SAFETY DATA SHEET

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

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Product identifier	Lenvatinib Capsules
Synonyms	4-[3-(Chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate; ER-203492-13; E7080; HOPE
Trade names	None identified
Chemical family	Mixture
Relevant identified uses of the substance or mixture and uses advised against	Bulk formulated pharmaceutical mixture/Formulated pharmaceutical product/ mixture packaged in final form for patient use; under investigation to treat cancer.
Note	This SDS is written to address potential worker health and safety issues associated with the handling of the formulated drug product. The toxicological and ecological properties of this mixture and/or its ingredients have not been fully characterized. This SDS will be revisited as more data become available.
Issue Date	24 April 2014

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture	**Drugs in the finished state and intended for the final user are not subject to labeling in the US, EU or Canada.** Please consult the prescribing/packaging information. **The classification and labelling listed below is for bulk drug product.**
Regulation (EC) 1272/ 2008 [GHS]	Specific Target Organ Toxicity (repeated exposure) - Category 1 (USA). Specific Target Organ Toxicity (repeated exposure) - Category 2 (EU). Reproductive Toxicity - Category 1B.

Directive 67/548/EEC or 1999/45/EC	Xn: R48/22; R61 (Repr. Cat. 2)

Label elements

CLP/GHS hazard pictogram	
CLP/GHS signal word	Warning
CLP/GHS hazard statements	H372 - Causes damage to kidney, bone, reproductive organs, gastrointestinal system, and adrenal system through prolonged or repeated exposure (USA). H373 - May damage kidney, bone, reproductive organs, gastrointestinal system, and adrenal system through prolonged or repeated exposure (EU). 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. P314 - Get medical advice/attention if you feel unwell. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.
EU symbol/indication of danger	 Xn - Harmful
Risk (R) Phrase(s)	R48/22 - Harmful: danger of serious damage to health by prolonged exposure if swallowed.
Safety Advice	S2 - Keep out of reach of children. S22 - Do not breathe dust. S36/37/39 - Wear suitable protective clothing, gloves and eye/face protection. S46 - If swallowed, seek medical advice immediately and show this container or label. S53 - Avoid exposure - Obtain special instructions before use.
Other hazards	Levantinib is a potent kinase inhibitor that specifically blocks the activity of growth factors involved in blood vessel formation. In human clinical studies, adverse events reported have included fatigue, hypertension, proteinuria, and a range of gastrointestinal complaints.
US Signal word	Attention

SECTION 2 - HAZARDS IDENTIFICATION …continued

US Hazard overview

Can cause damage to kidney, bone, reproductive organs, gastrointestinal system, and adrenal system based on animal data. Possible developmental hazard - may adversely affect the developing fetus or cause birth defects, based on animal data and mechanism of action.

Note

This mixture is classified as dangerous/hazardous according to Directive 1999/45/EC, Regulation EC No 1272/2008 (EU CLP) and applicable US regulations. See Section 16 for full text of EU and GHS classifications. The CLP/GHS classifications are based on Regulation (EC) 1272/2008. The EU symbol/indicator of danger, R Phrases and Safety Advice are based on Directive 1999/45/EC.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ ELINCS#	Amount	EU Classification	GHS Classification
Cellulose	9004-34-6	232-674-9	10-12%	Not classified	Not classified
Lenvatinib	857890-39-2	N/A	8-10%	Toxic - T: R48/25; R61	STOT-R1: H372; RT1B: H360D
Talc	14807-96-6	238-877-9	1-3%	Xi: R37	STOT-S3: H335

Note

The ingredient(s) listed above are considered hazardous. Cellulose is listed because it has OELs. The remaining components are non-hazardous and/or present at amounts below reportable limits. See Section 16 for full text of EU and GHS classifications. The EU classification is based on Directive 67/548/EEC and the CLP/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.

SECTION 4 - FIRST AID MEASURES …continued

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 toxic fumes of carbon monoxide and carbon dioxide, oxides of nitrogen, iron-containing compounds, sulfur-containing compounds, titanium-containing compounds, and chloride compounds.
Flammability/ Explosivity	No flammability information was identified. Lenvatinib is sensitive to ignition from an electrostatic source if dispersed as finely divided particles in a dust cloud at high concentrations (based on its explosive properties; See Section 9).
Advice for firefighters	In case of fire in the surroundings: use the appropriate extinguishing agent. Wear full protective clothing and an approved, positive pressure, self-contained breathing apparatus. Decontaminate all equipment after use.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures	Remove ignition sources. If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Do not breathe dust.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	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).

SECTION 6 - ACCIDENTAL RELEASE MEASURES …continued

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. Eliminate possible ignition sources (e.g., heat, sparks, flame, impact, friction, electricity), and follow appropriate grounding and bonding procedures. Wash thoroughly after handling.

Conditions for safe storage including any incompatibilities

Store refrigerated between 2° C to 8° C away from incompatible materials. Keep out of reach of children. Avoid extreme temperatures. 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

Compound	Issuer	Type	OEL
Cellulose	ACGIH, Australia, Belgium, Estonia, France, Portugal, Romania, Singapore, Spain	TWA-8 HR	10 mg/m³
	Ireland, United Kingdom	TWA-8 HR	10 mg/m³ (inhalable dust); 4 mg/m³ (respirable dust)
	Ireland	STEL	20 mg/m³ (total inhalable dust)
	Latvia	TWA-8 HR	2 mg/m³
	Mexico	TWA-8 HR/STEL	10/20 mg/m³
	NIOSH	TWA-8 HR	10 mg/m³ (total dust); 5 mg/m³ (respirable dust)
	OSHA	TWA-8 HR	15 mg/m³ (total dust); 5 mg/m³ (respirable fraction)

Control Parameters/ Occupational Exposure Limit Values

…continued

Compound	Issuer	Type	OEL
	United Kingdom	STEL	20 mg/m³ (inhalable dust); 12 mg/m³ (respirable dust)
Lenvatinib	Eisai	8-hour TWA	0.8 μg/m3
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)

Exposure/Engineering controls

None required for normal handling of packaged product. If capsules are crushed or broken, or if handling bulk mixture: Control exposures to below the OEL. Selection and use of engineering controls, containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Capsule transfers should be done utilizing closed systems and/or with local exhaust ventilation in place to limit to limit the potential for dust emissions. Open handling should not be performed when handling potent substances, or substances of unknown toxicity. Capsules should be handled inside a closed process, ventilated enclosure, isolator or device of equivalent or better control that is suitable for dusts and/or aerosols.

Respiratory protection

None required for normal handling of packaged product. If capsules are crushed or broken, or if handling bulk mixture: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. For routine handling tasks, an approved and properly fitted air-purifying respirator with appropriate HEPA filters should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use a powered air-purifying respirator equipped with appropriate HEPA filters or combination filters or a positive-pressure air-supplied respirator if there is any potential for an

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION …continued

Respiratory protection …continued	uncontrolled release, when exposure levels are not known, or in any other circumstances where a lower level of respiratory protection may not provide adequate protection.
Hand protection	Wear nitrile or other impervious gloves if skin contact is possible. 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.
Other protective measures	Wash hands in the event of contact with this product/mixture, 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	Capsule
Color	Cap: yellowish-red. Body: white (1 mg), yellowish-red (4 mg), and yellow (10 mg).
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	Not applicable.
Flash point	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Evaporation rate	Not applicable.
Flammability (solid, gas)	No information identified.
Upper/lower flammability or explosive limits	No information identified.
Vapor pressure	No information identified.
Vapor density	No information identified.
Relative density	No information identified.
Water solubility	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	Lenvatinib is sensitive to ignition from an electrostatic source and has the potential to explode at high dust concentrations based on the following data: Minimum Ignition Energy (MIE): 10 to 30 mJ.
Oxidizing properties	No information identified.

Other information

Molecular weight	Not applicable (Mixture)
Molecular formula	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	Avoid contact with heat, sparks, flames or other ignition sources. Avoid extreme temperatures.

SECTION 10 - STABILITY AND REACTIVITY …continued

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

Compound	Type	Route	Species	Dose
Cellulose	LC_{50}	Inhalation	Rat	>5800 mg/m³/4h
	LD_{50}	Oral	Rat	>5000 mg/kg
	LD_{50}	Dermal	Rabbit	>2000 mg/kg
Lenvatinib	LD_{50}	Oral	Rats	>2000 mg/kg
Talc	--	--	--	--

Irritation/Corrosion Talc can cause respiratory tract irritation.

Sensitization No studies identified.

STOT-single exposure No abnormalities or mortalities were observed in rats treated with single oral doses up to 500 mg/kg. At 1000 and 2000 mg/kg, lethality (3 of 10 animals) and overt clinical signs prior to deaths were observed in rats given oral doses. Macroscopic changes in the gastrointestinal tract were also observed in surviving animals at these doses. Lenvatinib was well tolerated at oral doses of up to 1000 mg/kg in dogs and monkeys, with vomiting and diarrhea, respectively, being the only observed effects.

STOT-repeated exposure/Repeat-dose toxicity In repeat oral toxicity studies in rats, adverse effects were seen at 10 mg/kg/day lenvatinib for up to 26 weeks in the following target organs: kidney, bone, teeth, brain, liver, reproductive organs, adrenal glands and gastrointestinal system (NOAEL = 0.4 mg/kg/day). In a 4-week study in rats, abnormal development of teeth was noted at oral doses as low as 1 mg/kg/day, while target organ effects and lethality were observed at oral doses of 10 and 100 mg/kg/day, respectively.

In monkeys, oral NOAELs of 0.3 and 0.1 mg/kg/day were identified in studies up to 4 and 39 weeks in duration, based on adverse effects noted at 30 mg/kg/day in the following target organs: kidney, liver, reproductive organs, and gastrointestinal system. In a 4-week study with dogs, similar target organs were affected at oral doses of ?2 mg/kg/day. Arterial fibrinoid necrosis was also seen in several organs in both species at 30 mg/kg/day (as well as some lethality in dogs).

Reproductive toxicity No data available.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Developmental toxicity	In embryo-fetal development studies in rats and rabbits, fetal external and skeletal anomalies were observed at oral doses of 0.1 mg/kg and higher in rats, and fetal external, visceral or skeletal anomalies were noted at oral doses of 0.1 and 0.5 mg/kg in rabbits.
Genotoxicity	Lenvatinib was negative for mutagenicity in an Ames bacterial cell mutagenicity assay, as well as negative for chromosomal aberrations in an *in vitro* mouse lymphoma assay.
Carcinogenicity	No data available.
Aspiration hazard	No data available.
Human health data	See "Section 2 - Other Hazards"
Additional information	The toxicological properties of this mixture have not been fully characterized.

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
Cellulose	--	--	--
Lenvatinib	--	--	--
Talc	--	--	--

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.
Note	Due to lack of data, avoid release to the environment.

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

SECTION 15 - REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture	This SDS 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.
OSHA Hazardous	**Drugs packaged in their finished state and intended for final users are not subject to labeling in the US or under GHS.** If handling the bulk formulation, the following labels apply: Yes. Attention. Can cause damage to kidney, bone, reproductive organs, gastrointestinal system, and adrenal system based on animal data. Possible developmental hazard - may adversely affect the developing fetus or cause birth defects, based on animal data and mechanism of action.
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.

SECTION 15 - REGULATORY INFORMATION …continued

California proposition 65	Not listed.
Additional information	No other information identified.

SECTION 16 - OTHER INFORMATION

Full text of R phrases and EU Classifications	X_i - Irritant. R37 - Irritating to respiratory system. Xn - Harmful. R48/22 - Harmful: Danger of serious damage to health by prolonged exposure if swallowed. T - Toxic. R48/25 - Toxic: Danger of serious damage to health by prolonged exposure if swallowed. Repr. Cat. 2 - Toxic for reproduction Category 2. R61 - May cause harm to the unborn child.
Full text of H phrases, P phrases and GHS classification	STOT-S3 - Specific Target Organ Toxicity Following Single Exposure Category 3. H335 - May cause respiratory irritation. STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. STOT-R2 - Specific Target Organ Toxicity Following Repeated Exposure Category 2. H372 - Causes damage to kidney, bone, reproductive organs, gastrointestinal system, and adrenal system through prolonged or repeated exposure. H373 - May causes damage to kidney, bone, reproductive organs, gastrointestinal system, and adrenal system through prolonged or repeated exposure. RT1B - Reproductive toxicity Category 1B. H360D - May damage the unborn child.
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; 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
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.