SAFETY DATA SHEET

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

Contact information

General

Alkermes, Inc.
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Emergency telephone number

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+1 (800) 424-9300 (USA and Canada)
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Product identifier

VIVITROL® (naltrexone for extended-release injectable suspension)

Trade names

VIVITROL®

Chemical family

Mixture - contains an opioid antagonist

Active ingredient

Naltrexone base anhydrous

Chemical name of active ingredient

(17-(cyclopropylmethyl)-4,5-alpha-epoxy-3,14-dihydroxy- morphaninan-6-one

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

Formulated pharmaceutical product packaged in final form for administration to patients; indicated for the treatment of alcohol and opioid dependence.

Note

This SDS has been developed to meet OSHA requirements. It is intended to classify potential hazards associated with exposure to the drug product; identify appropriate protective measures for exposure; and make such information available for communication to address potential worker health and safety issues associated with exposure to the material.

For information on the risks associated with use of the pharmaceutical product, including risks associated with administration, handling and storage, please consult the FDA-approved Prescribing Information and Medication Guide for VIVITROL.

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture

Regulation (EC) 1272/2008 [GHS]	Specific Target Organ Toxicity (single exposure) - Category 3.
Directive 67/548/EEC or 1999/45/EC	R67 - May cause drowsiness and dizziness.

Label elements

CLP/GHS hazard pictogram	
CLP/GHS signal word	Warning
CLP/GHS hazard statements	H336 - May cause drowsiness or dizziness.
CLP/GHS precautionary statements	P261 - Avoid breathing dust. P271 - Use only outdoors or in a well-ventilated area. P304 + P340 - IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing. P312 - Call a Poison Center or doctor/physician if you feel unwell. P403 + P233 - Store in a well-ventilated place. Keep container tightly closed. P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.
EU symbol/indication of danger	None required
Risk (R) Phrase(s)	R67 - May cause drowsiness and dizziness.
Safety Advice	S22 - Do not breathe dust. S36/37 - Wear suitable protective clothing and gloves.
Other hazards	The most common adverse effects associated with the therapeutic use of VIVITROL® include gastrointestinal disturbances (nausea, vomiting, and abdominal pain), injection site reactions (pruritus, nodules, and swelling), muscle cramps, dizziness or syncope, drowsiness or sedation, and decreased appetite. Other effects reported with naltrexone include headache, fatigue, sleepiness, low energy, anxiety, and rash. Consumption of ethanol may cause CNS depression, liver toxicity and adverse fetal effects when ingested by pregnant women, but this is not applicable with normal use of the product.
US Signal word	Attention
US Hazard overview	Contains naltrexone, an opioid antagonist. May cause dizziness and drowsiness.
NFPA System	Health = 1 Flammability = 1 Reactivity = 0

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ELINCS#	Amount	EU Classification	GHS Classification
Naltrexone	16590-41-3	240-649-9	~34%	Harmful - Xn: R22; R67	ATO4: H302; STOT-R3: H336
Ethanol	64-17-5	200-578-6	~1.5%	Highly flammable - F: R11	FL2: H225
Benzyl alcohol	100-51-6	202-859-9	~1.0%	Harmful - Xn: R20/22	ATO4: H302; ATI4: H332

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	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 naltrexone, an opioid antagonist. Medical conditions aggravated by exposure: Liver disorders, opioid dependence, and hypersensitivity. Treat symptomatically and supportively. If accidental exposure occurs to an individual who is also taking one or more concomitant medications, consult the respective pharmaceutical product package or prescribing information for potential drug interactions.

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, carbon dioxide and oxides of nitrogen.
Flammability/Explosivity	Contains residual amounts of flammable materials. Keep away from heat, sparks and flame.
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	Remove ignition sources. If material 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	If vials are crushed or broken, DO NOT RAISE DUST. Surround spill or powder with absorbents and place a damp cloth or towel over the area to minimize entry of powder into the air. 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	If vials are opened, crushed or broken, follow recommendations for handling formulated pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Wash thoroughly after handling.
Conditions for safe storage including any incompatibilities	Store refrigerated between 2 to 8° C to ensure product viability. Keep away from incompatible materials and ignition sources. Keep in tightly sealed containers in a well-ventilated area.
Specific end use(s)	No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note: Dispose of broken vials in a sharps container.

Control Parameters/Occupational Exposure Limit Values

Naltrexone

Issuer	Type	OEL
Alkermes	TWA-8 hrs	2.5 mcg/m3

Ethanol

Issuer	Type	OEL
ACGIH, NIOSH	TWA-8hrs	1000 ppm
NIOSH	IDLH	3300 ppm

Benzyl Alcohol

Issuer	Type	OEL
AIHA	TWA-8hrs	10 ppm

Exposure/Engineering controls

If 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, or particle sizing should be done within an approved emission control or containment system.

Respiratory protection

If 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 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

If vials are opened/crushed/broken: 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.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION…continued

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 material, 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	VIVITROL is supplied in single-use cartons. Each carton contains one 380-mg vial of VIVITROL microspheres.
Color	Off-white to light tan powder (naltrexone)
Odor	No information identified.
Odor threshold	No information identified.
pH	Not applicable.
Melting point/freezing point	168-170°C (naltrexone)
Initial boiling point and boiling range	Not applicable.
Flash point	Not applicable.
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	Sparingly soluble in water (naltrexone)
Solvent solubility	No information identified.
Partition coefficient (*n-octanol/water*)	No information identified.
Auto-ignition temperature	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES…continued

Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	No information identified.
Oxidizing properties	No information identified.

Other information

Molecular weight	65-95 kDaltons (341.4 g/mol for naltrexone anhydrous)
Molecular formula	$C_{20}H_{23}NO_4$ (naltrexone anhydrous)

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	No information identified.
Chemical stability	Chemically stable; pharmacological stability not guaranteed beyond expiration date imprinted on package.
Possibility of hazardous reactions	No information identified.
Conditions to avoid	Avoid extreme temperatures.
Incompatible materials	No information identified.
Hazardous decomposition products	No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note: **No toxicology data for the product/mixture were identified. The following data describe the active ingredient and/or the individual ingredients where applicable.**

Route of entry May be absorbed by inhalation and ingestion.

Acute toxicity

Compound	Type	Route	Species	Dose
Naltrexone	LD_{50}	Oral	Rat	1450 mg/kg
	LD_{50}	Oral	Mouse	1100 mg/kg
	LD_{50}	Oral	Guinea Pig	1490 mg/kg

Compound	Type	Route	Species	Dose
Ethanol	LD_{50}	Oral	Rat	7060 mg/kg
	LD_{50}	Oral	Mouse	3400 mg/kg
	LC_{50}	Inhalation	Rat	20000 ppm/10 hours
	LC_{50}	Inhalation	Mouse	39 g/m^3/4 hours
Benzyl alcohol	LC_{50}	Inhalation	Rat	8.8 mg/L/4 hours
	LD_{50}	Oral	Rat	1230 - 3100 mg/kg
	LD_{50}	Dermal	Rabbit	2000 mg/kg
	LD_{50}	Oral	Mouse	1150 - 1580 mg/kg

Irritation/Corrosion Naltrexone is not irritating to the skin of guinea pigs. Benzyl alcohol was slightly irritating to rabbit skin and irritating to rabbit eyes. Ethanol is a skin and eye irritant in animals.

Sensitization Naltrexone and benzyl alcohol were negative for sensitization in guineas pigs.

STOT-single exposure In the acute toxicity studies with rats, mice, and dogs (LD_{50} values listed above), deaths were the result of clonic-tonic convulsions and/or respiratory failure following naltrexone administration.

STOT-repeated exposure/Repeat-dose toxicity No significant findings were seen in dogs orally treated with naltrexone at up to 40 mg/kg/day for 90 days; an increase in vomiting was noted at doses ≥100 mg/kg/day.

NOAELs of ≥400 and ≥200 mg/kg/day were identified in rats and mice, respectively, orally treated with benzyl alcohol in repeat-dose toxicity studies for 2 years; higher doses affected body weight, and caused lesions of the brain, thymus, skeletal muscle, and kidneys.

Reproductive toxicity An increased incidence of pseudopregnancy and decrease in pregnancy rate was noted in female rats orally treated with 100 mg/kg/day naltrexone in a fertility study; no effects were seen in male rats at the same dose.

Developmental toxicity An increased incidence of early fetal loss was seen in rats and rabbits orally treated with ≥30 and ≥60 mg/kg/day naltrexone, respectively. However, no teratogenicity was observed in the surviving rat and rabbit offspring at oral doses up to 200 mg/ kg/day.

A NOAEL of 550 mg/kg/day for benzyl alcohol was identified in an oral developmental toxicity study with mice.

SECTION 11 - TOXICOLOGICAL INFORMATION…continued

Genotoxicity

Naltrexone was not genotoxic in bacterial, mammalian, or tissue culture systems, which included the Ames test, heritable translocations assay, sister chromatid exchange assay in Chinese hamster ovary cells, a mouse lymphoma assay, and *in vivo* mouse micronucleus assay. In contrast, naltrexone tested positive in the following assays: *Drosophila* recessive lethal frequency assay, non-specific DNA damage in repair tests with *E.Coli* and WI-38 cells, and urinalysis for methylated histidine residues.

Ethanol was positive in a number of genotoxicity assays. These effects may be due to a metabolite, acetaldehyde. Benzyl alcohol was negative in a battery of *in vitro* and *in vivo* genotoxicity screening tests.

Carcinogenicity

In 2-year carcinogenicity studies with rats and mice, no tumors were seen following oral treatment with naltrexone at doses up to 30 and 100 mg/kg/day, respectively. In rats, small increases in the incidence of testicular mesotheliomas in males and vascular tumors in males and females were noted at 100 mg/kg/day. Except for the vascular tumors in males, the incidences of these tumors exceeded the range seen in historical control groups.

Ethanol is considered a confirmed animal carcinogen with unknown relevance to humans by ACGIH and consumption of alcohol is listed by IARC as a group 1 carcinogen (carcinogenic to humans). Benzyl alcohol was not carcinogenic to rats and mice orally treated with up to 400 and 200 mg/kg/day, respectively, for 5 days/ week, for 2 years. 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
Naltrexone	--	--	--
Ethanol	LC_{50}/96h	Rainbow trout	12900 mg/L (flow through)
	LC_{50}/96h	Fathead minnow	15000 mg/L
	EC_{50}/48h	Daphnia magna	9268 mg/L
	EC_{50}/5-30 min	Photobacterium phosphoreum	~35000 mg/L
Benzyl alcohol	LC_{50}/48h	*Leuciscus idus* (freshwater fish)	646 mg/L
	LC_{50}/96h	Fathead minnow	460 mg/L
	EC_{50}/48h	Daphnia magna	≥100-360 mg/L
	EC_{50}/48h	Bacteria (*E.coli*)	1000 mg/L

SECTION 12 - ECOLOGICAL INFORMATION…continued

Persistence and Degradability	Benzyl alcohol and ethanol are readily biodegradable under aerobic and anaerobic conditions.
Bioaccumulative potential	Naltrexone and benzyl alcohol are not expected to bioaccumulate.
Mobility in soil	Naltrexone is expected to be highly mobile in soil.
Results of PBT and vPvB assessment	Not performed.
Other adverse effects	No data identified.
Note	No ecological information is available on VIVITROL®. The ecology data above are for its ingredient.

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 and in compliance with applicable environmental laws, e.g., appropriately permitted municipal or on- site wastewater treatment facility.

SECTION 14 - TRANSPORT INFORMATION

Transport	Based on the available data, this product 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 is not regulated as an environmental hazard or a marine pollutant.
Special precautions for users	Avoid release to the environment.
Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code	Not applicable.

SECTION 15 - REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture	This SDS complies with the requirements under current applicable regulations in the US and generally complies with relevant regulations in EU and Canada. Consult your local or regional authorities for more information.
Chemical safety assessment	Not conducted.
OSHA Hazardous	Yes. Attention. May cause dizziness or drowsiness.
WHMIS classification	Not required. 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.
SARA section 313	Not listed.
California proposition 65	Ethanol as contained in alcoholic beverages (and consumed) is listed as a reproductive toxicant, but this is not applicable with normal use of this product.
Additional information	No other information identified.

SECTION 16 - OTHER INFORMATION

Full text of R phrases and EU Classifications	F - Highly Flammable. R11 - Highly Flammable. Xi - Irritant. R36 - Irritating to eyes. Xn - Harmful. R22 - Harmful if swallowed. R20/22 - Harmful by inhalation and if swallowed. R66 - Repeated exposure may cause skin dryness or cracking. R67 - May cause drowsiness and dizziness.
Full text of H phrases, P phrases and GHS classification	FL2 - Flammable Liquid Category 2. H225 - Highly flammable liquid and vapor. EI2 - Eye irritant Category 2. H319 - Causes serious eye irritation. ATO4 - Acute Toxicity (Oral) Category 4. H302 - Harmful if swallowed. ATI4 - Acute Toxicity (Inhalation) Category 4. H332 - Harmful if inhaled. STOT-S3 - Specific Target Organ Toxicity Following Single Exposure Category 3. H336 - May cause drowsiness or dizziness. EUH066 - Repeated exposure may cause skin dryness or cracking.
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; 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

3rd.

Limitations

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 exposures and 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 associated with the use of the material. 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 known 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.

Caution should be used in the handling and use of the material because it is a pharmaceutical product. For information on the risks associated with use of the product, including risks associated with administration, handling and storage, please consult the FDA-approved Prescribing Information and Medication Guide for VIVITROL.