



SAFETY DATA SHEET

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

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Product identifier	Alitretinoin
Synonyms	(2E, 4E, 6Z, 8E)-3,7-dimethyl-9- (2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoic acid; 9- <i>cis</i> -retinoic acid; Eisai Material No. 300118
Trade names	Panretin [®] (final drug product)
Chemical family	Retinoids

**Relevant identified uses
of the substance or
mixture and uses
advised against** Active pharmaceutical ingredient; used for the treatment of AIDS-related Kaposi's sarcoma and other skin disorders.

Note This SDS is written to address potential worker health and safety issues associated with the handling of the active pharmaceutical ingredient.

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SECTION 2 - HAZARDS IDENTIFICATION

**Classification of the
substance or mixture**

**Regulation (EC) 1272/
2008 [GHS]** Specific Target Organ Toxicity (repeated exposure) - Category 1. Reproductive Toxicity - Category 1B.

**Directive 67/548/EEC
or 1999/45/EC** T - R48/24/25; R61 (Repr. Cat. 2)

SECTION 2 - HAZARDS IDENTIFICATION ...continued

Label elements

CLP/GHS hazard pictogram



CLP/GHS signal word

Danger

CLP/GHS hazard statements

H372 - Causes damage to skin, liver, kidney, bone and hematopoietic systems through prolonged or repeated exposure. H360D - May damage the unborn child.

CLP/GHS precautionary statements

P201 - Obtain special instructions before use. P202 - Do not handle until all safety precautions have been read and understood. P260 - Do not breathe dust. P264 - Wash hands thoroughly after handling. P270 - Do not eat, drink or smoke when using this product. P281 - Use personal protective equipment as required. P308 + P313 - If exposed or concerned: get medical advice/attention. P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.

Other hazards

Alitretinoin, a derivative of Vitamin A, is a naturally occurring endogenous retinoid used topically to treat skin lesions associated with AIDS-related Kaposi's sarcoma. Alitretinoin may also be given orally to treat severe chronic hand eczema that is unresponsive to other therapies, with a dose range of 10-30 mg/day. Retinoids, such as alitretinoin, modulate expression of specific genes that are involved in a number of vital cellular functions associated with development, growth and maintenance of cells. Following oral administration, the most frequent adverse effects were reversible and included headache, flushing, changes in lipid profiles in blood and thyroid hormone levels. Following topical application, the most common adverse effects included rash, pain, itching, dermatitis, tingling sensations, blistering and edema.

Exposure to retinoids has been associated with teratogenic effects and an increased incidence of spontaneous abortions. Although no clinical data specific to alitretinoin were identified, it should be considered teratogenic and/or embryolethal when administered systemically based on developmental effects seen in animal studies at low doses, consistent with the mechanism of action of retinoids.

Retinoids have been associated with photosensitivity, typically increased susceptibility to sunburn.

US Signal word

None required

US Hazard overview

Active pharmaceutical ingredient. Can cause damage to the liver, kidney, bone and hematopoietic systems based on human and animal data. Possible developmental hazard - may cause adverse developmental effects (based on animal data). Possible birth defect hazard - may cause birth defects (based on animal data).

SECTION 2 - HAZARDS IDENTIFICATION ...continued

Note This substance is classified as hazardous according to Directive 67/548/EEC, Regulation EC No 1272/2008 (EU-CLP), and applicable US regulations. The GHS classifications are based on Regulation (EC) 1272/2008. Its ecological properties have not been fully characterized.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

<u>Ingredient</u>	<u>CAS #</u>	<u>EINECS/ ELINCS#</u>	<u>Amount</u>	<u>EU Classification</u>	<u>GHS Classification</u>
Alitretinoin	5300-03-8	N/A	~100%	Toxic - T: R48/ 24/25; R61	STOT-R1: H372; RT1B: H360D

Note The ingredient listed above is considered dangerous/hazardous. See Section 16 for full text of EU and EU-CLP/GHS classifications. The EU classification is based on Directive 67/548/EEC and the GHS classification is based on Regulation (EC) 1272/2008.

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.

SECTION 4 - FIRST AID MEASURES ...continued

Indication of immediate medical attention and special treatment needed, if necessary	Medical conditions aggravated by exposure: Severe renal impairment; hypercholesterolemia or hypertriglyceridemia; and hypothyroidism. Treat symptomatically and supportively.
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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 toxic fumes of carbon monoxide and carbon dioxide.
Flammability/Explosivity	No explosivity or flammability data identified. High concentrations of finely divided airborne 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	Due to lack of data, avoid release to the environment.
Methods and material for containment and cleaning up	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 into solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container for disposal in accordance with applicable waste disposal regulations (see section 13). Decontaminate the area twice with an appropriate solvent (see section 9).
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 dust. Wash thoroughly after handling.
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SECTION 7 - HANDLING AND STORAGE ...continued

Conditions for safe storage including any incompatibilities	Store in a cool, dry area away from direct sunlight. Store locked up.
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**

<u>Compound</u>	<u>Issuer</u>	<u>Type</u>	<u>OEL</u>
Alitretinoin	Eisai, Inc.	TWA-8 HR	5 µg/m ³

Exposure/Engineering controls Control exposures to below the OEL (if available). Otherwise, 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 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 Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered. When the material is dissolved or suspended in an organic solvent, wear gloves that provide protection against the solvent.

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.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION ...continued

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

Appearance	Solid (powder)
Color	Yellow
Odor	No information identified.
Odor threshold	No information identified.
pH	No information identified.
Melting point/ freezing point	189-191° C
Initial boiling point and boiling range	No information identified.
Flash point	No information identified.
Evaporation rate	Not applicable.
Flammability (solid, gas)	No information identified.
Upper/lower flammability or explosive limits	No information identified.
Vapor pressure	1×10^{-7} mmHg @ 25°C (estimated)
Vapor density	No information identified.
Relative density	No information identified.
Water solubility	Insoluble in water.
Solvent solubility	Slightly soluble in ethanol (7.01 mg/g).
Partition coefficient (<i>n</i>-octanol/water)	LogP = 5.01-5.66 LogK _{ow} = 6.03
Auto-ignition temperature	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ...continued

Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	No information identified.
Oxidizing properties	No information identified.
Other information	
Molecular weight	300.3
Molecular formula	C ₂₀ H ₂₈ O ₂

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.
Hazardous decomposition products	No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Information on toxicological effects

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

Acute toxicity

<u>Compound</u>	<u>Type</u>	<u>Route</u>	<u>Species</u>	<u>Dose</u>
Alitretinoin	LD ₅₀	Oral	Rat	3,000 mg/kg

Irritation/Corrosion No data available on API.

Sensitization No data available on API.

STOT-single exposure No data identified.

SECTION 11 - TOXICOLOGICAL INFORMATION ...continued

STOT-repeated exposure/Repeat-dose toxicity	<p>Repeat-dose toxicity studies of up to 9 and 6 months' duration were conducted in dogs and rats, respectively (doses and route of administration not specified). Signs of toxicity were dose-related and occurred at exposures similar to the human therapeutic dose (based on plasma levels). Target organs identified include liver, kidney, liver, bone and hematopoietic system. Adverse effects were characteristic for retinoids and generally reversible.</p> <p>An oral NOAEL of 1 mg/kg/day was identified in a 28-day rat study. Toxicity was seen at lower doses in longer rat studies, though details were not identified.</p> <p>An oral NOAEL of 0.3 mg/kg/day was identified in a 28-day dog study.</p>
Reproductive toxicity	<p>In a study of fertility and early embryonic development in rats, no effects on fertility were observed at the highest dose tested (details not specified).</p>
Developmental toxicity	<p>Alitretinoin was shown to be teratogenic in rabbits treated during organogenesis at oral doses as low as 0.5 mg/kg/day. Teratogenicity was also observed in mice treated with a single oral dose of 50 mg/kg on day 11 of gestation. Embryoletality was observed in rats and rabbits treated with oral doses as low as 5 and 1.5 mg/kg/day, respectively. As with other retinoids, reversible effects on male reproductive organs were observed in dogs (details not specified).</p>
Genotoxicity	<p>Alitretinoin was negative in a battery of <i>in vitro</i> and <i>in vivo</i> genotoxicity assays.</p>
Carcinogenicity	<p>In 2-year carcinogenicity studies in rats and mice, no carcinogenic potential was noted. This substance is not listed by NTP, IARC, ACGIH or OSHA as a carcinogen.</p>
Aspiration hazard	<p>No data available.</p>
Human health data	<p>See "Section 2 - Other Hazards"</p>

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity	<u>Compound</u>	<u>Type</u>	<u>Species</u>	<u>Concentration</u>
	Alitretinoin	NOEC/ 6 days	Daphnia pulex (water flea)	100 µg/L
Persistence and Degradability		No data available.		
Bioaccumulative potential		No data available.		
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 Releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods Used product should be disposed of according to local, state, and federal regulations. All wastes containing the material should be properly labeled. Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. 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 substance 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 substance is not regulated as an environmental hazard or a marine pollutant.

Special precautions for users Substance not fully tested - avoid exposure. 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 complies with the requirements under US, EU and GHS (EU CLP - Regulation EC No 1272/2008) guidelines. Consult your local or regional authorities for more information.

Chemical safety assessment Not conducted.

SECTION 15 - REGULATORY INFORMATION ...continued

OSHA Hazardous	Yes. Can cause damage to the liver, kidney, bone and hematopoietic systems based on human and animal data. Possible developmental hazard - may cause adverse developmental effects (based on animal data). Possible birth defect hazard - may cause birth defects (based on animal data).
WHMIS classification	Not required. Drugs are not subject to WHMIS. This product has been classified in accordance with the hazard criteria of the Controlled Products Regulations and the SDS contains all of the information required by those regulations.
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 R phrases and EU Classifications	T - Toxic. R48/23/25 - Toxic: danger of serious damage to health by prolonged exposure through contact with skin and if swallowed. R61 - May cause harm to the unborn child.
Full text of H phrases, P phrases and GHS classification	STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. RT1B - Reproductive toxicity Category 1B. H360D - May damage the unborn child. H372 - Causes damage to organs through prolonged or repeated exposure.
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; API - Active Pharmaceutical Ingredient; 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; NOEC - No Observable Effect Concentration; 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; 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

SECTION 16 - OTHER INFORMATION ...continued

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.