and produce irritating vapors and toxic compounds (including carbon, sulfur, sodium and nitrogen oxides).

Reactivity Hazards: This product is not reactive.

Environmental Hazards: This product has not been tested for environmental harm; all release to the environment should be avoided.

Emergency Recommendations: Emergency responders must wear personal protective equipment suitable for the situation to which they are responding.

3. COMPOSITION and INFORMATION ON INGREDIENTS

CHEMICAL NAME	CAS #	EINECS #	% w/w	LABEL ELEMENTS EU Classification (67/548/EEC) GHS and EU Classification (1272/2008 EC) Risk Phrases/Hazard Statements
ACTIVE INGREDIENTS				
Ceftazidime Pentahydrate (6*R*,7*R*,*Z*)-7-(2-(2-aminothiazol-4-yl)-2-(2-carboxypropan-2-yloxyimino)acetamido)-8-oxo-3-(pyridinium-1-ylmethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate pentahydrate	78439-06-2	Not Listed	Proprietary	SELF CLASSIFICATION EU 67/548 Classification: Harmful, Irritant Risk Phrase Codes: R33, R42/43 Hazard Symbols: Xn/Xi GHS and EU 1272/2008 Classification: Skin Sensitization Cat. 1B, Skin Sensitization Cat. 1, STOT (Ingestion-Multiple Organs) RE Cat. 2 Hazard Codes: H317, H334, H373 Hazard Symbol/Pictogram: GHS07, GHS08
Avibactam Sodium sodium [(2S,5R)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl] sulfate	1192491-61-4	Not Listed	Proprietary	SELF CLASSIFICATION EU 67/548 Classification: Harmful, Irritant Risk Phrase Codes: R33, R42/43 Hazard Symbols: Xn/Xi GHS and EU 1272/2008 Classification: Skin Sensitization Cat. 1B, Skin Sensitization Cat. 1, STOT (Ingestion-Multiple Organs) RE Cat. 2 Hazard Codes: H317, H334, H373 Hazard Symbol/Pictogram: GHS07, GHS08
EXCIPIENT				
Sodium Carbonate	497-19-8	207-838-8	Proprietary	SELF CLASSIFICATION EU 67/548 Classification: Irritant Risk Phrase Codes: R36 Hazard Symbols: Xi GHS and EU 1272/2008 Classification: Acute Oral Toxicity Cat. 5, Eye Irritation Cat. 2A Hazard Codes: H303, H319 Hazard Symbol/Pictogram: GHS07

See Section 16 for full classification information of this product.

4 FIRST-AID MEASURES

PROTECTION OF FIRST AID RESPONDERS: First-aid responders should not attempt to treat victims of exposure to this material without adequate personal protective equipment. Rescuers should be taken for medical attention, if necessary.

DESCRIPTION OF FIRST AID MEASURES: Contaminated individuals must be taken for medical attention if any adverse effects occur. Remove contaminated clothing and shoes. Take a copy of this SDS to health professional with victim. Wash clothing and thoroughly clean shoes before reuse.

Inhalation: If aerosols are inhaled, remove victim to fresh air. If necessary, use artificial respiration to support vital functions. Seek medical attention if adverse effect occurs after removal to fresh air.

Skin Exposure: If the product contaminates the skin and adverse effect occurs, begin decontamination with running water. Minimum flushing is for 20 minutes. Do not interrupt flushing. Remove exposed or contaminated clothing, taking care not to contaminate eyes. Seek medical attention if adverse effect occurs after flushing.

Eye Exposure: If particulates from this product enter the eyes, open victim's eyes while under gently running water. Use sufficient force to open eyelids. Have victim "roll" eyes. Minimum flushing is for 20 minutes. Do not interrupt flushing. Seek immediate medical attention after flushing if adverse effect occurs.

Ingestion Exposure: If this product is swallowed, CALL PHYSICIAN OR POISON CONTROL CENTER FOR MOST CURRENT INFORMATION. If professional advice is not available, do not induce vomiting. Rinse mouth with water immediately. Victim should drink large quantities of water. If milk is available, victim should drink it after drinking water. Never induce vomiting or give diluents (milk or water) to someone who is unconscious, having convulsions, or unable to swallow.

IMPORTANT SYMPTOMS AND EFFECTS: See Sections 2 (Hazard Identification) and 11 (Toxicological Information).

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: In therapeutic use, liver or kidney disease or conditions, renal impairment, particularly colitis may be may be aggravated. Persons with previous hypersensitivity reactions to other cephalosporins, penicillins, or carbapenems gravis should not be given this medication. Workplace exposure may also aggravate these conditions.

IMMEDIATE MEDICAL ATTENTION AND SPECIAL TREATMENT NEEDED: Treat symptoms and eliminate exposure. There is no specific antidote for this drug. Treatment should be symptomatic and supportive. Persons developing hypersensitivity reactions should receive immediate medical attention. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of “antibiotic-associated colitis.” After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. Institute surgical evaluation as clinically indicated.

5. FIRE-FIGHTING MEASURES

FLASH POINT: Not established.

AUTOIGNITION TEMPERATURE: Not established.

5. FIRE-FIGHTING MEASURES (Continued)

FLAMMABLE LIMITS & METHOD OF DETERMINATION (in air by volume, %): Not determined.

FIRE EXTINGUISHING MEDIA: Use extinguishing media appropriate for surrounding fire.

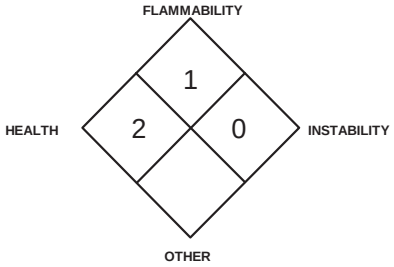
UNSUITABLE EXTINGUISHING MEDIA: None known.

SPECIFIC HAZARDS ARISING FROM THE PRODUCT: This product must be substantially pre-heated before ignition can occur. When involved in a fire, this material may decompose and produce irritating vapors and toxic compounds (including carbon, sulfur, sodium and nitrogen oxides).

Explosion Sensitivity to Mechanical Impact: Not sensitive.

Explosion Sensitivity to Static Discharge: Large, finely-divided dust clouds of this product have the potential to ignite explosively.

NFPA RATING



Hazard Scale: **0** = Minimal **1** = Slight **2** = Moderate **3** = Serious **4** = Severe

SPECIAL PROTECTIVE ACTIONS FOR FIRE-FIGHTERS: Incipient fire responders should wear eye protection. Structural firefighters must wear Self-Contained Breathing Apparatus (SCBA) and full protective equipment. Contaminated protective equipment should be thoroughly washed with running water prior to removal of SCBA respiratory protection. Firefighters whose protective equipment becomes contaminated should thoroughly shower with warm, soapy water and should receive medical evaluation if they experience any adverse effects.

6. ACCIDENTAL RELEASE MEASURES

PERSONAL PRECAUTIONS: In the event of a spill, clear the area and protect people. Avoid aerosols of this product during spill response procedures.

PROTECTIVE EQUIPMENT:

Small Spills: For incidental spills (e.g., 5 g), wear double latex or nitrile disposable gloves and eye protection.

Large Spills: For large spills (e.g., greater than 5 g), protective apparel should be used with a respirator when there is any danger of airborne dusts being generated. Minimum Personal Protective Equipment should be rubber gloves, rubber boots, face shield, and Tyvek suit.

METHODS FOR CLEANUP AND CONTAINMENT:

Small Spills: Solids should be gently covered with wet absorbent pads.

Large Spills: Trained personnel following pre-planned procedures should handle non-incidental releases. Access to the spill areas should be restricted. Sweep up spilled product carefully, avoiding the generation of airborne dusts.

All Spills: Decontaminate the area of the spill thoroughly using detergent and water. Move to a secure area. Do not mix with wastes from other materials. If necessary, discard contaminated response equipment or rinse with soapy water before returning such equipment to service. Dispose of in accordance with applicable international, national, state, and local procedures (see Section 13, Disposal Considerations).

ENVIRONMENTAL PRECAUTIONS: Prevent material from entering sewer or confined spaces, waterways, soil or public waters. Do not flush to sewer. For spills on water, contain, minimize dispersion and collect.

7. HANDLING and USE

NOTE: Consistent with the OSHA Bloodborne Pathogen regulation (29 CFR 1910.1030), observe Universal Precautions while using this product. Place used or product-contaminated hypodermic needles and syringes in a rigid “Sharps” container. Do not recap or clip used or product-contaminated hypodermic needles.

PRODUCT PREPARATION INSTRUCTIONS FOR MEDICAL PERSONNEL: Handle this material following standard medical practices and following the recommendations presented on the Package Insert.

PRECAUTIONS FOR SAFE HANDLING: All employees who handle this product should be trained to handle it safely. Particular care in working with this product must be practiced in pharmacies and other preparation areas, during manufacture of this compound, and during patient administration. As with all chemicals, avoid getting this product ON YOU or IN YOU. Wash thoroughly after handling this product or equipment and containers that contain this product. Do not eat or drink while using this product. Avoid breathing airborne mists or spray generated by this product. Ensure this product is used with adequate ventilation (refer to Section 8, Exposure Controls-Personal Protection). Remove contaminated clothing immediately. Keep container tightly closed when not in use. Open containers slowly on a stable surface in areas that have been designated for use of this product. Wipe down areas in which this product is used, so that product does not accumulate. Empty containers may contain residual material; therefore, empty containers should be handled with care.

PRODUCT PREPARATION INSTRUCTIONS FOR MEDICAL PERSONNEL: Handle this material following standard medical practices and following the recommendations presented on the Package Insert.

CONDITIONS FOR SAFE STORAGE: Containers of this product must be properly labeled. Store containers in a cool, dry location, away from direct sunlight and sources of intense heat. The sterile powder is stable under refrigeration: 20 to 25°C (68 to 77°F). Store away from incompatible materials (see Section 10, Stability and Reactivity). Material should be stored in secondary containers. Keep containers tightly closed when not in use. Inspect all incoming containers before storage, to ensure containers are properly labeled and not damaged. Refer to NFPA 654, *Prevention of Fire and Dust Explosions from the Manufacturing, Processing and Handling of Combustible Particulate Solids* for additional information on storage. Have appropriate extinguishing equipment in the storage area (e.g., sprinkler system, portable fire extinguishers). Empty containers may contain residual material; therefore, empty containers should be handled with care and disposed of properly.

SPECIFIC END USE(S): This product human pharmaceutical. Follow all industry standards for use of this product.

8. EXPOSURE CONTROLS - PERSONAL PROTECTION

EXPOSURE LIMITS/CONTROL PARAMETERS:

Ventilation and Engineering Controls: Use with adequate ventilation. Ensure eyewash stations and deluge showers are available and accessible in areas where this product is used. Wipe down work areas routinely to prevent accumulation of material. Follow standard medical product handling procedures. During decontamination of work surfaces, workers should wear the same equipment recommended in Section 6 (Accidental Release Measures) of this SDS.

Occupational/Workplace Exposure Limits/Guidelines:

CHEMICAL NAME	CAS #	EXPOSURE LIMITS IN AIR							
		ACGIH-TLVs		OSHA-PELs		NIOSH-RELs		NIOSH	OTHER
		TWA mg/m^3	STEL mg/m^3	TWA mg/m^3	STEL mg/m^3	TWA mg/m^3	STEL mg/m^3	IDLH mg/m^3	mg/m^3
Avibactam Sodium	1192491-61-4	NE	NE	NE	NE	NE	NE	NE	NE
Ceftazidime Pentahydrate	78439-06-2	NE	NE	NE	NE	NE	NE	NE	NE
Sodium Carbonate	497-19-8	NE	NE	NE	NE	NE	NE	NE	NE

NE = Not Established See Section 16 for Definitions of Other Terms Used

International Occupational Exposure Limits: No additional exposure limits have been established by various countries for the components of this product. Exposure limits can be added; individual country authorities should be contacted to check on more current limits.

PERSONAL PROTECTIVE EQUIPMENT: Use of personal protective equipment must be in compliance with U.S. OSHA 29 CFR Subpart I (beginning at 1910.132), Canadian CSA Standards Z94.4-02 and Z94.3-02, EU EN 529:2005, CEN/TR 15419:2006, and CR 13464:1999. Please reference applicable regulations and standards for relevant details.

Respiratory Protection: Maintain airborne contaminant concentrations below exposure limits listed above if applicable. If necessary, use only respiratory protection authorized under appropriate regulations. Oxygen levels below 19.5% are considered IDLH by U.S. OSHA. In such atmospheres, use of a full-facepiece pressure/demand SCBA or a full facepiece, supplied air respirator with auxiliary self-contained air supply is required under U.S. OSHA's Respiratory Protection Standard (1910.134-1998).

Eye Protection: No eye protection is normally needed during medical administration of this product. During operations in which dusts of the product may be generated, splash goggles or safety glasses should be considered.

Hand Protection: During medical administration of this product, medical latex or nitrile gloves should be worn to avoid absorption of the product. During manufacture or other similar industrial operations, wear the appropriate hand protection for the process. Use double gloves for spill response, as stated in Section 6 (Accidental Release Measures) of this SDS.

Body Protection: Use appropriate protective clothing for the task (e.g., lab coat, etc.). If necessary, refer to the U.S. OSHA Technical Manual (Section VII: Personal Protective Equipment) or other appropriate regulations.

9. PHYSICAL and CHEMICAL PROPERTIES

The following information is for the product.

FORM: Powdered solid.
COLOR: As described in Section 2.
ODOR: Odorless.
ODOR THRESHOLD: Not applicable.
HOW TO DETECT THIS SUBSTANCE (identification properties): The appearance of this product is a distinguishing characteristic.

The following information is for the Avibactam Sodium active ingredient.

FORM: Crystalline solid.
COLOR: White.
MOLECULAR FORMULA: $C_7H_{10}N_3O_6SNa$
MOLECULAR WEIGHT: 287.23
ODOR: Odorless.
ODOR THRESHOLD: Not applicable.
DECOMPOSITION TEMPERATURE: Not available.
FLASH POINT: Not available.
BOILING POINT @ 760 mmHg: Not available.
MELTING POINT: Not available.
RELATIVE VAPOR DENSITY (air = 1): Not available.
EVAPORATION RATE (n-BuAc = 1): Not available.
SPECIFIC GRAVITY (water = 1): Not available.
pH: Not available.
VAPOR PRESSURE @ 25°C: Not available.
SOLUBILITY IN WATER: Not available.
OTHER SOLUBILITY: Not available.
COEFFICIENT OF OIL/WATER DISTRIBUTION (PARTITION COEFFICIENT): Not available.

The following information is for the Ceftazidime Pentahydrate active ingredient.

FORM: Crystalline solid.
COLOR: White.
MOLECULAR FORMULA: $C_{22}H_{32}N_6O_{12}S_2$
MOLECULAR WEIGHT: 636.6
ODOR: Odorless.
ODOR THRESHOLD: Not applicable.
DECOMPOSITION TEMPERATURE: Not available.
FLASH POINT: Not available.
BOILING POINT @ 760 mmHg: Not available.
MELTING POINT: 150°C (302°F)
RELATIVE VAPOR DENSITY (air = 1): Not available.
EVAPORATION RATE (n-BuAc = 1): Not available.
SPECIFIC GRAVITY (water = 1): Not available.
pH: Not available.
VAPOR PRESSURE @ 25°C: Not available.
SOLUBILITY IN WATER: Not available.
OTHER SOLUBILITY: Not available.
COEFFICIENT OF OIL/WATER DISTRIBUTION (PARTITION COEFFICIENT): Log P: -1.6 [predict.]

10. STABILITY and REACTIVITY

CHEMICAL STABILITY: This product is not reactive.

DECOMPOSITION PRODUCTS: Combustion: If exposed to extremely high temperatures, the products of thermal decomposition may include irritating fumes and toxic gases (e.g. carbon, sulfur, sodium and nitrogen oxides). **Hydrolysis:** None known.

10. STABILITY and REACTIVITY (Continued)

MATERIALS WITH WHICH SUBSTANCE IS INCOMPATIBLE: This product is generally compatible with other common materials in a medical facility, may be incompatible with strong acids and bases.

POSSIBILITY HAZARDOUS REACTION/POLYMERIZATION: Will not occur.

CONDITIONS TO AVOID: Avoid heat, light, and contact with incompatible chemicals.

11. TOXICOLOGICAL INFORMATION

SYMPTOMS OF EXPOSURE BY ROUTE OF EXPOSURE: The health hazard information provided below is pertinent to medical employees using this product in an occupational setting. The following paragraphs describe the symptoms of exposure by route of exposure.

Inhalation: Inhalation of dusts from the lyophilized material or mists or sprays of reconstituted solution may irritate the mucous membranes and upper respiratory tract. Inhalation may induce coughing or bronchospasm. Exposure to by inhalation may cause significant respiratory reactions in susceptible individuals. Symptoms may include severe difficulty in breathing, coughing, wheezing and bronchospasm. Severe reactions can be fatal.

Contact with Skin or Eyes: Skin contact may cause mild irritation, which is alleviated upon rinsing with soap and water. Prolonged or repeated skin contact may cause dermatitis (dry, red skin). Eye contact with this product may cause transient irritation. Exposure may cause allergic skin reactions in susceptible individuals. Symptoms may include skin eruptions, rash, itching.

Skin Absorption: No data is available on potential absorption of this product through intact skin.

Ingestion: Ingestion is not a significant route of occupational overexposure. Acute ingestion of large quantities of this product or chronic ingestion caused by poor hygiene practices may be harmful and symptoms described for "Other Potential Health Effects".

Injection: Accidental injection of this product, by a contaminated needle or via laceration or puncture wound from a contaminated object may cause systemic effects. Local redness and pain are the primary symptoms in an occupational setting. Additional symptoms may include those described for "Other Potential Health Effects".

HAZARDOUS MATERIAL IDENTIFICATION SYSTEM

HEALTH HAZARD	(BLUE)	2*
FLAMMABILITY HAZARD	(RED)	1
PHYSICAL HAZARD	(YELLOW)	0

PROTECTIVE EQUIPMENT

EYES	RESPIRATORY	HANDS	BODY
	SEE SECTION 8		SEE SECTION 8

For Routine Industrial Use and Handling Applications

Hazard Scale: **0** = Minimal **1** = Slight **2** = Moderate
3 = Serious **4** = Severe * = Chronic hazard

OTHER POTENTIAL HEALTH EFFECTS-Therapeutic Doses: In therapeutic use the most common adverse effects reported include anxiety, dizziness, abdominal pain, constipation, nausea and vomiting. Significant adverse effects to the central nervous system have occurred. Severe hypersensitivity reactions have been reported from therapeutic use. Chronic exposure can result in *Clostridium difficile*-associated diarrhea (CDAD), which may range in severity from mild diarrhea to fatal colitis. There is a risk of the development of drug-resistant bacteria. These effects may be possible as a result of workplace exposure. The actual risk in the workplace is not known. In therapeutic use the following additional adverse effects described by body system have included:

- ***Blood and Lymphatic System:*** High blood eosinophil count, involving white blood cell disorder leading to infections, blood platelet decrease.
- ***Investigations:*** Increased gamma-glutamyltransferase, prolonged prothrombin time.
- ***Metabolism:*** Abnormal low blood potassium levels.
- ***Renal and Urinary System:*** Acute renal failure, renal impairment.
- ***Skin:*** Rash.

Additionally, adverse reactions reported with Ceftazidime alone that were not reported in AVYCAZ clinical trials are listed below:

- ***Blood and Lymphatic System:*** Acute failure of bone marrow to make white blood cells, anemia due to abnormal breakdown of red blood cells (RBCs), decrease in the number of white blood cells, high level of blood lymphocytes, abnormally low level of blood neutrophils, high platelet counts in the blood.
- ***Body as a Whole:*** Infusion site inflammation, injection site bruising, injection site swelling and inflammation of vein, injection site blood clotting, lack of taste.
- ***Liver:*** Jaundice
- ***Infections and Infestations:*** Candidiasis (yeast infections).
- ***Investigations:*** Increased blood lactate dehydrogenase.
- ***Nervous System:*** Sensations of tickling, tingling, burning, pricking, or numbness, seizures, non-convulsive status epilepticus, encephalopathy, coma, hand tremors, neuromuscular excitability, and muscle twitching.
- ***Renal and Urinary System:*** Tubulointerstitial nephritis (form of liver disease).
- ***Reproductive System:*** Vaginal inflammation.
- ***Skin:*** Swelling of face and tongue, rash with welts that can be red or purple and/or with blisters, itching, Stevens-Johnson syndrome, toxic epidermal necrolysis (skin reaction that can cause destruction of skin and can be fatal), hives.

HEALTH EFFECTS OR RISKS FROM EXPOSURE: An Explanation in Lay Terms. Exposure to this product may cause the following health effects:

Acute: Accidental ingestion may be harmful. Eye contact with dusts may cause mechanical irritation. Inhalation of dusts from product may also cause effects described under 'Other Potential Health Effects'.

Chronic: Repeated workplace exposure to the skin contact may cause dermatitis (dry, red skin). Chronic therapeutic use or workplace exposure may cause effects described under 'Other Potential Health Effects'.

11. TOXICOLOGICAL INFORMATION (Continued)

TARGET ORGANS: It is anticipated that for Occupational Exposure the target organs are: **Acute:** Skin, eyes, respiratory system. **Chronic:** In therapeutic use this product may have an impact on the body systems described under 'Other Potential Health Effects'.

IRRITANCY OF PRODUCT: This product is may cause mechanical eye irritation and may be irritating to the respiratory system. Prolonged skin contact may be irritating.

SENSITIZATION TO THE PRODUCT: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs. In therapeutic use, skin rash, itching, hives, wheezing, serum sickness, high blood eosinophil count, involving white blood cell disorder leading to infections, and drug fever have been reported.

TOXICITY DATA: Currently, the following toxicity data are available for the active ingredient, Ceftazidime Pentahydrate. No data are available for the Avibactam Sodium active ingredient. Data are available for excipients, but are not provided in this SDS. Contact Actavis for more information.

CEFTAZIDIME PENTAHYDRATE:

LD_{50} (Intraperitoneal-Rat) 10 gm/kg
LD_{50} (Intraperitoneal-Mouse) 12 gm/kg
LD_{50} (Subcutaneous-Rat) 20 gm/kg
LD_{50} (Subcutaneous-Mouse) 20 gm/kg
LD_{50} (Intravenous-Rat) 6100 mg/kg
LD_{50} (Intravenous-Mouse) 6300 mg/kg
TDLo (Intravenous-Rat) 13,500 mg/kg: female 17-22 day(s) after conception lactating female 21 day(s) post-birth: Reproductive: Effects on Newborn: growth statistics (e.g.%, reduced weight gain)

CEFTAZIDIME PENTAHYDRATE (continued):

TDLo (Intravenous-Rat) 11 gm/kg: female 7-17 day(s) after conception: Reproductive: Maternal Effects: parturition; Effects on Embryo or Fetus: extra-embryonic structures (e.g., placenta, umbilical cord), fetotoxicity (except death, e.g., stunted fetus)
TDLo (Intravenous-Rat) 22 gm/kg: female 7-17 day(s) after conception: Reproductive: Specific Developmental Abnormalities: musculoskeletal system
TDLo (Intravenous-Rat) 2750 mg/kg: female 7-17 day(s) after conception: Reproductive: Effects on Newborn: live birth index (measured after birth)
TDLo (Intravenous-Rabbit) 1300 mg/kg: female 6-18 day(s) after conception: Reproductive: Effects on Embryo or Fetus: fetotoxicity (except death, e.g., stunted fetus)

CARCINOGENIC POTENTIAL OF COMPONENTS: Carcinogenic studies are not available for this combination drug or the individual active ingredients, Avibactam Sodium and Ceftazidime Pentahydrate.

Components are not found on the following lists: U.S. EPA, U.S. NTP, U.S. OSHA, U.S. NIOSH, GERMAN MAK, IARC, or ACGIH and therefore are neither considered to be nor suspected to be cancer-causing agents by these agencies.

REPRODUCTIVE TOXICITY INFORMATION: There are no adequate and well-controlled studies of this combination drug in pregnant women; however, this drug is not expected may cause fetal harm when administered to a pregnant woman. In the workplace, the risk to the fetus should be communicated and the appropriate action should be taken to prevent exposure in accordance with company policy and regulatory requirements. This product is rated by the FDA for therapeutic risk as Pregnancy Risk Category B (Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks).

Mutagenicity: Ceftazidime and Avibactam were each evaluated for mutagenic potential in several *in vitro* and *in vivo* assays.

Ceftazidime: Ceftazidime was negative for mutagenicity in a mouse micronucleus test and an Ames test.

Avibactam: Avibactam was negative for genotoxicity in the Ames assay, unscheduled DNA synthesis, chromosomal aberration assay, and a rat micronucleus study.

Embryotoxicity/Teratogenicity: Animal reproductive toxicity studies have been conducted individually with Ceftazidime and Avibactam. No studies are available for the combination drug.

Ceftazidime: Reproduction studies have been performed in mice and rats at doses up to 40 times the human dose and showed no evidence of harm to the fetus due to Ceftazidime.

Avibactam: Avibactam was not teratogenic in rats or rabbits. In the rat, intravenous studies showed no embryofetal toxicity at doses of 1000 mg/kg/day, approximately 9 times the human dose based on exposure (AUC). In a rat pre- and postnatal study at up to 825 mg/kg/day intravenously (11 times the human exposure based on AUC), there were no effects on pup growth and viability. A dose-related increase in the incidence of renal pelvic and ureter dilatation was observed in female weanling pups that was not associated with pathological changes to renal parenchyma or renal function, with renal pelvic dilatation persisting after female weanling pups became adults. Reproductive studies performed during early pregnancy in rabbits showed no effects on embryofetal development at doses of 100 mg/kg, twice the human exposure (AUC). At higher doses, increased post-implantation loss, lower mean fetal weights, delayed ossification of several bones and other anomalies were observed.

Reproductive Toxicity: Avibactam had no adverse effects on fertility of male and female rats given up to 1 g/kg/day (approximately 20 fold higher than the recommended clinical dose on a body surface area basis). There was a dose-related increase in the percentage of pre- and post-implantation loss relative to controls, resulting in a lower mean litter size at doses 0.5 g/kg and greater with intravenous administration to female rats beginning 2 weeks prior to mating. Ceftazidime is excreted in human milk in low concentrations. It is not known whether Avibactam is excreted into human milk, although Avibactam was shown to be excreted in the milk of rats in a dose dependent manner. Many drugs can be present in breast milk, causing adverse effects to breast-fed babies.

ACGIH BIOLOGICAL EXPOSURE INDICES (BEIs): Currently, ACGIH Biological Exposure Indices (BEIs) have not been determined for the components of this product.

12. ECOLOGICAL INFORMATION

ALL WORK PRACTICES MUST BE AIMED AT ELIMINATING ENVIRONMENTAL CONTAMINATION.

MOBILITY: This product has not been tested for mobility in soil.

PERSISTENCE AND BIODEGRADABILITY: This product has not been tested for persistence or biodegradability.

BIO-ACCUMULATION POTENTIAL: This product has not been tested for bio-accumulation potential.

ECOTOXICITY: This product may be harmful to aquatic and terrestrial organisms; all releases to terrestrial, atmospheric and aquatic environments should be avoided. No aquatic toxicity data are available for the active ingredient.

12. ECOLOGICAL INFORMATION (Continued)

OTHER ADVERSE EFFECTS: This product does not contain any component with known ozone depletion potential.

RESULTS OF PBT AND vPvB ASSESSMENT: No Data Available. PBT and vPvB assessments are part of the chemical safety report required for some substances in European Union Regulation (EC) 1907/2006, Article 14.

ENVIRONMENTAL EXPOSURE CONTROLS: Controls should be engineered to prevent release to the environment, including procedures to prevent spills, atmospheric release and release to waterways.

13. DISPOSAL CONSIDERATIONS

WASTE TREATMENT/DISPOSAL METHODS: Waste disposal must be in accordance with appropriate Federal, State, and local regulations.

PRECAUTIONS TO BE FOLLOWED DURING WASTE HANDLING: Wear proper protective equipment when handling waste materials.

U.S. EPA WASTE NUMBER: Not applicable to wastes consisting only of this product.

PRECAUTIONS TO BE FOLLOWED DURING WASTE HANDLING: Wear proper protective equipment when handling waste materials.

EUROPEAN WASTE CODES: Wastes from Human or Animal Health Care or Related Research: 18 01 08: Medicines Other Than Those Mentioned in 18 01 07.

14. TRANSPORTATION INFORMATION

U.S. DEPARTMENT OF TRANSPORTATION REGULATIONS: This product is not classified as dangerous goods, per U.S. DOT regulations, under 49 CFR 172.101.

TRANSPORT CANADA, TRANSPORTATION OF DANGEROUS GOODS REGULATIONS: This product is not classified as Dangerous Goods, per regulations of Transport Canada.

INTERNATIONAL AIR TRANSPORT ASSOCIATION (IATA): This product is not classified as Dangerous Goods, by rules of IATA.

INTERNATIONAL MARITIME ORGANIZATION (IMO) DESIGNATION: This product is not classified as Dangerous Goods by the International Maritime Organization.

EUROPEAN AGREEMENT CONCERNING THE INTERNATIONAL CARRIAGE OF DANGEROUS GOODS BY ROAD (ADR): This product is not classified by the United Nations Economic Commission for Europe to be dangerous goods.

TRANSPORT IN BULK ACCORDING TO THE IBC CODE: Not applicable.

ENVIRONMENTAL HAZARDS: This product does not meet the criteria of environmentally hazardous according to the criteria of the UN Model Regulations (as reflected in the IMDG Code, ADR, RID, and ADN) and no component is specifically listed in Annex III under MARPOL 73/78.

15. REGULATORY INFORMATION

UNITED STATES REGULATIONS:

U.S. SARA Reporting Requirements: The components of this product are not subject to the reporting requirements of Sections 302, 304, and 313 of Title III of the Superfund Amendments and Reauthorization Act.

U.S. SARA Threshold Planning Quantity (TPQ): There are no specific Threshold Planning Quantities for any component of this product. The default Federal SDS submission and inventory requirement filing threshold of 10,000 lb (4,540 kg) therefore applies, per 40 CFR 370.20.

U.S. CERCLA Reportable Quantities (RQ): Not applicable.

U.S. TSCA Inventory Status: This product is regulated under Food and Drug Administration standards; it is not subject to requirements under TSCA.

Other U.S. Federal Regulations: Regulations of the FDA under the Federal Food, Drug and Cosmetic Act are applicable when this material is used in pharmaceutical preparations. Under the Hazard Communication Standard (HCS), Section (b)(5)(ii) drugs are subject to labeling requirements by the FDA under the Federal Food, Drug and Cosmetic Act and are exempt from labeling provisions of the HCS; this section of the HCS exempts only labeling requirements and not requirements for a Safety Data Sheet for drugs.

California Safe Drinking Water and Toxic Enforcement Act (Proposition 65): No component of this product is on the California Proposition 65 Lists.

CANADIAN REGULATIONS:

Canadian DSL Inventory Status: This product regulated by the Therapeutic Products Programme (TPP) of Health Canada and so it excepted from requirements of the DSL/NDSL Inventory.

Canadian Environmental Protection Act (CEPA) Priorities Substances Lists: The components of this product are not on the CEPA Priorities Substances Lists.

Canadian WHMIS Classification and Symbol: The WHMIS Requirements of the Hazardous Products Act does not apply in respect of the advertising, sale or importation of any cosmetic, device, drug or food within the meaning of the Food and Drugs Act.

EUROPEAN REGULATIONS:

Safety, Health, and Environmental Regulations/Legislation Specific for the Product: When formulated in a finished medicinal product for human use, this material is subject to Directive 2001/83/EC and subsequent amendments to the directive.

Chemical Safety Assessment: No Data Available. The chemical safety assessment is required for some substances according to European Union Regulation (EC) 1907/2006, Article 14.

16. OTHER INFORMATION

ANSI LABELING (Based on 129.1, Provided to Summarize Occupational Exposure Hazards): WARNING! MAY BE HARMFUL IF SWALLOWED. MAY CAUSE RESPIRATORY SYSTEM AND EYE IRRITATION. INGESTION AND INHALATION MAY CAUSE SEVERE ALLERGIC REACTION IN SUSCEPTIBLE PERSONS. CHRONIC INGESTION AND INHALATION MAY CAUSE ADVERSE SYSTEMIC EFFECTS. COMBUSTIBLE IF EXPOSED TO HIGH TEMPERATURES. Do not taste or swallow. Avoid contact with skin, eyes, and clothing. Keep container closed. Use gloves, safety glasses, and appropriate respiratory and body protection. **FIRST-AID:** If exposed, seek immediate medical attention. If swallowed, do not induce vomiting. If alert, give victim up to three glasses of water. Never give anything by mouth to an unconscious person. In case of contact, flush skin with copious amounts of warm water for 20 minutes. Remove contaminated clothing and shoes. If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. **IN CASE OF FIRE:** Use water fog, dry chemical or CO_2, or alcohol foam. **IN CASE OF SPILL:** Refer to Safety Data Sheet for complete spill response procedures. Spill response should be performed by persons properly trained to do so. Decontaminate area with bleach and detergent solution and triple rinse area. Place spill debris in a suitable container. Refer to SDS for additional information.

GLOBAL HARMONIZATION AND EU CLP REGULATION (EC) 1272/2008 LABELING AND CLASSIFICATION: According to Article 1, item 5 (a) of CLP Regulation (EC) 1272/2008, medicinal products in the finished state for human use, as defined in 2001/83/EC, are excepted from classification and other criteria of 1272/2008.

EU LABELING AND CLASSIFICATION 67/548/EEC: According to Article 1 of European Union Council Directive 92/32/EEC, medical products in the finished state for human use (as defined by European Union Council Directives 67/548/EEC and 87/21/EEC) are not subject to the regulations and administrative provisions of European Union Council Directive 92/32/EEC.

CLASSIFICATION FOR COMPONENTS:

CLP Regulation (EC) 1272/2008:

Avibactam Sodium: This is a self-classification.

Classification: Skin Sensitization Category 1B, Skin Sensitization Category 1, Specific Target Organ Toxicity (Ingestion-Multiple Organs) Repeated Exposure Category 2

Hazard Statement Codes: H317: May cause an allergic skin reaction. H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled. H373: May cause damage to organs through prolonged or repeated exposure.

Ceftazidime Pentahydrate: This is a self-classification.

Classification: Skin Sensitization Category 1B, Skin Sensitization Category 1, Specific Target Organ Toxicity (Ingestion-Multiple Organs) Repeated Exposure Category 2

Hazard Statement Codes: H317: May cause an allergic skin reaction. H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled. H373: May cause damage to organs through prolonged or repeated exposure.

Sodium Carbonate: This is a self-classification.

Classification: Acute Oral Toxicity Category 5, Eye Irritation Category 2A

Hazard Statement Codes: H303: May be harmful if swallowed. H319: Causes serious eye irritation.

All Other Components: No classification has been published or is applicable.

Full Text EU 67/548/EEC:

Avibactam Sodium: This is a self-classification.

Classification: Harmful, Irritant

Risk Phrases: R42/43: May cause sensitisation by inhalation and skin contact. R33: Danger of cumulative effects.

Ceftazidime Pentahydrate: This is a self-classification.

Classification: Harmful, Irritant

Risk Phrases: R42/43: May cause sensitisation by inhalation and skin contact. R33: Danger of cumulative effects.

Sodium Carbonate: This is a self-classification.

Classification: Irritant

Risk Phrases: R36: Irritating to eyes.

All Other Components: No classification has been published or is applicable.

REFERENCES AND DATA SOURCES: Contact the supplier for information.

METHODS OF EVALUATING INFORMATION FOR THE PURPOSE OF CLASSIFICATION: Bridging principles were used to classify this product.

REVISION DETAILS: New.

PREPARED BY: CHEMICAL SAFETY ASSOCIATES, Inc. • PO Box 1961, Hilo, HI 96721 • 800/441-3365 • 808/969-4846
DATE OF PRINTING: March 2, 2015