SAFETY DATA SHEET

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

Contact information

General

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Product identifier	Palonosetron Hydrochloride/ Fosnetupitant phosphate DP
Synonyms	None identified
Trade names	None identified
Chemical family	Mixture - contains an isoquinoline derivative (palonestron HCl) and a butyramide derivative prodrug (fosnetupitant phosphate)
Relevant identified uses of the substance or mixture and uses advised against	Bulk formulated pharmaceutical mixture/ Formulated pharmaceutical product in vials; used to treat nausea.
Note	The physical, chemical, toxicological and ecological properties of this mixture 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

Globally Harmonized System [GHS]	Reproductive Toxicity - Category 2.
Other/Supplemental	Mixture not yet fully tested

Label elements

SECTION 2 - HAZARDS IDENTIFICATION …continued

GHS hazard pictogram

GHS signal word Warning

GHS hazard statements H361d - Suspected of damaging the unborn child.

GHS precautionary statements P201 - Obtain special instructions before use. P202 - Do not handle until all safety precautions have been read and understood. P280 - Wear protective gloves/eye protection/face protection. P308 + P313 - IF exposed or concerned: get medical advice/attention. P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.

Other hazards Contains active pharmaceutical ingredients that block specific neurotransmitters involved in feelings of nausea, indicated for the treatment of post-chemotherapy nausea and vomiting. Palonosetron hydrochloride (HCl) blocks a specific serotonin receptor and fosnetupitant phosphate is a prodrug that is metabolized to its active form netupitant, an NK1 receptor blocker. Adverse effects were not identified, but are expected be similar to palonosetron hydrochloride/netupitant and may include: headache, constipation, diarrhea, dizziness, transient changes in heart rate, weakness, hyperkalemia (increased blood potassium levels), and anxiety. In clinical trials, IV doses of fosnetupitant 260 mg/ palonosetron HCl 0.25 mg were investigated.

Prolongation of the QT interval (a component of the heart's electrical cycle) may also occur with use based on effects observed in non-clinical studies with netupitant and palonosetron at very high doses; this is a known class effect of similar serotonin receptor antagonists.

Based on the mechanism of action and effects observed in non-clinical studies in rabbits with netupitant, a potential for palonosetron/fosnetupitant to cause developmental toxicity cannot be excluded in the absence of data.

Note This mixture/product 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
Fosnetupitant	1703748-89-3	N/A	20-25%	RT2: H373; ATO4: H302
EDTA Sodium	64-02-8	200-573-9	0.5-1%	EI1: H318
Palonosetron hydrochloride	135729-62-3	N/A	0.01-0.05 %	ATO4: H302; Carc2: H351; STOT-R1: H372

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS …continued

Note	The ingredient(s) listed above are considered hazardous. The remaining components are not hazardous and/or present at amounts below reportable limits. Palonosetron is reported even though it is below the reportable limit because it is one of the active ingredients. Ranges are listed as they are a trade secret. See Section 16 for full text of EU and GHS classifications.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures	
Immediate Medical Attention Needed	Yes. If exposed or concerned: Get medical advice/attention.
Eye Contact	If easy to do, remove contact lenses, if worn. Immediately flush eyes with copious quantities of water for at least 15 minutes. If irritation occurs or persists, notify medical personnel and supervisor.
Skin Contact	Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.
Inhalation	Immediately move exposed subject to fresh air. If not breathing, give artificial respiration. If breathing is labored, administer oxygen. Immediately notify medical personnel and supervisor.
Ingestion	Do not induce vomiting unless directed by medical personnel. Do not give anything to drink unless directed by medical personnel. Never give anything by mouth to an unconscious person. Notify medical personnel and supervisor.
Protection of first aid responders	See Section 8 for Exposure Controls/Personal Protection recommendations.
Most important symptoms and effects, both acute and delayed	See Sections 2 and 11.
Indication of immediate medical attention and special treatment needed, if necessary	Contains palonosetron HCl - specific serotonin receptor antagonist, and fosnetupitant phosphate- an NK1 receptor antagonist. Medical conditions aggravated by exposure: Cardiovascular disorders. 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, hydrofluoric acid, hydrogen chloride and other fluorine- 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.

SECTION 5 - FIREFIGHTING MEASURES…continued

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 vials are crushed or broken, cordon off spill area. 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	If vials are crushed or broken, dispose of broken glass in a sharps container. 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 solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container suitable 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 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 room temperature (< 25°C), away from incompatible materials. Avoid extreme temperatures.
Specific end use(s)	Pharmaceutical.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Fosnetupitant	Helsinn Birex	OEL	100 µg/m³ for netupitant
EDTA Sodium	--	--	--
Palonosetron hydrochloride	Helsinn Birex	OEL	0.8 µg/m³

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION…continued

Exposure/Engineering controls	If handling bulk product or vials are opened/crushed/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	If handling bulk product or vials are opened/crushed/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 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	If handling bulk product or vials are opened/crushed/broken: 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	Crystalline powder in vials
Color	White to yellowish

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	Freely soluble (palonosetron HCl)
Solvent solubility	Soluble in propylene glycol; slightly soluble in ethanol and 2-propanol (palonosetron HCl)
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	No information identified.
Conditions to avoid	No information identified.
Incompatible materials	No information identified.
Hazardous decomposition products	No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note **No data on the drug product/mixture were identified. The following information is for the constituent ingredients. In the case of fosnetupitant, its active form netupitant is described.**

Information on toxicological effects

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

Acute toxicity

Compound	Type	Route	Species	Dose
Fosnetupitant	LD_{50}	Oral	Rat	2000 mg/kg for Netupitant
EDTA Sodium	--	--	--	--
Palonosetron hydrochloride	Maximum Tolerated Dose (MTD)	Oral	Rat	250 mg/kg (palonosetron)
	MTD	Oral	Mouse	100 mg/kg (palonosetron)
	MTD	Oral	Dog	50 mg/kg (palonosetron)
	MTD	IV	Rat	10 mg/kg (palonosetron)
	MTD	IV	Mouse	10 mg/kg (palonosetron)
	MTD	IV	Dog	20 mg/kg (palonosetron)
	LD_{50}	Oral	Rat	500 mg/kg

Irritation/Corrosion No skin irritation at injection sites was noted in rabbits, rats, or dogs following repeated IV injections of palonosetron. Following powder inhalation, netupitant may cause anesthetizing effects to the nose and throat for 24 hours. EDTA sodium is a mild skin irritant, but a potent eye irritant (further details not identified).

Sensitization Palonosetron was not a photosensitizer in guinea pigs.

STOT-single exposure	Inactivity, tremors, ataxia, and labored breathing were noted in rats, mice, and dogs administered single oral or IV doses of palonosetron up to 250, 100, and 50 mg/kg/day or 10, 10, and 20 mg/kg/day, respectively.
STOT-repeated exposure/Repeat-dose toxicity	Phospholipidosis (excessive phospholipid in unspecified tissues) was noted in rats treated orally with 30 mg/kg/day netupitant for 26 days (NOAEL=10 mg/kg/day). The effects were reversible or partially reversible following a recovery period (details not identified). Repeated oral dose toxicity studies for palonosetron were conducted in mice, rats, and dogs for up to 3 months. Increased mortality was noted in male and female mice at doses ≥90 and ≥120 mg/kg/day, respectively. Target organs in rats included the testes and bone in males at 60 mg/kg/day, as well as lymphoid tissue, spleen, kidney, thyroid, and adrenal gland in both sexes at 180 mg/kg/day. Decreased liver enzymes, cholesterol levels, and testicular weights were noted in dogs at 20 mg/kg/day. Repeated IV dose toxicity studies for palonosetron for up to 6 and 9 months' duration in rats and dogs, respectively, were also conducted. NOAELs of 7 and 6 mg/kg/day were identified in the rats (based on increased mortality at higher doses) and in the dogs (based on signs of nervous system toxicity [convulsions, ataxia, and subdued behavior]), respectively.
Reproductive toxicity	Netupitant did not impair fertility in rats at up to 30 mg/kg/day orally. No fertility impairment was noted in male (IV and oral) and female (oral) rats administered doses up to 10, 60, and 30 mg/kg/day palonosetron.
Developmental toxicity	No effects on embryo-fetal development were observed in rats administered up to 30 mg/kg netupitant in pregnant rats during organogenesis. However, fetal abnormalities and malformations in limbs, paws, ribs, and lungs were observed following administration to pregnant rabbits at doses of 10 mg/kg/day during organogenesis. Fetal eye and facial malformations were observed following administration of 30 mg/kg/day (maternally toxic doses). No evidence of teratogenicity was observed in rats and rabbits orally treated with up to 120 mg/kg/day palonosetron. A decrease in fetal body weight and ossification was noted at 60, but not 18, mg/kg/day in rats. No evidence of embryotoxicity was seen in rabbits at the highest dose of 120 mg/kg/day, even with some maternal deaths occurring at 90 mg/kg/day. Overall, palonosetron is not likely to be a developmental toxicant.
Genotoxicity	Netupitant was negative in an Ames test, a mouse lymphoma cell mutation test, and an *in vivo* rat micronucleus test. Palonosetron was negative in the Ames bacterial mutagenicity assay, an *in vitro* mutagenicity assay with Chinese hamster ovary (CHO) cells, an unscheduled DNA synthesis assay in liver cells, and an *in vivo* mouse micronucleus test. It was clastogenic in an *in vitro* chromosomal aberration assay using CHO cells. Overall, the genotoxic potential of palonosetron is low.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Carcinogenicity

Palonosetron was not carcinogenic in mice orally treated with doses up to 60 mg/kg/day for 2 years. In a 2-year rat study, oral doses of 60 mg/kg/day caused an increased incidence of adrenal gland tumors (both benign and malignant), benign pancreatic tumors, and benign and malignant pituitary gland tumors were observed in male rats. In female rats, benign and malignant liver tumors and increased incidence of thyroid tumors were noted at 90 mg/kg/day. No other components of the product present at levels greater than or equal to 0.1% are 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
Fosnetupitant	--	--	--
EDTA Sodium	--	--	--
Palonosetron hydrochloride	LC_{50} (time not specified)	Bluegill	22 mg/L
	EC_{50} (time not specified)	Microtox	45 mg/L

Persistence and Degradability

No data identified.

Bioaccumulative potential

No data identified.

Mobility in soil

No data identified.

Results of PBT and vPvB assessment

Not performed.

Other adverse effects

No data identified.

Note

The environmental characteristics of this product/mixture have not been fully investigated. Ecology hazards for its constituents are listed above. 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. 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 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	Mixture not fully tested - avoid exposure.
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.
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	STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. H372 - Causes damage to the cardiovascular, nervous, and gastrointestinal systems through prolonged or repeated exposure. ATO4 - Acute Toxicity (Oral) Category 4. H302 - Harmful if swallowed. EI1 - Eye irritant Category 1. H318 - Causes serious eye damage. RT2 - Reproductive toxicity Category 2. H361d - Suspected of damaging the unborn child. Carc2 - Carcinogenicity Category 2. H351 - Suspected of causing cancer.

SECTION 16 - OTHER INFORMATION …continued

Sources of data	Information from published literature, vendor SDSs, 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
Issue Date	10 July 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 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.