SAFETY DATA SHEET

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

Contact information

General

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Product identifier

Neratinib Tablets

Synonyms

PB-272, HKI-272; (E)-N-[4-[3-chloro-4-(pyridin-2-ylmethoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide; 2-Butenamide, *N*-[4-[[3-chloro-4-(2-pyridinylmethoxy)phenyl]amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-, (2*E*)-, (2*Z*)-2-butenedioate (1:1)

Trade names

Nerlynx™

Chemical family

Mixture containing an anilinoquinoline substance

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

Bulk formulated pharmaceutical product. Contains active pharmaceutical substance (neratinib maleate).

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

Globally Harmonized System [GHS]

Specific Target Organ Toxicity (repeated exposure) - Category 2. Irritant (eye) - Category 2A. Toxic to reproduction - Category 2. Aquatic toxicity (acute) - Category 1. Aquatic toxicity (chronic) - Category 2.

Label elements

SECTION 2 - HAZARDS IDENTIFICATION …continued

GHS hazard pictogram

GHS signal word Warning

GHS hazard statements H373 - May cause damage to the liver, skin, and gastrointestinal tract through prolonged or repeated exposure. H319 - Causes serious eye irritation. H361d - Suspected of damaging the unborn child. H410 - Very toxic to aquatic life with long-lasting effects.

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. P273 - Avoid release to the environment. P280 - Wear protective gloves/eye protection/face protection. P305 + P351 + P338 - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P308 + P313 - If exposed or concerned: get medical advice/attention. P337 + P313 - If eye irritation persists: Get medical advice/attention. P391 - Collect spillage. P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.

Other hazards Neratinib is an irreversible inhibitor of the HER-2 receptor tyrosine kinase with potential antineoplastic activity. It is being investigated for the treatment of breast cancer and other solid tumors. Oral doses in clinical trials were 240 mg/day. Adverse effects in clinical trials included diarrhea, nausea, vomiting, and fatigue. Tyrosine kinases, including HER-2, are important mediators of embryonic development. As neratinib is a HER-2 inhibitor, the risk of adverse effects in pregnancy is high, consistent with adverse effects reported in non-clinical developmental toxicity studies at doses ≥6 mg/kg/day.

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
Neratinib maleate	915942-22-2	N/A	<50%	STOT-R2:H373; EI-2A: H319; RT-2: H361d; AA1: H400; CA1:H410
Myocrystalline cellulose	9004-34-6	N/A	<15%	Not Classified
Colloidal Silicon Dioxide	7631-86-9	NA	<5%	Not Classified

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS …continued

Ingredient	CAS #	EINECS/ ELINCS#	Amount	GHS Classification
Titanium dioxide	13463-67-7	236-675-5	<1%	Not classified
Polyethylene oxide/ polyethylene glycol	25322-68-3	500-038-2	<1%	Not classified
Iron oxide	1309-37-1	215-168-2	<1%	Not Classified
Talc	14807-96-6	238-877-9	<1%	STOT-S3: H335

Note The ingredients listed above are considered hazardous. Titanium dioxide is included because it is present at ≥0.1% and is IARC-listed, though the listing is not relevant to this particular dosage form (see section 11). Polyethelyne glycol, colloidal silicon dioxide, talc, and iron oxide are listed because they are present at ≥0.1% and have OELs. The remaining ingredients are non-hazardous or present 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 lens, 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 If exposed to broken tablets, dust or powder, 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 If swallowed in large quantities, get medical attention. 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	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, or chlorine-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 crush, break or chip tablets. 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 tablets are spilled, scoop up and dispose of in a manner that is compliant with federal, state or local laws. If tablets are crushed/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. Scoop up broken pieces. Place spill materials into a leak-proof container 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	Follow recommendations for handling potent pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Wash thoroughly after handling. If tablets are crushed or broken, dust containing drug substance may be released. Minimize dust generation and accumulation. Avoid breathing dust.
Conditions for safe storage including any incompatibilities	Neratinib tablets should be stored at controlled room temperature with desiccant; excursions permitted 15°C-30°C (59°F-86°F). Keep the container tightly closed.
Specific end use(s)	Pharmaceutical

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Neratinib maleate	Puma	Occupational Exposure Band	OEB3 - Contact Hazards Unknown (control exposure to the range of >10 µg/m³ to <100 µg/m³)
Myocrystalline cellulose	ACGIH	TLV	10 mg/m³
	NIOSH	REL	10 mg/m³ (total); 5 mg/m³ (respirable)
Colloidal Silicon Dioxide	OSHA	PEL	80 mg/m³
	NIOSH	REL	6 mg/m³
Titanium dioxide	ACGIH, Australia, Belgium, Bulgaria, Latvia, Poland, Portugal, Romania, Singapore, Spain, OSHA (vacated)	TWA-8 HR	10 mg/m³
	Austria	TWA-8 HR	5 mg/m³ (respirable fraction)
	Austria	STEL (2 x 60 min)	10 mg/m³ (respirable fraction)
	Denmark	TWA-8 HR	6 mg/m³ (as Ti)

Control Parameters/ Occupational Exposure Limit Values

…continued

Compound	Issuer	Type	OEL
	Estonia, Lithuania, Sweden	TWA-8 HR	5 mg/m³
	France, Mexico	TWA-8 HR	10 mg/m³ (as Ti)
	Greece	TWA-8 HR	10 mg/m³ (inhalable fraction); 5 mg/m³ (respirable fraction)
	Ireland, United Kingdom	TWA-8 HR	10 mg/m³ (total inhalable dust); 4 mg/m³ (respirable dust)
	Mexico	STEL	20 mg/m³ (as Ti)
	NIOSH	IDLH	5000 mg/m³
	Romania	STEL	15 mg/m³
	United Kingdom	STEL	30 mg/m³ (total inhalable); 12 mg/m³ (respirable)
Polyethylene oxide/ polyethylene glycol	ECHA	DNEL	500 µg/m³
	AIHA	8-hour TWA	10 mg/m³ (Polyethylene glycols MW >200)
Iron oxide	OSHA	PEL	10 mg/m³
	ACGIH	TLV	5 mg/m³ (respirable fraction)
Talc	ACGIH, Austria, NIOSH, Portugal, Spain	TWA-8 HR	2 mg/m³ (respirable fraction; containing no asbestos and <1% crystalline silica)
	Australia	TWA-8 HR	2.5 mg/m³ (containing no asbestos)
	Belgium, Greece, Hungary	TWA-8 HR	2 mg/m³ (respirable fraction)
	Ireland	TWA-8 HR	0.8 mg/m³ (respirable dust)
	Netherlands	TWA-8 HR	0.25 mg/m³
	Poland	TWA-8 HR	1 mg/m³ (respirable dust)
	Romania	TWA-8 HR	2 mg/m³ (total dust)
	United Kingdom	TWA-8 HR/STEL	1 mg/m³/3 mg/m³ (respirable dust)

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION …continued

Exposure/Engineering controls	If handling either bulk tablets or damaged tablets (i.e.,crushed or broken: exposed powder): 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	If handling either bulk tablets or damaged tablets (i.e.,crushed or broken: exposed powder): 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	Not normally needed. When handling broken tablets or dust: 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 with broken tablets 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

Appearance	Tablet, debossed with W104
Color	Red

Odor	No information identified.
Odor threshold	No information identified.
pH	No information identified.
Melting point/ freezing point	No information identified.
Initial boiling point and boiling range	No information identified.
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	No information identified.
Solvent solubility	No information identified.
Partition coefficient (*n-octanol/water*)	No information identified.
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	No information identified.
Oxidizing properties	No information identified.

Other information

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

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	No information identified.
Chemical stability	Stable under normal handling and storage conditions.
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

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, skin contact and ingestion.

Acute toxicity

Compound	Type	Route	Species	Dose
Neratinib maleate	LD_{50}	Oral	Rat	>700 mg/kg
	LD_{50}	Oral	Mouse	>2000 mg/kg
Colloidal Silicon Dioxide	LD_{50}	Oral	Rat	3,160 mg/kg
	LD_{50}	Dermal	Rabbit	>2,000 mg/kg
	LC_{50} (1 hour)	Inhalation	Rat	>2.2 mg/L
Titanium dioxide	LD_{50}	Oral	Rat	>10000 mg/kg
	LD_{50}	Oral	Mouse	>10000 mg/kg
	LD_{50}	Dermal	Rabbit	>10000 mg/kg
Polyethylene oxide/ polyethylene glycol	LD_{50}	Oral	Rat	>30,000 mg/day
	LD_{50}	Dermal	Rabbit	>20,000 mg/kg
Talc	--	--	--	--

Irritation/Corrosion In rabbits, neratinib was non-irritating to skin but mildly irritating to the eyes.

Sensitization No studies identified.

STOT-single exposure For neratinib, the rat oral NOAEL was 200 mg/kg. Rat and mouse intraperitoneal NOAELs were <200 mg/kg. No details were identified.

STOT-repeated exposure/Repeat-dose toxicity	Neratinib was tested in oral rat studies, ranging from 2 weeks to 6 months. Toxicity increased with dose and duration of exposure; NOAELs at 2 weeks and 6 months were 30 and 10 mg/kg/day, respectively. In 2-week rat studies, mortalities were reported at 100 mg/kg/day. Inflammation of the GI tract and liver damage were noted, along with atrophy of the thymus, spleen, and lymph nodes and increased numbers of white blood cells. In 1-month studies, local abrasions and other effects on the skin were noted at 45 mg/kg/day. In 13-week studies at doses of up to 15 mg/kg/day, minimal signs of liver damage were noted but were not considered significant. In the 6-month studies, reversible effects to the liver, small and large intestines, and skin were noted at the high dose of 30 mg/kg/day. The NOAEL in dog studies (2 weeks to 9 months of duration) was 6 mg/kg/day. Some evidence of GI toxicity and inflammation were noted at 9 mg/kg/day.
Reproductive toxicity	For neratinib, no effects on fertility were noted in male or female rats at an oral dose of 15 mg/kg/day. Reduced body weight gains and changes in estrous cycling were noted at this dose in females.
Developmental toxicity	At doses ≥6 mg/kg/day, neratinib resulted in abortions and maternal toxicity, including effects on maternal body weight gain, maternal food consumption, and clinical signs. Neratinib-related increases in embryo-fetal death were observed at doses ≥6 mg/kg/day.
Genotoxicity	Neratinib was negative for genotoxicity *in vitro* (Ames assay, human lymphocyte *in vitro* chromosome aberration assay), and *in vivo* (mouse micronucleus test).
Carcinogenicity	Neratinib was not carcinogenic in a 6-month transgenic mouse study (doses of up to 50 and 125 mg/kg/day in males and females, respectively). No signs of carcinogenicity were reported in the interim 1-year evaluation of a 2-year rat study (doses of of up to 10 mg/kg/day). Titanium dioxide is listed by IARC as a Group 2B Carcinogen (possibly carcinogenic to humans) and by ACGIH as A4 (not classifiable as a human carcinogen). However, these classifications are only applicable to the inhalation route of exposure. NTP determined that oral titanium dioxide was not carcinogenic. None of the other components of the 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 studies identified
Human health data	See "Section 2 - Other Hazards"
Additional information	The toxicological properties of this mixture have not been fully characterized for occupational exposures

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
Neratinib maleate	72h EC_{50}	Green Algae	0.103 mg/L
	NOEC (21-day reproduction)	Water flea	0.510 mg/L
	NOEC/33 days	Fathead minnow	0.029 mg/L
	LOEC/33 days	Fathead minnow	0.055 mg/L
Titanium dioxide	LC_{50}/48h	Leuciscus idus	>1000 mg/L
Polyethylene oxide/ polyethylene glycol	EC_{50} (24 h)	*Daphnia magna* (daphnid)	>1000 mg/L
	LC_{50} (96 h)	*Poecilia reticulata* (freshwater fish)	>100 mg/L
Talc	--	--	--

Persistence and Degradability Neratinib is not readily biodegradable; the degradation half-life was 402.8 hours in the activated sludge test.

Bioaccumulative potential No data identified.

Mobility in soil No data available.

Results of PBT and vPvB assessment No data available.

Other adverse effects Neratinib maleate disappeared rapidly from the water layers and migrated to the sediment layers. It demonstrated some transformation in aerobic test systems (about 25%). The parent DT_{50} value from the water layers was 1.3 days. The DT_{90} value was approximately 6 days.

Note The environmental characteristics of this mixture have not been fully investigated. The above data are for the active ingredient and/or any other ingredient(s) where applicable. 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.

SECTION 14 - TRANSPORT INFORMATION

Transport Based on the available data, this product/mixture is regulated as a hazardous material/dangerous good under EU ADR/RID, US DOT, Canada TDG, IATA, or IMDG.

SECTION 14 - TRANSPORT INFORMATION …continued

UN number	3077
UN proper shipping name	Environmentally Hazardous Substance, Solid, n.o.s.
Transport hazard classes and packing group	Hazard Class 9; Packing group III
Environmental hazards	Based on the available data, this product/mixture 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	Not listed
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	AA1- Acute aquatic toxicity Category 1. H400 - Very toxic to aquatic life. CA2 - Chronic Aquatic Toxicity Category 2. H411 - Toxic to aquatic life with long lasting effects. STOT-R2 - Specific Target Organ Toxicity Following Repeated Exposure Category 2. H373 - May cause damage to liver, skin, or GI tract through prolonged or repeated exposure. EI2A - Eye irritant Category 2A. H319 - Causes serious eye irritation. RT2 - Reproductive toxicity Category 2. H361d - Suspected of damaging the unborn child. CA1 - Chronic Aquatic Toxicity Category 1. H410 - Very toxic to aquatic life with long lasting effects.

SECTION 16 - OTHER INFORMATION …continued

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	10 April 2017
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 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.