SAFETY DATA SHEET

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

Contact information

General

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+ 1 (480) 666-0610 (*Monday-Friday 9 am to 5 pm EST Availability*)

Product identifier

Tapinarof cream

Synonyms

5-[(E)-2-Phenylethyl]-2-(propan-2-yl)benzene-1,3-diol; 3,5-Dihydroxy-4-isopropylstilbene; Benvitimod (discontinued name); DMVT-505; WB-1001; WBI-1001; GSK2894512 formulated product.

Trade names

None identified

Chemical family

Mixture - contains a stilbene

Relevant identified uses of the substance or mixture and uses advised against

Bulk formulated pharmaceutical mixture; being investigated for the topical treatment of atopic dermatitis and plaque psoriasis.

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.

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture

The classification and labeling listed below is for bulk drug product.

Globally Harmonized System [GHS]

Aquatic toxicity (chronic) - Category 3.

Label elements

SECTION 2 - HAZARDS IDENTIFICATION …continued

GHS hazard pictogram	None required
GHS signal word	None required
GHS hazard statements	H412 - Harmful to aquatic life with long lasting effects.
GHS precautionary statements	P273 - Avoid release to the environment. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.
Other hazards	Tapinarof is an activator of aryl hydrocarbon receptor (AhR), a critical regulator of immune responses. The most common adverse effects reported in clinical trials were inflammation of the skin and hair follicles, sore throat, skin and upper respiratory tract infection, headache, acne, and worsening/flare of disease.
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
Tapinarof	79338-84-4		0.5-3%	AT1:H400
Diethylene glycol monoethyl ether	111-90-0	203-919-7	1-10%	Not classified
2, 6-di-tert-butyl-p-cresol (butylated hydroxytoluene)	128-37-0	204-881-4	0-1%	ATO4: H302
Propylene glycol	57-55-6	200-338-0	0-10%	Not classified
Steareth 2 and 20	9005-00-9	500-017-8	1-10%	EI2B:H320

Note The substance(s) listed above are considered hazardous. Propylene glycol and diethylene glycol monoethyl ether are included because they have OELs and are present at or above 1%. The remaining components are not hazardous and/or present at amounts below reportable limits. Amounts are listed as ranges; the exact percentage of composition is withheld as a trade secret. See Section 16 for full text of GHS classifications.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures

Immediate Medical Attention Needed	Yes

SECTION 4 - FIRST AID MEASURES …continued

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: None known or reported. Treat symptomatically and supportively.

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/or sodium-containing compounds.
Flammability/ Explosivity	No information identified.
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/mixture 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 mist/spray.

SECTION 6 - ACCIDENTAL RELEASE MEASURES …continued

Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	DO NOT CAUSE MATERIAL TO BECOME AIRBORNE. For small spills, soak up material with absorbent, e.g., paper towels. For large spills, cordon off spill area and minimize the spreading of spilled material. Soak up material with absorbent. Collect spilled material, absorbent, and rinse water into suitable containers for proper 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	Follow recommendations for handling pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Avoid breathing mist/spray. Wash thoroughly after handling.
Conditions for safe storage including any incompatibilities	Keep away from heat, sparks and open flame. Store in original tightly closed container.
Specific end use(s)	No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note	Wash hands, face and other potentially exposed areas immediately in the event of physical contact.

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Tapinarof	Dermavant	TWA 8-HR	40 µg/m³
Diethylene glycol monoethyl ether	AIHA	TWA-8 HR	25 ppm
	Estonia	TWA-8 HR	10 ppm (skin)
	Germany	Ceiling	100 mg/m³ (inhalable fraction)
	Germany	TWA-8 HR	50 mg/m³ (inhalable fraction)
	Germany	TWA-8 HR	6 ppm
	Sweden	STEL	30 ppm
	Sweden	TWA-8 HR	15 ppm

Control Parameters/ Occupational Exposure Limit Values

…continued

Compound	Issuer	Type	OEL
2, 6-di-tert-butyl-p-cresol (butylated hydroxytoluene)	ACGIH, Belgium, Italy, Portugal, Spain	OEL-TWA 8-Hr	2 mg/m³ (inhalable fraction, aerosol and vapor)
	Austria, Bulgaria, Denmark, Finland, France, Greece, Ireland, NIOSH, Slovenia, United Kingdom	OEL-TWA 8-Hr	10 mg/m³
	Germany	OEL-TWA 8-Hr	20 mg/m³ (inhalable fraction)
	OSHA	PEL (vacated)	10 mg/m³
Propylene glycol	AIHA	TWA-8 HR	10 mg/m³
	Ireland, United Kingdom	TWA-8 HR	150 ppm (total vapor and particulates), 10 mg/m³ (particulates)
	Latvia, Lithuania	TWA-8 HR	7 mg/m³
	United Kingdom	STEL	450 ppm (total particulate and vapor), 30 mg/m³ (particulate)
Steareth 2 and 20	--	--	--

Exposure/Engineering controls

None required for normal handling of packaged product. If handling bulk formulation: 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. Solutions can be handled outside a containment system or without local exhaust ventilation (LEV). Use engineered LEV and/or enclosure for high-energy operations such as spraying. All containers for solutions and slurries must be covered while being transferred.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION …continued

Respiratory protection	None required for normal handling of packaged product. If handling bulk formulation: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. Respirators are generally not required. At minimum, a tight-fitting full-face respirator with HEPA filters is required for spill cleanup.
Hand protection	None required for normal handling of packaged product. If handling bulk formulation: Wear nitrile or other impervious gloves if skin contact is possible.
Skin protection	Wear disposable coveralls appropriate to the task, booties, and safety glasses with side shields. Ensure gloves are protective against solvents in use. 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 degowning practices
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 mixture/product, 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). Decontaminate all protective equipment following use.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance	High viscous liquid or semisolid.
Color	White to pale brown.
Odor	No information identified.
Odor threshold	No information identified.
pH	5.8-6 (10% suspension, 19 °C) (tapinarof).
Melting point/ freezing point	146-147 °C (tapinarof).
Initial boiling point and boiling range	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Flash point	No information identified.
Evaporation rate	No information identified.
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	Insoluble (0.014 mg/mL).
Solvent solubility	No information identified.
Partition coefficient (*n-octanol/water*)	5.03-5.06 across pH range 5-9.
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.
Viscosity	High viscous liquid or semisolid.
Explosive properties	Not explosive (tapinarof).
Oxidizing properties	Not oxidizing (tapinarof).

Other information

Molecular formula	Not applicable (Mixture)
Molecular weight	Not applicable (Mixture)

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	No information identified.
Chemical stability	No information identified.
Possibility of hazardous reactions	Not expected to occur.
Conditions to avoid	No information identified.
Incompatible materials	No information identified.

SECTION 10 - STABILITY AND REACTIVITY …continued

Hazardous decomposition products No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note No data for this product/mixture were identified. The following data describe the active ingredient and/or the individual ingredients where applicable.

Information on toxicological effects

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

Acute toxicity

Compound	Type	Route	Species	Dose
Tapinarof	--	--	--	--
Diethylene glycol monoethyl ether	LD_{50}	Oral	Rat	1920 - >5000 mg/kg
	LD_{50}	Oral	Mouse/ Rabbit	>2000 mg/kg
	LD_{50}	Dermal	Rabbit	>2000 mg/kg
	LC_{50}	Inhalation	Rat	>5240 mg/m³
2, 6-di-tert-butyl-p-cresol (butylated hydroxytoluene)	LD_{50}	Oral	Rat	890 mg/kg
Propylene glycol	LD_{50}	Oral	Rat	20000 mg/kg
	LD_{50}	Oral	Mouse	22000 mg/kg
	LD_{50}	Oral	Rabbit	18500 mg/kg
	LD_{50}	Oral	Dog	22000 mg/kg
	LD_{50}	Oral	Guinea Pig	18350 mg/kg
	LD_{50}	Dermal	Rabbit	20800 mg/kg
	LC_{50} (4 hour)	Inhalation	Rat	>44.9 g/m³/4H
Steareth 2 and 20	LD_{50}	Oral	Rat	25000 mg/kg

Irritation/Corrosion In rabbits, tapinarof (concentration of 8%) caused negligible skin irritation and was practically non-irritating to the eye.

Sensitization No dermal sensitization occurred in guinea pigs (concentrations up to 8%) or mice (concentrations up to 4%). A phototoxicity study using hairless mice was also negative.

STOT-single exposure In rats, tapinarof did not cause toxicity at oral or SC doses of 10 mg/kg or dermal doses of 480 mg/kg. In rabbits, tapinarof did not cause toxicity at dermal doses of 640 mg/kg.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

STOT-repeated exposure/Repeat-dose toxicity

In a 28-day rat dermal study, ≥4% cream (≥240 mg/kg/day) caused skin dryness, redness, thickening, and tearing, which peaked during Week 3 of dosing and then subsided. Other effects included: skin growth with necrotic areas and pus, decreased number of red blood cells, increased white blood cells and liver weight, enlarged lymph nodes. No effects were reported at 1% (60 mg/kg/day).

In a 28-day rabbit dermal study, mild skin reactions were noted at 3% (225 mg/kg/day) and 4% (320 mg/kg/day). At 6% (480 mg/kg/day), skin dryness, loss of elasticity, skin thickening, localized increase of connective tissue cells or white blood cells, inflammation, fluid accumulation, pus, as well as body weight loss, and liver toxicity. Effects on the biliary system and thymus were also noted. The NOAEL was 1% (80 mg/kg/day).

Reproductive toxicity

In rats, tapinarof had no effect on female/male reproductive parameters at SC doses up to 30 mg/kg/day for up to 26 weeks.

In guinea pigs, tapinarof had no effect on female/male reproductive organs at dermal doses up to 60 mg/kg/day (concentration of 3%) for 39 weeks.

Developmental toxicity

In rats, tapinarof caused a decrease in fetal body weights and incomplete ossification of the nasal bones at SC doses of 34 mg/kg/day; NOAEL: 6.9 mg/kg/day.

In rabbits, tapinarof caused maternal toxicity (reduced body weight gain), post-implantation loss, and fetal skeletal variations at 3 mg/kg/day SC; NOAEL: 1 mg/kg/day. In another study, SC infusion did not cause marked maternal/fetal toxicity; NOAEL: 3 mg/kg/day.

Genotoxicity

Tapinarof was not genotoxic *in vitro* (Ames assay, chromosomal aberration test in Chinese hamster ovary cells, mouse lymphoma) or *in vivo* (mouse micronucleus assay).

Carcinogenicity

No data available. None of the components of this mixture 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
Tapinarof	EC_{50} (3 h)	Residential sludge	>32 mg/L
	NOEC	Residential sludge	10 mg/L
	EC_{50} (96 h), QSAR estimate	Algae	0.1-1 mg/L
	EC_{50} (48 h)	Water flea (Dalphnia magna)	0.49 mg/L

SECTION 12 - ECOLOGICAL INFORMATION …continued

Toxicity …continued

Compound	Type	Species	Concentration
	NOEC	Water flea (Dalphnia magna)	0.36 mg/L
	EC_{50} (96 h), QSAR estimate	Fish	0.1-1 mg/L
Diethylene glycol monoethyl ether	LC_{50}/96h	Fish (various species)	>1000 mg/L
	EC_{50}/48h	Freshwater invertebrates	>1000 mg/L
2, 6-di-tert-butyl-p-cresol (butylated hydroxytoluene)	--	--	--
Propylene glycol	EC_{50} (96h)	Green algae (Selenastrum capricornutum)	19,600 mg/L
	LC_{50} (48 h)	*Daphnia magna* (water flea)	43,500 mg/L
	LC50 (24 h)	Carassius auratus (fresh water fish)	>5000 mg/L
	LC_{50} (96 h)	Lepomis macrochirus, bluegill sunfish	>10,000 ppm
	LC_{50} (96 h)	*Oncorhynchus mykiss* (rainbow trout)	51,600 mg/L
	LC_{50} (96 h)	Pimephales promelas (fathead minnow)	54,900 mg/L
Steareth 2 and 20	--	--	--

Persistence and Degradability
For tapinarof:
Not inherently biodegradable.
Percent degradation (aerobic biodegradation-inherent): 42% ultimate biodegradation, 82% primary degradation.

Bioaccumulative potential
Tapinarof will tend to bioaccumulate in the food chain.

Mobility in soil
No data available.

Results of PBT and vPvB assessment
No data available.

Other adverse effects
No data available.

Note
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 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 mixture/product is regulated as an environmental hazard or a marine pollutant.
Special precautions for users	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	CA3 - Chronic Aquatic Toxicity Category 3. H412 - Harmful to aquatic life with long lasting effects.
Sources of data	Information from published literature and internal company data.

SECTION 16 - OTHER INFORMATION …continued

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; PBT - Persistent, Bioaccumulative, and Toxic; 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; vPvB - Very Persistent and Very Bioaccumulative; WHMIS - Workplace Hazardous Materials Information System

Issue Date

13 May 2019

Revisions

This is the first version of this SDS.

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.