SAFETY DATA SHEET

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

Contact information

General

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Product identifier Enasidenib Tablets

Synonyms For enasidenib: 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2- yl)amino]propan-2-ol methanesulfonate AG-221 mesylate; CC-90007; AGI-12910; AG-221

Trade names IDHIFA™

Chemical family Mixture - contains a substituted triazine

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

Note 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.

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. Consult prescribing/packaging information. **The classification and labeling listed below is for bulk drug product.**

Globally Harmonized System [GHS]

Specific Target Organ Toxicity (repeated exposure) - Category 1. Reproductive Toxicity - Category 2.

Label elements

GHS hazard pictogram

GHS signal word

Danger

GHS hazard statements

H372 - Causes damage to the immune system through prolonged or repeated exposure. H361f - Suspected of damaging fertility.

GHS precautionary statements

P260 - Do not breathe dust. P264 - Wash hands thoroughly after handling. P264 - Wash hands thoroughly after handling. P270 - Do not eat, drink or smoke when using this product. P280 - Wear eye/face protection. P308 + P313 - IF exposed or concerned: get medical advice/attention. P314 - Get medical advice/attention if you feel unwell. P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.

Other hazards

Enasidenib is an orally available anticancer drug. The most commonly reported adverse effects in cancer patients were elevated bilirubin, gastrointestinal disturbances (*e.g.*, nausea, vomiting, diarrhea), and decreased appetite. Less frequently albeit more severe adverse effects included leukocytosis (increased white blood cell counts) and differentiation syndrome, including fever, acute kidney failure, dyspnea (shortness of breath), acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, and hepatic, renal, or multi-organ dysfunction.

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
Cellulose	9004-34-6	232-674-9	55-60%	Not classified
Enasidenib	1446502-11-9	N/A	20-30%	STOT-R1: H372; RT2: H361f

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS …continued

Note	The ingredients listed above are considered hazardous. Cellulose (in microcrystalline form) is included 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 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 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	If swallowed, call a physician immediately. 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, fluorine-containing compounds, and sulfur-containing compounds.

SECTION 5 - FIREFIGHTING MEASURES …continued

Flammability/ Explosivity	No explosivity or flammability data identified. If tablets are crushed or broken, high concentrations of finely divided airborne organic particles can potentially explode if ignited.
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	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.
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 broken or crushed, or handling bulk pharmaceutical mixture: 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.
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 contact with eyes, skin and other mucous membranes. Wash thoroughly after handling. Avoid breathing dust.
Conditions for safe storage including any incompatibilities	Store at 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature]. Keep bottle tightly closed. Store in original bottle (with a desiccant canister) to protect from moisture.
Specific end use(s)	No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

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)
	United Kingdom	STEL	20 mg/m³ (inhalable dust); 12 mg/m³ (respirable dust)
Enasidenib	Celgene	8-hour TWA	300 µg/m³

Exposure/Engineering controls

None required for handling of packaged product. If handling bulk or if tablets are crushed or broken: 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. Use local exhaust and/or enclosure at dust-generating points. Emphasis is to be placed on closed material transfer systems and process containment, with limited open handling of powders. High-energy operations such as milling, particle sizing, spraying or fluidizing should be done within an approved emission control or containment system.

Respiratory protection

None required for handling of packaged product. If handling bulk or if tablets are crushed or broken: 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 fitted air-purifying respirator with 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 HEPA filters or combination filters or a positive-pressure air-supplied

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION …continued

Respiratory protection …continued	respirator if there is any potential for an 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	None required for normal handling of packaged product. Wear nitrile or other impervious gloves if skin contact with capsules is possible.
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 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). Decontaminate all protective equipment following use.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance	Tablet
Color	Yellow
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.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

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	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

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
Cellulose	LC_{50}	Inhalation	Rat	>5800 mg/m³/4h
	LD_{50}	Oral	Rat	>5000 mg/kg
	LD_{50}	Dermal	Rabbit	>2000 mg/kg
Enasidenib	Minimum Lethal Dose	Oral	Dog	150 mg/kg
	Minimum Lethal Dose	Oral	Monkey	>500 mg/kg

Irritation/Corrosion No studies identified.

Sensitization No studies identified.

STOT-single exposure In dogs, cardiovascular effects and mortality were reported after single oral doses ≥150 mg/kg enasidenib and single doses of up to 50 mg/kg were tolerated. In monkeys, mild emesis was noted at 100 mg/kg enasidenib, while higher doses tested up to 500 mg/kg resulted in impaired equilibrium, hunched posture, decreased activity, intermittent tremors, excessive salivation, frothy mouth, and inappetence. No deaths were reported in monkeys.

STOT-repeated exposure/Repeat-dose toxicity In a 28-day rat study, evidence of target organ toxicity was noted in the gastrointestinal tract, liver, lung, lymphoid tissues, skeletal muscle, renal and adrenal systems, bone, and/or male and female reproductive organs at ≥60 mg/kg/day. Additional biochemical changes and testicular effects (including seminiferous tubular degeneration and reduced sperm counts) were noted in a 90-day study at 40 mg/kg/day. Overall, oral NOAELs in male and female rats were 10 and 40 mg/ kg/day, respectively.

In a 90-day monkey study reduced body weight and food consumption were noted at 12 and ≥4 mg/kg/day, respectively. Minimal to moderate clinical pathology changes and minor microscopic findings in lymphoid tissues and bone marrow were also reported, but not considered adverse. Additional gastrointestinal effects, periarteritis in multiple organs, and hematological changes were reported at 10 mg/kg/day in a 4-week study. The overall oral NOAEL in monkeys was 4 mg/kg/day.

Reproductive toxicity No definitive studies identified that assessed enasidenib-related effects on fertility. However, degeneration and atrophy were noted in male reproductive organs in rats in repeat-dose oral toxicity studies with enasidenib.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Developmental toxicity	Developmental toxicity (primarily decreased fetal weights and incomplete sternal ossification) was observed in rats treated orally with enasidenib, at 60 mg/kg; a NOAEL of 20 mg/kg/day was identified. In rabbits, no evidence of toxicity was seen at the highest dose tested (the NOAEL was 20 mg/kg/day).
Genotoxicity	Enasidenib was negative for mutagenicity in the Ames assay and negative for clastogenicity in an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells with and without metabolic activation. It was negative in an *in vivo* rat bone marrow micronucleus assay.
Carcinogenicity	No studies identified. The ingredients in this mixture are not 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
Cellulose	--	--	--
Enasidenib	--	--	--

Persistence and Degradability	No data available.
Bioaccumulative potential	No data available.
Mobility in soil	No data available.
Results of PBT and vPvB assessment	No data available.
Other adverse effects	No data available.
Note	The environmental characteristics of this product/mixture have not been fully investigated. Releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods	Dispose of wastes by appropriately permitted chemical waste incinerator in accordance to prescribed federal, state, and local guidelines. 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 onsite 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 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	H372 - Causes damage to the immune system through prolonged or repeated exposure. STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. H361f - Suspected of damaging fertility. RT2 - Reproductive toxicity Category 2.
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; 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

1 May 2019

Revisions

This is the second version of this SDS. Updated classifications and common adverse effects and classifications in Section 2. Updated product identifier, and information in Sections 8 (OEL), 9, and 11.

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.

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