SAFETY DATA SHEET

SECTION 1 - IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/ UNDERTAKING

Contact information

General

The Medicines Company
8 Sylvan Way, Parsippany, NJ 07054
Main: +1 (973) 290-6000 or +1 (800) 388-1183 (toll free)
Fax: +1 (973) 656-9898
E-mail: medical.information@themedco.com

Emergency telephone number

+1 (800) 264-4662 *(Available at all times)*

Product identifier	Angiomax® (bivalirudin) for Injection (lyophilized cake)
Synonyms	Bivalirudin for Injection
Trade names	Angiomax®
Chemical family	Mixture - contains synthetic peptide
Relevant identified uses of the substance or mixture and uses advised against	Bulk formulated pharmaceutical product/ Formulated pharmaceutical product packaged in final form for patient use; indicated for use as an anticoagulant
Note	This SDS is written to address potential worker health and safety issues associated with the handling of the formulated drug product.

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture	**Drugs in the finished state and intended for the final user are not subject to labeling in the US, EU or Canada.** Please consult the prescribing/packaging information. **The classification and labeling listed below is for bulk drug product, packaged in vials.**
Globally Harmonized System [GHS]	Irritant (skin) - Category 2.

Label elements

SECTION 2 - HAZARDS IDENTIFICATION …continued

GHS hazard pictogram

GHS signal word Warning

GHS hazard statements H315 - Causes skin irritation.

GHS precautionary statements P264 - Wash hands thoroughly after handling. P280 - Wear eye/face protection. P302 + P352 - IF ON SKIN: Wash with plenty of soap and water. P363 - Wash contaminated clothing before reuse. P321 - Specific treatment (see First Aid information on product label and/or Section 4 of the SDS). P332 + P313 - If skin irritation occurs: Get medical advice/attention. P362 - Take off contaminated clothing and wash before reuse.

Other hazards Bivalirudin is a direct thrombin inhibitor. In addition to bleeding (primarily at site of arterial puncture) and hemorrhage, adverse events most commonly reported with therapeutic use include headache, thrombocytopenia, and fever. Cardiovascular effects (including blood pressure drop and increased risk of blood clot formation) have been noted. As a peptide, bivalirudin is likely to be degraded in the gastrointestinal tract in the event of accidental ingestion.

Note This mixture is classified as hazardous under GHS as implemented by Regulation EC No 1272/2008 (EU CLP), WHMIS 2015 (Health Canada), and Hazard Communication Standard No. 1910.1200 (US OSHA).

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ ELINCS#	Amount	GHS Classification
Bivalirudin	128270-60-0	N/A	60-70%	Not classified
Sodium Hydroxide	1310-73-2	215-185-5	3-4%	SC1: H314

Note The ingredient(s) listed above are considered hazardous. Bivalirudin is listed because it is pharmacologically active. The remaining components are not hazardous and/or present at amounts below reportable limits. See Section 16 for full text of GHS classifications.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures	
Immediate Medical Attention Needed	Yes
Eye Contact	If easy to do, remove contact lenses, if worn. Immediately flush eyes with copious quantities of water for at least 15 minutes. If irritation occurs or persists, notify medical personnel and supervisor.
Skin Contact	Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.
Inhalation	Immediately move exposed subject to fresh air. If not breathing, give artificial respiration. If breathing is labored, administer oxygen. Immediately notify medical personnel and supervisor.
Ingestion	Do not induce vomiting unless directed by medical personnel. Do not give anything to drink unless directed by medical personnel. Never give anything by mouth to an unconscious person. Notify medical personnel and supervisor.
Protection of first aid responders	See Section 8 for Exposure Controls/Personal Protection recommendations.
Most important symptoms and effects, both acute and delayed	See Sections 2 and 11.
Indication of immediate medical attention and special treatment needed, if necessary	Medical conditions aggravated by exposure: bleeding disorders. Seek immediate medical attention if any of these signs of very serious bleeding occur: chest pain, vision problems, confusion, slurred speech, weakness on one side of the body. Treat symptomatically and supportively. If accidental exposure occurs to an individual who is also taking one or more concomitant medications, consult the respective package or prescribing information for potential drug interactions.

SECTION 5 - FIREFIGHTING MEASURES

Extinguishing media	Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.
Specific hazards arising from the substance or mixture	No information identified. May emit carbon monoxide, carbon dioxide, oxides of nitrogen and other nitrogen-containing compounds.
Flammability/ Explosivity	No explosivity or flammability data identified. High airborne concentrations of finely divided organic particles can potentially explode if ignited.
Advice for firefighters	Wear full protective clothing and a self-contained breathing apparatus with a full facepiece operated in the pressure demand or other positive pressure mode. Decontaminate all equipment after use.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures	If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Do not breathe dust.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	If vials are crushed or broken, DO NOT RAISE DUST. Surround spill or powder with absorbents and place a damp cloth or towel over the area to minimize entry of powder into the air. Add excess liquid to allow the material to enter solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container suitable for disposal in accordance with applicable waste disposal regulations (see Section 13). Decontaminate the area twice.
Reference to other sections	See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling	If vials are opened, crushed or broken, follow recommendations for handling bulk pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Avoid breathing dust. Wash thoroughly after handling.
Conditions for safe storage including any incompatibilities	Store at room temperature between 68-77°F (20-25°C) away from light and moisture. Brief storage between 59-86°F (15-30°C) is permitted. Reconstituted material may be stored at 2-8°C for up to 24 hours. Diluted material at concentrations of 0.5-5 mg/mL is stable at room temperature for up to 24 hours. Do not freeze reconstituted or diluted mixture.
Specific end use(s)	Anticoagulant

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note	Wash hands, face and other potentially exposed areas immediately in the event of physical contact. Dispose of broken vials/syringes in a sharps container.

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Bivalirudin	--	--	--
Sodium Hydroxide	ACGIH, Czech Republic, Denmark, Finland, NIOSH, Portugal, Spain, Sweden, Australia, Mexico	Ceiling	2 mg/m³
	Austria, Belgium, Bulgaria, Finland, France, Hungary, Lithuania, Slovak Republic, Slovenia, Spain, OSHA	TWA-8 HR	2 mg/m³
	Austria	STEL (8 x 5 min)	4 mg/m³
	Czech Republic, Estonia, Sweden	TWA-8 HR	1 mg/m³
	Hungary, Ireland, Slovenia, Singapore	STEL	2 mg/m³
	Latvia, Poland	TWA-8 HR	0.5 mg/m³
	NIOSH	IDLH	10 mg/m³
	Poland	STEL	1 mg/m³

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION …continued

Exposure/Engineering controls	None required for normal handling of packaged product. If handling bulk product or if vials are opened/crushed/broken: Selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Open handling should not be performed when handling potent substances, or substances of unknown toxicity. Material should be handled inside a closed process, ventilated enclosure, isolator or device of equivalent or better control that is suitable for dusts and/or aerosols.
Respiratory protection	None required for normal handling of packaged product. If handling bulk product or if vials are opened/crushed/broken: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. For routine powder handling tasks, an approved and properly worn powered air-purifying respirator equipped with HEPA filters or combination filters should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use a positive-pressure air-supplied respirator if there is any potential for an uncontrolled release, when exposure levels are not known, or in any other circumstances where air purifying respirators may not provide adequate protection.
Hand protection	None required for the normal handling of packaged product. Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered.
Skin protection	Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Base the choice of skin protection on the job activity, potential for skin contact and solvents and reagents in use.
Eye/face protection	Wear safety glasses with side shields, chemical splash goggles, or full face shield, if necessary. Base the choice of protection on the job activity and potential for contact with eyes or face. An emergency eye wash station should be available.
Environmental Exposure Controls	Avoid release to the environment and operate within closed systems wherever practicable. Air and liquid emissions should be directed to appropriate pollution control devices. In case of spill, do not release to drains. Implement appropriate and effective emergency response procedures to prevent release or spread of contamination and to prevent inadvertent contact by personnel.
Other protective measures	Wash hands in the event of contact with this substance, especially before eating, drinking or smoking. Protective equipment is not to be worn outside the work area (e.g., in common areas or out-of-doors).

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties	

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Appearance	Lyophilized cake (in single-use, glass vial) Each vial contains 250 mg, to which 5 mL of Sterile Water for Injection, USP is added for reconstitution; reconstitution yields a clear to opalescent solution.
Color	White Colorless to slightly yellow (reconstituted)
Odor	No information identified.
Odor threshold	No information identified.
pH	5.0-6.0 (when reconstituted in 5 mL water)
Melting point/ freezing point	No information identified.
Initial boiling point and boiling range	Not applicable.
Flash point	Not applicable.
Evaporation rate	Not applicable.
Flammability (solid, gas)	No information identified.
Upper/lower flammability or explosive limits	No information identified.
Vapor pressure	No information identified.
Vapor density	No information identified.
Relative density	No information identified.
Water solubility	≥140 mg/mL (pH 4.6-5.6), 1-10 mg/mL (pH 3.3-4.0) (bivalirudin)
Solvent solubility	Insoluble in acetonitrile, chloroform, octanol, and ethyl acetate. Sparingly soluble in acetone and sec-butanol (bivalirudin).
Partition coefficient (*n-octanol/water*)	No information identified.
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.
Viscosity	Not applicable.
Explosive properties	No information identified.
Oxidizing properties	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Other information

Molecular weight Not applicable (Mixture)

Molecular formula Not applicable (Mixture)

SECTION 10 - STABILITY AND REACTIVITY

Reactivity No information identified.

Chemical stability Stable under recommended handling and storage conditions.

Possibility of hazardous reactions Not expected to occur.

Conditions to avoid Avoid extreme temperatures. Moisture. Do not freeze when reconstituted.

Incompatible materials No information identified.

Hazardous decomposition products No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note No data for the mixture were identified. Data below are for the active ingredient and/or other ingredients, where applicable.

Information on toxicological effects

Route of entry May be absorbed by inhalation, skin contact and ingestion.

Acute toxicity

Compound	Type	Route	Species	Dose
Bivalirudin	Minimum lethal IV dose	Intravenous	Rat	50 mg/kg
Sodium Hydroxide	--	--	--	--

Irritation/Corrosion Sodium hydroxide is corrosive to the eye and skin *in vitro* and *in vivo*.

Sensitization Bivalirudin was not antigenic in guinea pigs

STOT-single exposure No mortality was observed in mice treated with single intravenous (IV) or subcutaneous (SC) doses up to 200 mg/kg bivalirudin. No mortality was observed in rats treated with single SC doses as high as 200 mg/kg bivalirudin. Additionally, no deaths were observed in monkeys treated with single IV doses up to 100 mg/kg bivalirudin.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

STOT-repeated exposure/Repeat-dose toxicity	Rat, 28-day IV; At ≥75 mg/kg/day effects included spleen enlargement, liver toxicity and effects on bone marrow. Mortality was observed at doses ≥250 mg/kg/day. Hemorrhage of internal organs was observed at ≥500 mg/kg/day. NOAEL = 25 mg/kg/day. Monkey, 28-day IV: Target organs included the heart and skeletal muscle. NOEL = 45 mg/kg/day. Monkey, 28-day SC: No target organs identified. Maximum tolerated dose = 36 mg/kg/day.
Reproductive toxicity	No reproductive toxicity was observed in rats administered SC doses up to 150 mg/kg/day bivalirudin.
Developmental toxicity	No developmental toxicity was noted in rats and rabbits administered SC doses up to 150 mg/kg/day bivalirudin.
Genotoxicity	Negative in several genotoxicity studies.
Carcinogenicity	No studies identified. None of the components of the product present at levels greater than or equal to 0.1% are listed by NTP, IARC, ACGIH or OSHA as a carcinogen.
Aspiration hazard	No data available.
Human health data	See "Section 2 - Other Hazards"

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
Bivalirudin	--	--	--
Sodium Hydroxide	Toxic range	freshwater fish and invertebrates	20 to 40 mg/L (data on pH changes unavailable)

Persistence and Degradability	Sodium hydroxide rapidly dissolves and dissociates in water. No data were available for other ingredients.
Bioaccumulative potential	Bioaccumulation is not relevant for sodium hydroxide. No data were available for other ingredients.
Mobility in soil	No data available.
Results of PBT and vPvB assessment	Not performed.
Other adverse effects	No data available.

SECTION 12 - ECOLOGICAL INFORMATION …continued

Note	The environmental characteristics of this product/mixture have not been fully investigated. Aquatic toxicity of sodium hydroxide is related to the effects of pH changes. Sodium hydroxide in neutralized mixtures is not considered toxic to the environment. Because data on other ingredients were not identified, releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods	Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Do not send down the drain or flush down the toilet. All wastes containing the material should be properly labeled. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater treatment facility.

SECTION 14 - TRANSPORT INFORMATION

Transport	Based on the available data, this product/mixture is not regulated as a hazardous material/dangerous good under EU ADR/RID, US DOT, Canada TDG, IATA, or IMDG.
UN number	None assigned.
UN proper shipping name	None assigned.
Transport hazard classes and packing group	None assigned.
Environmental hazards	Based on the available data, this product/mixture is not regulated as an environmental hazard or a marine pollutant.
Special precautions for users	Due to lack of data, avoid release to the environment.
Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code	Not applicable.

SECTION 15 - REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture	This SDS generally complies with the requirements listed under current guidelines in the US, EU and Canada. Consult your local or regional authorities for more information.
Chemical safety assessment	Not conducted.
TSCA status	Drugs are exempt from TSCA.
SARA section 313	Not listed.
California proposition 65	Not listed.
Additional information	No other information identified.

SECTION 16 - OTHER INFORMATION

Full text of H phrases and GHS classifications	SC1 - Skin corrosion Category 1. H314 - Causes severe skin burns and eye damage. SI2 - Skin irritant Category 2. H315 - Causes skin irritation.
Sources of data	Information from published literature and internal company data.
Abbreviations	ACGIH - American Conference of Governmental Industrial Hygienists; ADR/RID - European Agreement Concerning the International Carriage of Dangerous Goods by Road/Rail; AIHA - American Industrial Hygiene Association; CAS# - Chemical Abstract Services Number; CLP - Classification, Labelling, and Packaging of Substances and Mixtures; DNEL - Derived No Effect Level; DOT - Department of Transportation; EINECS - European Inventory of New and Existing Chemical Substances; ELINCS - European List of Notified Chemical Substances; EU - European Union; GHS - Globally Harmonized System of Classification and Labeling of Chemicals; IARC - International Agency for Research on Cancer; IDLH - Immediately Dangerous to Life or Health; IATA - International Air Transport Association; IMDG - International Maritime Dangerous Goods; LOEL - Lowest Observed Effect Level; LOAEL - Lowest Observed Adverse Effect Level; NIOSH - The National Institute for Occupational Safety and Health; NOEL - No Observed Effect Level; NOAEL - No Observed Adverse Effect Level; NTP - National Toxicology Program; OEL - Occupational Exposure Limit; OSHA - Occupational Safety and Health Administration; PNEC - Predicted No Effect Concentration; SARA - Superfund Amendments and Reauthorization Act; STOT - Specific Target Organ Toxicity; STEL - Short Term Exposure Limit; TDG - Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act; TWA - Time Weighted Average; WHMIS - Workplace Hazardous Materials Information System
Issue Date	8 August 2016
Revisions	Updated general format for compliance with most recent regulatory requirements in the US, EU, and Canada. Updated contact information.

Disclaimer

The above information is based on data available to us and is believed to be correct. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions.

No representation, warranty, or guarantee, express or implied (including a warranty of fitness or merchantability for a particular purpose), is made with respect to the materials, the accuracy of this information, the results to be obtained from the use thereof, or the hazards connected with the use of the material. Caution should be used in the handling and use of the material because it is a pharmaceutical product. The above information is offered in good faith and with the belief that it is accurate. As of the date of issuance, we are providing all information relevant to the foreseeable handling of the material. However, in the event of an adverse incident associated with this product, this Safety Data Sheet is not, and is not intended to be, a substitute for consultation with appropriately trained personnel.