Safety Data Sheet

Prepared to U.S. OSHA (HazCom 1910.1200), Canadian WHMIS 2015 (HPR-GHS) and the Global Harmonization Standard

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

PRODUCT IDENTIFIER

Product Identifier/Trade Name (As Labeled): **ZORYVE Cream**
Other Means Of Identification: ARQ-151 Roflumilast Cream – Finished Pharmaceutical Product
Recommended Product Use: Formulated Pharmaceutical
Restrictions On Use: Other Than Recommended Pharmaceutical Use

SUPPLIER OF THE SAFETY DATA SHEET

U.S. Supplier/Manufacturer's Name: **Arcutis Biotherapeutics, Inc.**

Address: 3027 Townsgate Rd., Suite 300 Westlake Village, CA 91361 USA
Business Phone: 805-418-5006 (9:00 am - 5:30 pm PST)
Email Address For Product and SDS Information: logistics@arcutis.com
Date of Preparation: March 20, 2023
Date of Revision: May 8, 2024: Version 3

Note: This SDS is written to address potential worker health and safety issues associated with the handling of the formulated product/mixture. Workers manufacturing this product/mixture should consult the SDS of each hazardous ingredient for hazard information and handling recommendations. This SDS will be revisited if more data become available.

2. HAZARD IDENTIFICATION

GLOBAL HARMONIZATION LABELING AND CLASSIFICATION: Pharmaceutical products in finished form are regulated under the U.S. FDA and are not subject to regulations pertaining to the U.S. Global Harmonization Standard under OSHA. Furthermore, finished pharmaceutical products are also not regulated in Canada under WHMIS 2015 and the Global Harmonization Standard they are regulated under the Canadian Food and Drugs Act (FDA). Drugs, as defined under the FDA are excluded from requirements under WHMIS 2015 requirements.

Percent of Unknown Acute Toxicity: The percentage of unknown toxicity by all Oral Route: > 51%; Dermal Route: > 52%; Inhalation:> 52%

3. COMPOSITION and INFORMATION ON INGREDIENTS

CHEMICAL NAME	CAS #	% w/w	GHS Classification under U.S. OSHA Hazard Communication Standard and Canadian WHMIS 2015 Hazard Statements
Diethylene Glycol Monoethyl Ether	111-90-0	20-35%	Not Classified
2-Methyl-2,4-pentanediol (hexylene glycol)	107-41-5	1-3%	Harmonized Classification: Skin Irritation Cat. 2, Eye Corrosion/Irritation Cat. 2A Notified Classification: Reproductive Toxicity Cat. 2 Hazard Statements: H315: Causes skin irritation. H319: Causes serious eye irritation. H361d: Suspected of damaging the unborn child.
Roflumilast	162401-32-3	0.01-0.5%	Notified Classification: Reproductive Toxicity Cat. 2, Skin Irritation Cat. 2, Eye Corrosion/Irritation Cat. 2A Hazard Statements: H315: Causes skin irritation. H319: Causes serious eye irritation. H361fd: Suspected of damaging fertility Suspected of damaging the unborn child.
Methylparaben	99-76-3	Trace	Health Hazards Not Otherwise Classified: Under Assessment as an Endocrine Disruptor
Propylparaben	94-13-3	Trace	Health Hazards Not Otherwise Classified: Under Assessment as an Endocrine Disruptor
Purified Water	7732-18-5	Balance	Not Classified

The classifications given above are from the most current EU ECHA Database records for each ingredient compound, as of the date of preparation of this SDS. The substance(s) listed above are considered hazardous. The remaining components are not hazardous and/or present at amounts below reportable limits. Diethylene Glycol Monoethyl Ether is included because it has OELs and is present at or above 1%. Amounts are listed as ranges; the exact percentage of composition is withheld as a trade secret.

4. FIRST-AID MEASURES

Protection of First Aid Responders — Rescuers should not attempt to retrieve victims of exposure to this material without adequate personal protective equipment. Rescuers should be taken for medical attention, if necessary. Only trained personnel should administer supplemental oxygen and/or cardio-pulmonary resuscitation, if necessary.

Description of First Aid Measures (General) — Exposed individual(s) must be taken for medical attention if exposure causes adverse effects. Take copy of label and SDS to physician or other health professional with victim(s). Remove individual(s) to fresh air, as quickly as possible.

Inhalation Exposure — If this product is accidentally inhaled, remove exposed individual to fresh air. If necessary, use artificial respiration to support vital functions. Seek medical attention if adverse effect occurs after removal to fresh air.

4. FIRST-AID MEASURES (Continued)

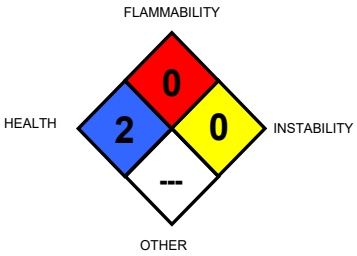
Description of First Aid Measures (continued))	
Skin Exposure	If contact with skin causes adverse effects, begin decontamination with running water. Minimum flushing is for 15 minutes. Do not interrupt flushing. Remove exposed or contaminated clothing, taking care not to contaminate eyes. Seek medical attention if adverse effect occurs after flushing.
Eye Exposure	If this product enters the eyes, open contaminated individual's eyes while under gently running water. Use sufficient force to open eyelids. Have individual "roll" eyes. Minimum flushing is for 15 minutes. Do not interrupt flushing. Seek immediate medical attention after flushing.
Ingestion Exposure	If this product is swallowed, CALL PHYSICIAN OR POISON CONTROL CENTER FOR MOST CURRENT INFORMATION. DO NOT INDUCE VOMITING. Rinse mouth with water immediately if individual is conscious. Never induce vomiting or give diluents (milk or water) to someone who is unconscious, having convulsions, or unable to swallow. If vomiting occurs, lean patient forward or place on left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Seek medical attention.
Important Symptoms and Effects, Whether Acute or Delayed/Chronic	May be harmful if swallowed. All potential effects are dependent on concentration and duration of exposure. This information is derived from effects described after therapeutic use or in clinical trials.
Acute Exposure	
Symptoms/Effects After Inhalation	Sneezing, coughing.
Symptoms/Effects After Skin Contact	None currently known.
Symptoms/Effects After Ingestion	Nausea. Vomiting.
Symptoms/Effects After Eye Contact	Mild to moderate irritation of eye tissue.
Chronic Exposure	
Symptoms/Effects After Inhalation	None known.
Symptoms/Effects After Skin Contact	Headache, diarrhea, nausea, insomnia, application site pain, upper respiratory tract infection, urinary tract infection.
Symptoms/Effects After Ingestion	None currently known.
Symptoms/Effects After Eye Contact	None currently known.
Symptoms/Effects After Exposure by Route(s) Not Identified or From Animal Data	The trace active ingredient has shown reproductive effects (based on animal data-no human data available).
Medical Conditions Aggravated By Exposure	Acute or chronic conditions or disorders as described above or involving the "Target Organs" (see Section 11, "Toxicological Identification") may be aggravated by exposure to this product.
Indication of Immediate Medical Attention and Special Treatment if Needed	Treat symptoms and eliminate exposure. In the event of an overdose, administer support medical care as soon as possible. Hemodialysis is unlikely to be of benefit given the extensive protein binding of roflumilast.

5. FIRE-FIGHTING MEASURES

Flash Point	Not applicable.
Autoignition Temperature	Product not tested.
Flammable Limits in Air	Product not tested.
Fire Extinguishing Media	Fire extinguishing materials that can be used against fires of this product include carbon dioxide, dry chemical powder, 'ABC' Class, or appropriate foam. The effect on surrounding materials must be considered.
Unsuitable Fire Extinguishing Media	None known.
Special Hazards Arising From the Product	This product is not flammable or combustible. If containers are heated or punctured, rupture may occur. If involved in a fire, the product can produce carbon monoxide, carbon dioxide, oxides of nitrogen or fluorine and other nitrogen- and fluorine-containing compounds.
Explosion Sensitivity to Mechanical Impact	Not sensitive.
Explosion Sensitivity to Static Discharge	Not sensitive.
Special Protective Actions for Fire-Fighters	Structural fire-fighters must wear Self-Contained Breathing Apparatus and full protective equipment. Chemical resistant clothing may be necessary. Move containers from the fire area if it can be done without risk to personnel. Water spray can be used to cool fire-exposed containers. Water fog or spray can also be used by trained fire-fighters to disperse this product's vapors and to protect personnel. If possible, prevent runoff water from entering storm drains, bodies of water, or other environmentally sensitive areas. Rinse contaminated equipment thoroughly with soapy water before returning such equipment to service.

5. FIRE-FIGHTING MEASURES (Continued)

NFPA RATING



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

6. ACCIDENTAL RELEASE MEASURES

Personal Precautions and Emergency Procedures	Uncontrolled releases should be responded to by trained personnel using pre-planned procedures. Evacuate all non-emergency response individuals prior to response. Proper protective equipment should be used. This product is not flammable or combustible and does not present any significant health hazards to emergency response personnel. However, prior to entering the spill an assessment must be made to determine the presence of other materials and their hazard(s). Call CHEMTREC (1-800-424-9300) for emergency assistance. Or if in Canada, call CANUTEC (613-996-6666).
Personal Protective Equipment	The spill response incident commander should assess the spill area in order to determine the level of PPE needed.
Methods for Clean-Up and Containment	The methods described below are to be done only after a full assessment of the spill area has been made to identify all hazards.
All Spills	Access to the spill area should be restricted. Carefully absorb liquids using polypads or other non-reactive absorbent. For large spills, dike or otherwise contain spill and absorb spill with polypads or other non-reactive absorbent material. Place all spill residue in a double plastic bag or other containment and seal. Decontaminate the area thoroughly. Do not mix with wastes from other materials. Dispose of in accordance with applicable Federal, State, and local procedures (see Section 13, Disposal Considerations). For spills on water, contain, minimize dispersion and collect. Dispose of recovered material and report spill per regulatory requirements.
Environmental Precautions	Implement appropriate and effective emergency response procedures to prevent release or spread of contamination and to prevent inadvertent contact by personnel; run-off water may be contaminated by other materials and should be contained to prevent possible environmental damage.
Reference to Other Sections	See information in Section 8 (Exposure Controls – Personal Protection) and Section 13 (Disposal Considerations) for additional information.

7. HANDLING and STORAGE

Precautions For Safe Handling	All employees who handle this material should be trained to handle it safely. Minimize all exposure to this substance. As with all chemicals, avoid getting this product on you or in you. Keep away from incompatible materials. Containers of this product must be properly labeled.
Hygiene Measures	Do not eat, drink, smoke, or apply cosmetics while handling this product. Wash thoroughly after handling this product. If product enters the eyes, rinse thoroughly with running water for at least 15 minutes, rolling eyes. If release of canned product contact the eyes, seek immediate medical attention.
Conditions for Safe Storage and Any Incompatibilities	Inspect all incoming containers before storage to ensure containers are properly labeled and not damaged.
Storage Conditions	Store locked up. Store containers in a cool, dry location, away from direct sunlight, sources of intense heat, or where freezing is possible. Material should be stored away from incompatible materials. Inspect all incoming containers before storage, to ensure containers are properly labeled and not damaged.
Incompatibilities	Refer to Section 10 (Stability and Reactivity) for information on incompatible materials.
Recommended Storage Temperature	Room temperature (20–25°C (68-77°F).
Protective Practices During Maintenance of Contaminated Equipment	Follow practices indicated in Section 6 (Accidental Release Measures). Always use this product in areas where adequate ventilation is provided. Decontaminate equipment thoroughly, before maintenance begins. Collect all rinsates and dispose of according to applicable Federal, State, Provincial or local procedures, or applicable standards of the U.S. and Canada.
Product Use(s)	Finished pharmaceutical product for therapeutic use.

8. EXPOSURE CONTROLS - PERSONAL PROTECTION

Control Parameters, Including Occupational Exposure Guidelines or Biological Exposure Limits and the Source of Those Values

Handle with adequate ventilation to ensure exposure levels are maintained below the limits provided in this section, if applicable. Exhaust directly to the outside, taking necessary precautions for environmental protection. Ensure eyewash/safety shower stations and appropriate fire protection is available near areas where this product is used.

Ventilation and Engineering Controls

If container is damaged: Control exposures to below the OEL (for the active ingredient(s) if available). Selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Utilize closed and sealed systems whenever possible. Solutions used for procedures where aerosolization may occur (e.g., spraying, pumping, open transfers,) must be handled using an engineered local exhaust ventilation (LEV) and/or enclosure or isolator system. Control the potential for spills and leaks by securing all connections. Use clean-in-place systems.

Occupational/Workplace Exposure Limits/Guidelines

The following limits are in place from the U.S. and Canadian agencies that promulgate OELs in the workplace for the protection of workers.

Chemical Name	CAS #	Issuer	Value
Roflumilast	162401-32-3	Arcutis	OHC 3 – Potent*
Diethylene Glycol Monoethyl Ether	111-90-0	U.S. WEEL TWA	25 ppm
		Canada-Ontario Limit Value 8 hours	30 ppm; 65 mg/m³
		Canada-Yukon Territories 8-hr limit	100 ppm; 540 mg/m³
		Canada-Yukon Territories 15 min. Ceiling	150 ppm; 810 mg/m³
2-Methyl-2,4-pentanediol (hexylene glycol)	107-41-5	U.S. ACGIH TLV TWA	25 ppm *(V); 50 mg/m³ *(V); 10 mg/m³; (inhalable fraction) *(H)
		U.S. ACGIH TLV STEL Ceiling(C)	50 ppm ;10 mg/m³
		U.S. NIOSH REL (ceiling)	25 ppm; 125 mg/m³
		Canada-Ontario Limit Value Short Term	25 ppm*(1)
		Canada-Québec Limit Value Short Term	25 ppm*(1); 121 mg/m³*(1)
		Canada-Alberta 15 min. Ceiling	25 ppm; 121 mg/m³
		Canada-British Columbia 15 min. Ceiling	25 ppm
		Canada-Northwest Territories Ceiling	25 ppm

*An OHC of 3 corresponds to an OEL of 0.03 to 10 µg/m^3
*(H): Aerosol only
*(V): Vapor fraction
*(1): ceiling limit value

ACGIH Biological Exposure Indices

Currently, no BEIs have been established for components of this product.

Individual Protection Measures, Such as Personal Protective Equipment

The following information on appropriate Personal Protective Equipment is provided to assist employers in complying with OSHA regulations found in 29 CFR Subpart I (beginning at 1910.132), U.S. Federal OSHA Respiratory Protection Standard (29 CFR 1910.134), 29 CFR 1910.133 for eye protection, 29 CFR 1910.138 for hand protection, 29 CFR 1910.136 for foot protection, or equivalent standards of Canada (including CSA Standard Z94.4-02, CSA Standard Z94.3-02, CSA Standard Z94.4-93 for respiratory protection, CSA Standard Z94.3-M1982, *Industrial Eye and Face Protectors and* CSA Standard Z195-M1984, *Protective Footwear*). Please reference applicable regulations and standards for relevant details.

Respiratory Protection

None required for normal handling of product. Maintain airborne contaminant concentrations below exposure limits listed in this section, if applicable. If container is damaged: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. A powered air-purifying respirator (PAPR) with HEPA filters and head cover is required when performing aerosol-generating uses. An airline respirator or self-contained breathing apparatus (SCBA) and disposable outerwear is required for spill cleanup.

Eye Protection

None required for normal handling of product. If container is damaged: Wear safety glasses with side shields, chemical splash goggles 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.

Hand Protection

None required for normal handling of product. When the material is diluted in an organic solvent, wear gloves that provide protection against the solvent.

Body Protection

None required for normal handling of product. If container is damaged: Wear gown or other body covering appropriate to the task, booties, gloves and safety glasses. Protective garments (coveralls, disposable coveralls, lab coats) are not to be worn in common areas (e.g., cafeterias) or out-of-doors. Employees must be trained in proper gowning and de-gowning practices. An anteroom or transition area must be used for gowning and de-gowning.

Other Protective Measures

Full-body chemical protective clothing is recommended for emergency response procedures. If necessary, refer to applicable regulations and standards. If a hazard of injury to the feet exists due to falling objects, rolling objects, where objects may pierce the soles of the feet or where employee's feet may be exposed to electrical hazards, use foot protection, as described in appropriate regulations and standard.

8. EXPOSURE CONTROLS - PERSONAL PROTECTION (Continued)

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.

9. PHYSICAL and CHEMICAL PROPERTIES

Physical Form	Creamy liquid.
Color	White to off-white
Molecular Weight	Mixture
Molecular Formula	Mixture
Odor	Not determined.
Odor Threshold	Not determined.
Boiling Point	100°C (212°F)
Melting Point	50-58°C (122-136.4°F)
Freezing Point	Not determined.
Percent Solids	Not determined.
Viscosity	Not determined.
Vapor Pressure	Not determined.
Vapor Density (air = 1)	Greater than 1.
VOC Content	Not determined.
Specific Gravity (water = 1)	Not determined.
pH	4.8-6.0
Evaporation Rate (nBuAc = 1)	Not determined.
Expansion Ratio	Not determined.
Solubility in Water	Partially soluble.
Solubility in Solvents	Not determined.
Log Coefficient Kow	3.99 (Roflumilast)
Flammability	Not flammable.
Flash Point	Not determined.
Net Heat of Combustion of total Package	Not determined.
Autoignition Temperature	Not determined.
Flammability Limits in Air (LEL & UEL)	Not determined.
Lbs. Volatile/Gallon	Not determined.
Explosive Properties	None.
Oxidizing Properties	Not an oxidizer.
How to Detect this Substance (Identification Properties)	The physical form and color may be a good identification property in event of a release.

10. STABILITY and REACTIVITY

Reactivity	Not reactive.
Chemical Stability	Stable under conditions of standard temperature and pressure.
Decomposition Products/Combustion	Carbon oxides, alcohols (from multiple ingredients), hydrogen chloride gas, hydrogen fluoride, nitrogen oxides (based upon active ingredient), peroxides (from DGME).
Decomposition Products/Hydrolysis	None known.
Material with Which Product is Incompatible	Product may be incompatible with strong acids and alkalis, chlorates and nitrates (based on component incompatibilities).
Possibility of Hazardous Reaction/Polymerization	Will not undergo hazardous polymerization.
Conditions to Avoid	Avoid exposure to extreme temperatures and incompatible chemicals.

11. TOXICOLOGICAL INFORMATION

Acute Toxicity for Product:	This product has not been fully tested for acute toxicity by any route.
Oral Toxicity-acute	No data available; not fully tested.
Dermal Toxicity-acute	No data available; not fully tested.
Inhalation Toxicity-acute	No data available; not fully tested.
Injection Toxicity-acute	No data available; not fully tested.
Acute Toxicity Estimates (ATEs) for Product	Oral: > 31,600 mg/kg; Dermal: > 47,700 mg/kg; Inhalation: > 51.11 mg/L

11. TOXICOLOGICAL INFORMATION (Continued)

Acute Toxicity for Components:	The available acute toxicity data presented in this SDS are for the ingredients of 1 percent or more concentration and for the Active Pharmaceutical Ingredient (API) Roflumilast.
Oral Toxicity-acute	Roflumilast: LD_{50} (rat) 400-700 mg/kg, LD_{50} (dog) > 18 mg/kg Diethylene Glycol Monoethyl Ether: LD_{50} (rat) 6031 mg/kg (OECD 401) 2-Methyl-2,4-Pentanediol (Hexylene Glycol): LD_{50} (rat) > 2000 mg/kg (OECD 420)
Dermal Toxicity-acute	Roflumilast: No data available. Diethylene Glycol Monoethyl Ether: LD_{50} (rabbit) 9143 mg/kg (OECD 402) 2-Methyl-2,4-Pentanediol (Hexylene Glycol): LD_{50} (rat) > 2000 mg/kg (OECD 420)
Inhalation Toxicity-acute	Roflumilast: No data available. Diethylene Glycol Monoethyl Ether: LD_{50} (rat) 4-hrs 5.2 mg/L (no guideline available) 2-Methyl-2,4-Pentanediol (Hexylene Glycol): LD_{50} (rat) 8-hrs 60 mg/L; no deaths (OECD 420)
Injection Toxicity-acute	No data available.
Other Toxicity Data	None.
Potential Acute Adverse Effects by Route of Exposure for Product	The potential adverse effects information provided below is pertinent to medical employees handling this product in an occupational setting or to employees involved in the use or distribution of this product. The following paragraphs describe the symptoms of exposure by route of exposure. All possible effects would be determined by concentration and duration of exposure.
Oral Exposure-acute	Ingestion of the product is not a normal route of exposure in the workplace. If accidentally ingested, digestive upset, nausea or vomiting may occur. Ingestion may be harmful.
Dermal Exposure-acute	This product is designed to be applied to the skin. Mild irritation to the skin may occur in persons sensitive to ingredients.
Inhalation Exposure-acute	Inhalation of product vapors may cause irritation of the respiratory system, with coughing, sneezing and possible difficulty breathing; these symptoms are expected to be alleviated after exposure to fresh air. Chronic inhalation of vapors may cause adverse effects to the liver, based on the presence of Diethylene Glycol Monoethyl Ether.
Injection Exposure-acute	Not a likely route of exposure during normal use and handling.
Potential Acute Adverse Effects from Therapeutic Use	The following information is based upon information reported from therapeutic use, clinical trials or from other products using Roflumilast as an Active Pharmaceutical Ingredient (API). More information may be found in the Prescribing Information Sheet for this product or related products with this API.
Oral Exposure	No data available.
Dermal Exposure	This product is designed to be applied to the skin. Mild irritation to the skin may occur in persons sensitive to ingredients.
Inhalation Exposure	Use of Roflumilast as a bronchodilator has been reported to cause a small number of individuals to experience Psychiatric Events (see information above under 'Other Potential Effects.' Chronic inhalation of vapors may cause adverse effects to the liver, based on the presence of Diethylene Glycol Monoethyl Ether.
Injection Exposure	No data available.
Other Potential Effects	Phase I studies in which Roflumilast was administered at single doses up to 5000 mcg showed an increase in the incidence of headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess, and arterial hypotension. Other reported effects include hypersensitivity reactions, rash, hives, tremor, respiratory tract infections, blood in the stools. An increased number of neuropsychiatric events (e.g., anxiety, depression, insomnia/sleep disorders, and rare instances of suicidal behaviors/ideation) have also been reported with use. Symptoms associated with overdosage have included dizziness, heart palpitations, lightheadedness, clamminess, and sudden blood pressure drop.
Specific Target Organ Toxicity (STOT) Single Exposure	No data available.
Specific Target Organ Toxicity (STOT) Repeated Exposure	No data available for components of greatest percentage; no component has been classified under GHS as a repeated dose toxicity compound. There is some evidence of potential elevation of liver enzymes and an increase in Roflumilast n-oxide when Roflumilast is administered orally in humans. No specific studies have been found for elevated liver enzymes or an increase in the Roflumilast metabolite from administration of Roflumilast via the dermal route. The following repeated dose toxicity is available for the product and/or Roflumilast from animal testing. Roflumilast Cream: Mice and minipigs, Dermal: no evidence of systemic toxicity. Roflumilast: Mouse (6 month), Oral NOAEL: 4 mg/kg/day Mouse (13-week), Dermal NOAEL: 1% w/w ARQ-151 cream (20 mg/kg/day), the highest dose tested. Rat (6-month), Oral NOAEL: 0.8 mg/kg/day Dog (12-month), Oral NOAEL: 0.6 mg/kg/day Monkey (42 weeks), Oral NOAEL: 0.25 mg/kg/day Minipig (9 month), Dermal NOAEL: 1% w/w ARQ-151 cream (20 mg/kg/day), the highest dose tested.
Aspiration Hazard	Not a likely hazard for this product due to its form. No data available or reports of aspiration.

11. TOXICOLOGICAL INFORMATION (Continued)

Irritancy of Product
Although some components meet the criteria for acute skin, eye or respiratory irritation/corrosion, test results for the product for acute eye and skin irritancy have shown that the product does not cause significant eye or skin irritancy. Prolonged contact with liquid or vapors of this product may irritate the skin and respiratory system, depending on duration and concentration of exposure. Prolonged eye contact will cause irritation.

Respiratory Irritancy/Corrosion
No specific data available.

Eye Irritancy/Corrosion
Roflumilast Cream: In vitro eye irritation (BCOP) study: not irritating.

Skin Irritancy/Corrosion
Roflumilast Cream: Minipigs: No irritation and no microscopic skin findings.

Sensitization Effects
No sensitization effects have been described for this product in workplace or therapeutic use.

Respiratory Sensitization
Not tested.

Skin Sensitization
No component is known to cause human sensitization. Roflumilast Cream: Guinea pig, not a dermal sensitizer.

Synergistic Effects-Therapeutic Use
Coadministration of Roflumilast with systemic CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously may increase roflumilast systemic exposure and may result in increased adverse reactions. Coadministration of roflumilast with oral contraceptives containing gestodene and ethinyl estradiol may increase Roflumilast systemic exposure and may result in increased side effects. Consult Prescribing Information Sheet for possible interactions with other therapeutic drugs.

Endocrine Toxicity
This product contains paraben compounds in trace amounts that are under assessment as possible endocrine disruptors.

Carcinogenic Potential of Components
No component of the product is listed by agencies tracking carcinogenic potential. The following animal data are available for Roflumilast.
Roflumilast: Mice, Oral NOAEL: 12 mg/kg/day (highest dose tested).
Mice, Dermal NOAEL: ≤1% w/w males, ≤0.5% w/w females Hamster, Oral LOAEL: ≥8 mg/kg/day; undifferentiated carcinomas of the nasal olfactory mucosa in females.

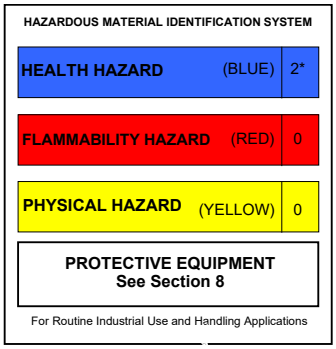
Reproductive Toxicity
No data are available on reproductive effects to humans for this product or its components. Animal data for the active ingredient, Roflumilast are given in the following paragraphs.

Mutagenicity
The components of this product are not reported to produce mutagenic effects in humans. Animal data for Roflumilast have been negative. Roflumilast: *In vitro:* Bacterial reverse mutation assay (*e.g.,* Ames test): negative.

Developmental Toxicity/ Embryotoxicity/Teratogenicity
No human data are available. The following animal data are available for the API.
Roflumilast: Mice (developmental and post-natal), Fetal Oral LOAEL: >2 mg/kg/day Effects: Increase in still births (>2 mg/k/day), pup mortality (6 mg/kg/day), decreased pup survival and forelimb grip reflex (12 mg/kg/day). Rats (developmental), Fetal oral LOAEL: ≥0.6 mg/kg/day Effects: Post-implantation loss.

Reproductive Toxicity
The components of this product are not reported to produce reproductive effects in humans. The following animal data are available for the API. Animal data indicate reduced fertility in male rats, however in a human spermatogenesis study, no effects on semen parameters were noted..

Adverse Effects on or Via Lactation
There is no information regarding the presence of Roflumilast in human milk, the effects on the breastfed infant, or the effects on milk production. However, Roflumilast and/or its metabolites are excreted into the milk of lactating rats *(see below)*. When a drug is present in animal milk, it is likely that the drug will present in human milk. Use of this product for lactating women is contraindicated, based on animal data.
Roflumilast: Roflumilast and/or its metabolite concentrations measured 8 hours after an oral dose of 1 mg/kg given to lactating rats were 0.32 and 0.02 mcg/g in the milk and pup liver, respectively.



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

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. It is expected that some biodegradation will occur to this product; however, no specific information is known. Test data for Roflumilast have shown it is not readily biodegradable: Biodegradation after 21 days: < 11.6% (OECD 301D).

12. ECOLOGICAL INFORMATION (Continued)

Bio-Accumulation Potential
This product has not been tested for bio-accumulation potential. No data for components indicate bio-accumulation potential.

Aquatic Toxicity
This product has not been tested for aquatic toxicity, however the estimated concentration at the point of entry is less than 1 ppb. Data are available for some components, as follows.
Roflumilast: LC50 (Brachydanio reiro zebra fish) 96-hr: 0.295 mg/L (OECD 203); EC50 (Daphnia magna giant water flea) 48-hr: > 0.43 mg/L (OECD 202); EC50 (Desmodesmus subspicatus) 72-hr: 0.043 mg/L (OECD 201)
Diethylene Glycol Monoethyl Ether: LC50 (Ictalurus punctatus channel catfish) 96-hr: 6010 mg/L (OECD 203); EC50 (Daphnia magna giant water flea) 48-hr: 1982 mg/L (OECD 202); (Pseudokirchneriella subcapitata green algae) 72-hr: 14,861 mg/L (OECD 201)
2-Methyl-2,4-Pentanediol (Hexylene Glycol): LC50 (fish) 96-hr: > 5000 mg/L (OECD 203); EC50 (Daphnia magna giant water flea) 48-hr: 2800 mg/L (OECD 202); (green algae) 72-hr: 429 mg/L (OECD 201)

Environmental Risk Assessment
An environmental Risk Assessment study for this product has been completed. Based on the results, the calculated Expected Introduction Concentration (EIC) of ARQ-151 at the point of entry into the aquatic environment is below 1 part per billion (ppb). The actual calculated value from the assessment is: EIC Aquatic: 0.009 ppb.

Endocrine Disrupting Properties
The trace paraben components are under assessment as potential endocrine disruptors. Endocrine disruptors that find their way into the environment can cause adverse effects on aquatic and terrestrial organisms.

Other Adverse Effects
The components of this product are not listed as having ozone depletion potential.

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 Disposal Methods
It is the responsibility of the generator to determine at the time of disposal whether the product meets the criteria of a hazardous waste per regulations of the area in which the waste is generated and/or disposed of. Waste disposal must be in accordance with appropriate Federal, State, Provincial and local regulations. This product, if unaltered by use, may be disposed of by treatment at a permitted facility or as advised by your local hazardous waste regulatory authority. Shipment of wastes must be done with appropriately permitted and registered transporters.

Disposal Containers
Waste materials must be placed in and shipped in appropriate poly or metal waste pails or drums. Permeable cardboard containers are not appropriate and should not be used. Ensure that any required marking or labeling of the containers be done to all applicable regulations.

Precautions to be Followed During Waste Handling
Wear proper protective equipment when handling waste materials. Dispose of in accordance with applicable Federal, State, and local procedures and standards.

U.S. EPA Waste Number
None applicable.

14. TRANSPORTATION INFORMATION

U.S. Department of Transportation Regulations
This product does not meet the criteria of Dangerous Goods under DOT regulations.

Transport Canada, Transportation of Dangerous Goods Regulations
This product does not meet the criteria of Dangerous Goods under Canadian TDG.

International Air Transport Association (IATA) Designation
This product does not meet the criteria of Dangerous Goods under IATA/ICAO rules.

15. REGULATORY INFORMATION

U.S. Regulations

EPA SARA Reporting Requirements

Chemical Name	Section 302 EHS (TPQ) (40 CFR 355, Appendix A)	Section 304 RQ (40 CFR Table 302.4)	Section 313 TRI (Threshold) (40 CFR 372.65)
Diethylene Glycol Monoethyl Ether	-------	-------	N230

EPA CERCLA Reportable Quantity (RQ)
Diethylene Glycol Monoethyl Ether: Although no specific RQ is assigned to this compound, as a glycol ether it is part of the generic or broad class 'Glycol Ethers,' and is classified as a CERCLA hazardous substance.

EPA TSCA Inventory Status
Drugs are exempt from TSCA rules.

EPA Clean Air Act (CAA)
No component has requirements under the Clean Air Act

EPA Clean Water Act (CWA)
No component is listed as Toxic or Priority Pollutant under EPA Clean Air Act (40 CFR Part 423, Appendix A) or as a Hazardous Substance in Table 116.4A or 4B.

EPA RCRA Part 266 Subpart P
This product may have requirements under the EPA RCRA Part 266 Subpart P regulations. Refer to the regulation for possible requirements related to disposal of waste pharmaceuticals.

California Safe Drinking Water and Toxic Enforcement Act (Proposition 65)
No component of this product is listed in the California Proposition 65 legislation. This product does not contain any substances known to the state of California to cause cancer, developmental and/or reproductive harm.

15. REGULATORY INFORMATION (Continued)

Canadian Regulations

DSL/NDSL Inventory Status All components of this product are on the Canadian DSL Inventory, except Roflumilast.

Canadian Environmental Protection Act (CEPA) Priorities Substances Lists

Chemical Name	CEPA Subsection 73(1) Status
Diethylene Glycol Monoethyl Ether	Met the criteria under subsection 73(1) of the Canadian Environmental Protection Act.
Methylparaben	Did not meet the criteria under subsection 73(1) of the Canadian Environmental Protection Act.
2-Methyl-2,4-pentanediol	Did not meet the criteria under subsection 73(1) of the Canadian Environmental Protection Act.
Propylparaben	Did not meet the criteria under subsection 73(1) of the Canadian Environmental Protection Act.
Roflumilast	No information.
White Petrolatum	Met the criteria under subsection 73(1) of the Canadian Environmental Protection Act.

16. OTHER INFORMATION

Preparation Date March 20, 2023

Revisions Details May 8, 2024: Review of SDS of all sections for currency of information and regulatory compliance. Change to SDS includes updated product name and removed strength.

References and Data Sources Information from published literature, regulatory authorities and internal company data.

Methods of Evaluating Information for the Purpose of Classification Finished pharmaceutical products are not regulated by GHS.

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Abbreviations and Acronyms ACGIH - American Conference of Governmental Industrial Hygienists;; AIHA - American Industrial Hygiene Association; CAS# - Chemical Abstract Services Number;; DNEL - Derived No Effect Level; DOT - Department of Transportation;; 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; 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

Disclaimer Information in this SDS is based on currently available data available and is believed to be correct. However, no warranty is expressed or implied regarding the accuracy of these data or the results to be obtained from the use thereof. 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 potent 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.

Arcutis Biotherapeutics assumes no responsibility for injury to the vendee or third persons proximately caused by the material if reasonable safety procedures are not adhered to as stipulated in the data sheet. Additionally, **Arcutis Biotherapeutics** assumes no responsibility for injury to vendee or third persons proximately caused by abnormal use of the material even if reasonable safety procedures are followed. Furthermore, vendee assumes the risk in his use of the material.