SAFETY DATA SHEET

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

Contact information

General

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Product identifier

INVELTYS™ (loteprednol etabonate ophthalmic suspension) 1%

Synonyms

(11β,17α)-17-[(Ethoxycarbonyl)oxy]-11-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylic acid chloromethyl ester; loteprednol etabonate ophthalmic suspension; KPI-121 1% Drug Product

Trade names

INVELTYS

Chemical family

Mixture - containing corticosteroid

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

Formulated pharmaceutical product/mixture packaged in final form for patient use. Indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Note

This SDS is written to address potential worker health and safety issues associated with the handling of the formulated product/mixture. It is not intended to provide information relevant to medicinal use of the product. Patients should consult prescribing information/package insert/product label or consult their pharmacist or physician.

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.

Globally Harmonized System [GHS]

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

Label elements

GHS hazard pictogram

GHS signal word

Danger

GHS hazard statements

H360D - May damage the unborn child. H373 - May cause damage to immune 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 dust/mist/ vapors/spray. P280 - Wear protective gloves/eye protection/face protection. P308 + P313 - IF exposed or concerned: get medical advice/attention. P501 - Dispose of contents/container to location in accordance with local/regional/national/ international regulations.

Other hazards

INVELTYS contains the active ingredient loteprednol etabonate - a synthetic corticosteroid with anti-inflammatory properties. Effects reported in clinical trials included blurry vision, discomfort on instillation (burning, itching, feeling of foreign body), and sensitivity to light. With prolonged use there is a risk of developing glaucoma, eye infections, or delayed wound healing.

Corticosteroids, as a class, have been associated with immunosuppression, as well as disturbances of the hypothalamic-pituitary-adrenal (HPA) axis. They have also been associated with fetal growth retardation if administered late in pregnancy. Malformation were also frequently reported with systemic exposure in non-clinical studies. Although loteprednol etabonate is considered a "soft steroid" (designed to be rapidly inactivated upon entering circulation) and it appears to act more locally, a potential for the drug to adversely affect pregnancy outcomes if accidentally inhaled or ingested in a workplace setting cannot be excluded.

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
Loteprednol etabonate	82034-46-6	639-474-4	1 %	RT1B: H360D; STOTR1: H372
Edetate disodium	6381-92-6	613-386-6	<2%	EI2: H319; ATI4: H332; STOT-R2: H373
Glycerol	56-81-5	200-289-5	<2%	Not classified

Note The ingredient(s) listed above are considered hazardous and/or are the active ingredient. Glycerol is not classified but is included because it has an OEL. The remaining components are non-hazardous and/or present at amounts below reportable limits. See Section 16 for full text of GHS classifications. Amounts are listed as ranges; the exact percentage of composition is withheld as a trade secret.

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 Medical conditions aggravated by exposure: Viral, bacterial, or fungal infections. 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, and chlorine-containing compounds.
Flammability/ Explosivity	No explosivity or flammability data identified. As product is an aqueous suspension, it is not expected to be flammable or explosive.
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 product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Do not breathe mist/spray.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	DO NOT CAUSE MATERIAL TO BECOME AIRBORNE. For small spills, soak up material with absorbent, e.g., paper towels. For large spills, cordon off spill area and minimize the spreading of spilled material. Soak up material with absorbent. Place spill materials into a leak-proof container suitable for proper 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 potent pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Avoid breathing mist/spray. Wash thoroughly after handling.
Conditions for safe storage including any incompatibilities	Store at controlled room temperature (15°C to 25°C; 59°F to 77°F) out of direct sunlight and away from incompatible materials. Keep container tightly closed.
Specific end use(s)	Pharmaceutical

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note

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

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Loteprednol etabonate	--	--	--
Edetate disodium	--	--	--
Glycerol	ACGIH, Belgium, Netherlands, Portugal, United Kingdom, Mexico, Singapore	TWA-8 HR	10 mg/m³ (listed as glycerin mist)
	Estonia, France, Greece, Ireland, Poland, Spain	TWA-8 HR	10 mg/m³
	Finland	TWA-8 HR	20 mg/m³
	Switzerland	TWA-8 HR	50 mg/m³
	Switzerland	STEL	100 mg/m³ (inhalable)
	United Kingdom	STEL	30 mg/m³ (mist)

Exposure/Engineering controls

Control exposures to below the OEL (for the active ingredient(s) if available). 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 aerosol/mist-generating points. Use engineered local exhaust ventilation (LEV) and/or enclosure for procedures where aerosolization may occur such as opened transfers, pumping, and spraying. Solutions can be handled outside a containment system or without LEV during procedures with no potential for aerosolization. All containers for solutions and slurries must be covered while being transferred.

Respiratory protection

Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. At a minimum, a tight-fitting full-face respirator with HEPA filters is required when performing aerosol generating operations. A powered air-purifying respirator (PAPR) with HEPA filters and head cover is required for spill cleanup.

Hand protection

Wear nitrile or other impervious gloves if skin contact is possible. When the material is diluted in an organic solvent, wear gloves that provide protection against the solvent.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION …continued

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).

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance	Liquid
Color	White suspension
Odor	Odorless
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	Not flammable.
Evaporation rate	No information identified.
Flammability (solid, gas)	Not applicable.
Upper/lower flammability or explosive limits	Not flammable.
Vapor pressure	No information identified

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Vapor density	No information identified.
Relative density	No information identified.
Water solubility	Mixture - Loteprednol etabonate (insoluble) + non-hazardous excipients (soluble)
Solvent solubility	No information identified.
Partition coefficient (*n-octanol/water*)	No information identified.
Auto-ignition temperature	As an aqueous suspension, not likely to autoignite.
Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	As an aqueous suspension, not likely to explode.
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	Stable under normal handling and storage conditions.
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 data for this mixture were identified. The following data describe the active ingredient (loteprednol etabonate) 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
Loteprednol etabonate	Maximum Tolerated Dose (MTD)	Oral	Rat/Mouse	>4,000 mg/kg
	MTD	SC	Rat/Mouse	>1300 mg/kg
Edetate disodium	LD_{50}	Oral	Rat	>2000 mg/kg
	LC_{50} (6 hour)	Inhalation	Rat	1-5 mg/l
Glycerol	LD_{50}	Oral	Rat	>10000 mg/kg
	LD_{50}	Oral	Mouse	>= 4090 mg/kg
	LD_{50}	Dermal	Rat	>21900 mg/kg
	LC_{50}	Inhalation	Rat	>570 mg/m³/1 hour
	LD_{50}	Dermal	Mouse	>18700 mg/kg
	LD_{50}	Dermal	Rabbit	>10000 mg/kg

Irritation/Corrosion Edetate disodium can be a mild eye irritant. However, the formulation (containing up to 1% loteprednol etabonate) did not cause eye irritation.

Sensitization No studies identified.

STOT-single exposure No additional details were identified.

STOT-repeated exposure/Repeat-dose toxicity Systemic exposure to corticosteroids can cause immune supression. Inhaled edetate disodium caused lung damange in rats.

Reproductive toxicity For loteprednol etabonate, no fertility impairment was observed in male or female rats treated orally with doses up to 50 or 25 mg/kg/day, respectively.

Developmental toxicity Embryotoxicity and teratogenicity was observed following oral administration of loteprednol etabonate to rats and rabbits during organogenesis at maternally toxic doses of 50 and 3 mg/kg/day, respectively. Malformations included cleft palate, umbilical hernia, and aortic arch abnormalities in rats, and meningocele (a form of spina bifida) and carotid artery abnormalities in rabbits. The oral NOAEL in both species for developmental and maternal toxicity was 0.5 mg/kg/day.
In a peri-/post-natal rat study with loteprednol etabonate, low birth weight was noted at oral doses of 5 mg/kg/ day, while embryotoxicity (e.g., developmental retardation and poor survival) was evident at 50 mg/kg/day (the NOAEL was 0.5 mg/kg/day). Developmental effects were considered to be independent of maternal toxicity which occurred in the same dose range.

Genotoxicity Loteprednol etabonate was not not genotoxic in the Ames bacterial mutagenesis assay, an *in vitro* mouse lymphoma cell assay, an *in vitro* chromosomal aberration test using cultured human lymphocytes, and an *in vivo* mouse micronucleus test.

Carcinogenicity No data available. None of the components of the product mixture 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.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Human health data See "Section 2 - Other Hazards"

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
Loteprednol etabonate	--	--	--
Edetate disodium	LC_{50}/96h	*Leuciscus idus* (freshwater fish)	>500 mg/L
	EC_{50}/24h	*Daphnia magna* (crustacea)	>100 mg/L
	EC_{50}/72h	Algae (unspecified)	10-100 mg/L
Glycerol	--	--	--

Persistence and Degradability No data available.

Bioaccumulative potential No data available.

Mobility in soil No data available.

Results of PBT and vPvB assessment Not performed.

Other adverse effects No data available.

Note Ecological characteristics of this mixture were not available. Releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods Used product should be disposed of according to local, state, and federal regulations. All wastes containing the material should be properly labeled. Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater treatment facility.

SECTION 14 - TRANSPORT INFORMATION

Transport Based on the available data, this 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.

SECTION 14 - TRANSPORT INFORMATION …continued

Transport hazard classes and packing group	None assigned.
Environmental hazards	Based on the available data, this 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	RT1B - Reproductive toxicity Category 1B. H360D - May damage the unborn child. STOT-R2 - Specific Target Organ Toxicity Following Repeated Exposure Category 2. H373 - May cause damage to immune system through prolonged or repeated exposure. STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. H372 - Causes damage to immune system through prolonged or repeated exposure. ATI4 - Acute Toxicity (Inhalation) Category 4. H332 - Harmful if inhaled. EI2 - Eye irritant Category 2. H319 - Causes serious eye irritation.
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; PBT - Persistent, Bioaccumulative, and Toxic; 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; vPvB - Very Persistent and Very Bioaccumulative; WHMIS - Workplace Hazardous Materials Information System

Issue Date

19 February 2019

Revisions

This is the first version of this SDS

Disclaimer

The above information is based on data available to us and is believed to be correct. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions.

No representation, warranty, or guarantee, express or implied (including a warranty of fitness or merchantability for a particular purpose), is made with respect to the materials, the accuracy of this information, the results to be obtained from the use thereof, or the hazards connected with the use of the material. Caution should be used in the handling and use of the material because it is a potent pharmaceutical product. The above information is offered in good faith and with the belief that it is accurate. As of the date of issuance, we are providing all information relevant to the foreseeable handling of the material. However, in the event of an adverse incident associated with this product, this Safety Data Sheet is not, and is not intended to be, a substitute for consultation with appropriately trained personnel.