SAFETY DATA SHEET

SECTION 1 - IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND COMPANY

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Information/Emergency

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Product name	Belinostat – For Injection (IV)
Synonyms	N-hydroxy-3-(phenylsulphamoylphenyl) acrylamide, PXD101
Trade names	Not applicable
Chemical family	Mixture that contains an HDAC inhibitor of the hydroxamate class.
Product use	Bulk formulated pharmaceutical product / Formulated pharmaceutical product packaged in final form for patient use. Formulation is being investigated for the treatment of multiple solid tumors and hematological malignancies. It has been administered intravenously and orally in human clinical trials.
Note	This SDS is written to address potential worker health and safety issues associated with the handling of the formulated product. Workers manufacturing this product should consult the SDSs of each hazardous ingredient for hazard information and handling recommendations.
Issue Date	08 September 2010

SECTION 2 - HAZARDS IDENTIFICATION

Appearance	Yellow cake in clear glass vials
US Signal word	Warning
Hazard overview	Substance not yet fully tested. Under investigation as a treatment for cancer. May cause damage to the gastrointestinal tract, blood and the lymphoid/hematopoietic system, based on animal data. May form combustible dust concentrations in air during processing. Very sensitive to electrostatic ignition.
Known clinical effects	Treatment with belinostat has been generally well-tolerated. The most frequent treatment emergent adverse effects have been nausea, vomiting, fatigue, and diarrhea. In clinical studies with belinostat, the most frequent serious adverse events among the first 346 patients have been infections (11), hypersensitivity (4), nausea (3) and thrombocytopenia (3). Hemorrhage has also been reported in trials with belinostat.
GHS signal word	Warning - Substance not yet fully tested.

GHS classification Mutagenic - Category 2. Target organ systemic toxicity (repeat exposure) - Category 2.

SECTION 2 - HAZARDS IDENTIFICATION …continued

GHS hazard symbol

GHS hazard statements H341 - Suspected of causing genetic defects. H373 - May cause damage to gastrointestinal tract, blood and the lymphoid/hematopoietic system through prolonged or repeated exposure.

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 mist/vapors/ spray. 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. P405 - Store locked up. P501 - Dispose of contents/ container to location in accordance with local/regional/national/international regulations.

EU indicator of danger Xn - Harmful. Substance not yet fully tested.

EU classification R48/20/22, R68

Note This product/mixture is classified as 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 GHS classifications are based on Regulation (EC) 1272/2008.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ELINCS#	Amount	EU Classification	GHS Classification
Belinostat	414864-00-9	N/A	33%	Xn: R48/20/22, R68	GCM-2: H341; STOT-R2: H373
L-Arginine	74-79-3	N/A	66%	Not classified	Not classified

Note The ingredient(s) listed above are considered hazardous. The pharmacological and toxicological characteristics of this mixture have not been fully characterized. See Section 16 for full text of EU and GHS classifications. The GHS classifications are based on Regulation (EC) 1272/2008.

SECTION 4 - 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 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.
Note to physician	Medical conditions aggravated by exposure: Patients with a history of sensitivity or allergy to compounds of the hydroxamate class or arginine should not be given belinostat. Treat symptomatically and supportively. If accidental exposure occurs to an individual who is also taking one or more concomitant medications, consult the respective package or prescribing information for potential drug interactions.
Protection of first aid responders	See Section 8 for Exposure Controls/Personal Protection recommendations.

SECTION 5 - FIRE FIGHTING MEASURES

Flammability/Explosivity	Avoid generating dust; fine dust dispersed in air in sufficient concentrations, and in the presence of an ignition source, is a potential dust explosion hazard.
Extinguishing media	Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.
Fire fighting instructions	Wear full protective clothing and an approved, positive pressure, self-contained breathing apparatus. Wash all equipment thoroughly after use.
Hazardous combustion products	No information identified. May emit toxic fumes of carbon monoxide, carbon dioxide, oxides of nitrogen, and sulfur-containing compounds.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions	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. Eliminate all ignition sources. Collect spilled material in a manner that minimizes the generation of airborne dust. Do not use vacuum for clean-up unless explosion-proof equipment is used and precautions are taken to prevent static charging of material.

SECTION 6 - ACCIDENTAL RELEASE MEASURES …continued

Spill cleanup methods Avoid dispersal of dust in the air (i.e., clearing dust surfaces with compressed air). Nonsparking tools should be used.
For small spills (such as in a laboratory), soak up material with absorbent, e.g., damp paper towel, and wash spill area thoroughly with soap and water. For large spills in manufacturing, use an industrial vacuum cleaner equipped with a high efficiency particulate (HEPA) filter if available. Alternatively if in solid or dried form, do not raise dust. Surround spill or powder with absorbents and place a damp cloth or towel over the area to minimize powder from entering the air. Add excess liquid to allow for the material to enter solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container suitable for disposal. Decontaminate area a second time. Dispose of material in a manner that is compliant with federal, state and local laws.

Environmental precautions Do not empty into drains. Avoid release to the environment.

SECTION 7 - HANDLING AND STORAGE

General handling Avoid contact with eyes, skin and other mucous membranes. If vials are crushed or broken, drug product may be released into the air. Minimize generation and accumulation of airborne material. Follow recommendations for handling bulk formulated/packaged cytotoxic pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Wash thoroughly after handling.

Storage conditions Store refrigerated between 15 to 30° C. Protect from light. Store in a tightly sealed container. Store locked up.

Specific Use(s) No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Belinostat	--	--	--
L-Arginine	Russia	TWA-8 HR (MAC)	10 mg/m (aerosol)

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

DNELs/PNECs None identified.

Exposure/Engineering controls	Spectrum considers Belinostat to be Category 4 of 5 (Potent) based on its toxicity and potency properties. In general, Category 4 handling practices, some of which are described in general in this Section, should be employed. 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. Nitrogen may be necessary to keep the oxygen level well below the minimum oxygen concentration of 11-12%. Temperature controls for drying should be utilized to ensure that the chemical is never heated above 60º C. Use only appropriately classified electrical equipment and powered industrial trucks.
Respiratory protection	None required for normal handling of packaged product. If handling bulk solution or if vials are broken: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. 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 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	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 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.
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).
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 9 - PHYSICAL AND CHEMICAL PROPERTIES

Physical form/Appearance	Yellow solution in clear glass vials
Color	Yellow
Odor	No information identified.

Odor threshold	No information identified.
pH	9.0-9.9
Taste	Bitter
Boiling point/boiling range	No information identified.
Melting point/melting range	No information identified.
Flash point	No information identified.
Evaporation rate	No information identified.
Flammability (solid, gas)	No information identified.
Explosive properties	No information identified.
Upper/lower flammability or explosive limits	No information identified.
Oxidizing properties	No information identified.
Vapor pressure	No information identified.
Molecular weight	318.35 (belinostat)
Molecular formula	$C_{15}H_{14}N_2O_4S$ (belinostat)
Density	No information identified.
Specific gravity	No information identified.
Viscosity	No information identified.
Water solubility	Slightly soluble in distilled water (0.14 mg/mL) (belinostat)
Solvent solubility	Slightly soluble in 1,2-propanediol (about 0.2 mg/mL) and polyethylene glycol 400 (about 1.5 mg/mL), and freely soluble in ethanol (>200 mg/mL) (belinostat)
Autoflammability	No information identified.
Partition coefficient (*n-octanol/water*)	1.62 (belinostat)
Vapor density	No information identified.
Relative density	No information identified.
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.

Other

Explosion Strength <u>if in powder form</u>:

Max. Explosion Pressure (bar) 7.9
Max. Rate of Pressure Rise (bar/s): 896
Kst Value (bar m/s): 243
ST Rating: ST2
Explosion Hazard: Strong explosion!
Elecrostatic Properties:
Volume Resistivity (ohm.m) Ambient R.H.: >1014
Low R.H.: >1014
Charge Decay Time (hours) Ambient R.H. stainless tube: 19
Low R.H.: 54
Chargeability (C/kg) Ambient R.H. stainless tube:-3.4 x 10-5
Low R.H.: -1.1 x 10-5

Ignitability <u>if in powder form</u>:

Minimum Ignition Energy –MIE (mJ): <3

Minimum Ignition Temperature –MIT (C): 480-500

Minimum Explosible Concentration – (g/m3): 30-40
Limiting Oxygen (vol%) 11-12%
Thermal Stability: Accelerating Rate Calorimetry (ARC)
Exotherm: 400 J/g
Onset: 129.1º C

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	No information identified.
Chemical stability	Chemically stable; pharmacological stability not guaranteed beyond expiration date imprinted on package.
Conditions to avoid	Avoid extreme temperatures.
Materials to avoid/Incompatible materials	No information identified.
Hazardous decomposition products	No information identified.
Hazardous polymerization	Not expected to occur.

SECTION 11 - TOXICOLOGY INFORMATION

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

Acute toxicity

Compound	Type	Route	Species	Dose
Belinostat	Minimum Lethal Dose	Intravenous	Rat	>100 mg/kg
	Minimum Lethal Dose	Intravenous	Mice	>100 mg/kg
	Maximum Tolerated Dose	PO	Rat	>100 mg/kg
	Maximum Tolerated Dose	PO	Dog	25-50 mg/kg
L-Arginine	--	--	--	--

Additional acute toxicity information In rats, intravenous doses of 520 mg/kg resulted in bone marrow toxicity in an *in vitro* genotoxicity study. In dogs, doses of 90 mg/kg were not tolerated and resulted in study discontinuation following a single dose.

Irritation/Corrosion No data available.

Sensitization No data available.

Repeat-dose toxicity In rats the toxicological observations after intravenous treatment were limited to reduced body weight gain, reduced food consumption, and decreases in white blood cells (WBC). At 100 mg/kg/day, which was the highest dose level tested in rats, thymus atrophy was observed in addition to the initial signs of toxicity. In dogs the signs of toxicity after intravenous treatment at the lowest dose level tested (10 mg/kg/day) were vomiting and indications of delayed testis maturation. At higher dose levels above 25 mg/kg/day the clinical signs also included soft, mucoid or liquid feces, a decrease in WBC and lymphoid and thymus atrophy.

In rats decreased body weight and reduced food consumption was observed after oral treatment at all dose levels tested (5 to 150 mg/kg/bid). Inflammatory lesions in the stomach as evidence of belinostat local toxicity were also observed at all dose levels. In rats depression of white blood cells was observed at 25 mg/kg bid and above. At doses above 100 mg/kg bid thymus atrophy was observed in addition to the initial signs of toxicity. In dogs the lowest dose levels (5 and 12.5 mg/kg bid) caused locally toxic effects such as decreased body weight, reduced food consumption and inflammatory lesions in the stomach. At the lowest dose tested (5 mg/kg/bid) lymphoid and thymus atrophy was observed. In dogs gastrointestinal toxicity was severe and dose-limiting at the highest dose levels tested (25 and 35 mg/kg/bid). Clinical observations included vomiting, decreased food intake, diarrhea, body weight loss and reduced food consumption. Depression of WBC was observed.

SECTION 11 - TOXICOLOGY INFORMATION …continued

Repeat-dose toxicity
…continued

Rats tolerated the highest oral dose administered (200/250 mg/kg/day) with no treatment-related mortality and unremarkable clinical signs. Dogs did not tolerate oral administration of 50 and 70 mg/kg/day. These dose levels resulted in discontinuation of treatment and mortality. A dose of 10 mg/kg/day was well tolerated in dogs. Rats were administered belinostat via gavages in an aqueous vehicle with L-arginine. Dogs were administered dry powder in capsule.

The gastrointestinal tract was a target organ in dogs: an apparent direct effect on the gastrointestinal tract mucosa caused ulcerative lesions that resulted in a deteriorating clinical condition at dose levels of 50 and 70 mg/kg/day. Other target organs of toxicity in non-clinical studies included the hematopoietic system, immune system, genitourinary system and dermal system.

Reproductive toxicity No data available.

Developmental toxicity No data available.

Genotoxicity Belinostat was positive in the following tests: an intravenous *in vivo* genotoxicity rat bone marrow micronucleus assay, an *in vitro* Ames bacterial cell mutagenicity assay, and in an *in vitro* mouse lymphoma gene mutation assay.

Carcinogenicity No long-term studies in animals have been performed to evaluate the carcinogenic potential of belinostat. This substance is not listed by NTP, IARC, ACGIH or OSHA as a carcinogen.

Aspiration hazard No data available.

Human health data Treatment with belinostat has been generally well tolerated. The most frequent treatment emergent related effects have been nausea, vomiting, fatigue, and diarrhea. In clinical studies with belinostat, the most frequent serious adverse events among the first 346 patients have been infections (11), hypersensitivity (4), nausea (3) and thrombocytopenia (3). Hemorrhage has also been reported in trials with belinostat.

SECTION 12 - ECOLOGICAL INFORMATION

Aquatic toxicity

Compound	Type	Species	Concentration
Belinostat	--	--	--
L-Arginine	--	--	--

Aquatic Toxicity No data identified.

Mobility No data identified.

Adsorption coefficient (Koc) No data identified.

Persistence and Degradability No data available.

Bioaccumulative potential	Belinostat is not expected to bioaccumulate.
Results of PBT assessment	No data identified.
Note	Releases to the environment should be avoided.

SECTION 13 - DISPOSAL INFORMATION

Disposal procedures

Used product should be disposed of according to local, state, and federal regulations. Do not send down the drain or flush down the toilet. 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 - TRANSPORTATION 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.

SECTION 15 - REGULATORY INFORMATION

Compliance

This SDS complies with the requirements under US, EU and GHS (EU CLP - Regulation EC No 1272/2008) guidelines. Drugs packaged for final use by the patient/consumer are not subject to labeling in the US, EU or Canada. Please consult the prescribing/packaging information.

The following information is for bulk Belinostat solution

OSHA Hazardous

Yes. May cause damage to gastrointestinal tract, blood and lymphoid/ hematopoietic system, based on animal data. Mutagenic - material may cause genetic defects (based on mechanism of action).

EU label pictogram(s)

Xn - Harmful

EU classification	Harmful; Xn. Substance not yet fully tested.
Risk phrases	R48/20/22 - Harmful: danger of serious damage to health by prolonged exposure through inhalation and if swallowed. R68 - Possible risk of irreversible effects.
Safety phrases	S36/37 - Wear suitable protective clothing and gloves. S45 - In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible). S53 - Avoid exposure - obtain special instructions before use.

SECTION 15 - REGULATORY INFORMATION …continued

GHS pictogram(s)	 Health Hazard
GHS signal word	Warning - Substance yet not fully tested.
GHS H and P phrases	H341 - Suspected of causing genetic defects. H373 - May cause damage to gastrointestinal tract, blood and the lymphoid/hematopoietic system through prolonged orrepeated exposure. P201 - Obtain special instructions before use. P202 - Do not handle until all safety precautions have been read and understood. P260 - Do not breathe dust. P281 - Use personal protective equipment as required. P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.
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. If this substance were not a drug, it would be classified as: D2B - Toxic - Materials causing other toxic effects.
WHMIS symbol(s)	 Class D - 2B
TSCA status	Not listed
SARA section 313	Not listed.
California proposition 65	Not listed.

SECTION 16 - OTHER

Full text of R phrases and EU Classifications	Xn - Harmful. R48/20/22 - Danger of serious damage to health by prolonged exposure through inhalation and if swallowed. R68 - Possible risk of irreversible effects.
Full text of H phrases, P phrases and GHS classification	GCM2 - Germ Cell Mutagenicity Category 2. STOT-R2 - Specific Target Organ Toxicity Following Repeated Exposure Category 2. H341 - Suspected of causing genetic defects. H373 - May cause damage to the gastrointestinal tract, blood, and lymphoid/hematopoietic system through prolonged or repeated exposure.
Recommended restrictions on use	Do not take internally.
Sources of data	Information from published literature and internal company data.

SECTION 16 - OTHER …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; 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	Updated formatting in compliance with General US, EU, and GHS requirements.
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.