SAFETY DATA SHEET

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

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Product identifier	Truvada® - Emtricitabine/Tenofovir Disoproxil Fumarate Tablets
Synonyms	**Active ingredients:** **Tenofovir Disoproxil Fumarate**: TDF, Tenofovir DF, bis(POC) PMPA, GS 4331-05 **Emtricitabine**: FTC, *cis*-(-)-FTC
Trade names	Truvada®
Chemical family	Nucleoside and nucleotide analog mixture
Relevant identified uses of the substance or mixture and uses advised against	Bulk formulated pharmaceutical product/mixture packaged in final form for patient use. Used in combination with other antiretroviral agents for the treatment of HIV- 1 infection in adults.
Note	This SDS for Truvada® Tablets is written to address potential worker health and safety issues associated with the handling of the formulated product.
Issue Date	28 October 2014

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.** Please consult the prescribing/packaging information. **The classification and labelling listed below is for bulk Truvada®.**
Regulation (EC) 1272/2008 [GHS]	Irritant (eye) - Category 1
Directive 67/548/EEC or 1999/45/EC	R41

Label elements

SECTION 2 - HAZARDS IDENTIFICATION …continued

CLP/GHS hazard pictogram	
CLP/GHS signal word	Danger
CLP/GHS hazard statements	H318 - Causes serious eye damage.
CLP/GHS precautionary statements	P280 - Wear eye/face protection. P305 + P351 + P338 - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P310 - Immediately call a Poison Center or doctor/ physician.
EU symbol/indication of danger	 Xi - Irritant
Risk (R) Phrase(s)	R41 - Risk of serious damage to eyes.
Safety Advice	S2 - Keep out of reach of children. S25 - Avoid contact with eyes. S26 - In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. S39 - Wear eye/face protection.
Other hazards	Adverse effects seen with therapeutic use of Truvada® include diarrhea, nausea, abdominal pain, flatulence, pancreatitis, weakness, headache, dizziness, insomnia, abnormal dreams, allergic reactions, skin discoloration, rash, muscular weakness, bone problems, including bone pain, softening or thinning (which may lead to fractures), changes in immune system (Immune Reconstitution Syndrome). Serious effects including lactic acidosis, renal impairment, including cases of acute renal failure, and effects on the liver, including hepatomegaly and developing fat in liver. The recommended dose of Truvada® is one tablet per day (containing 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate).
US Signal word	Warning
US Hazard overview	Causes eye irritation. Used as an antiretroviral agent for the treatment of HIV-1 infection.
Note	This product/mixture is classified as dangerous/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. The EU symbol/indicator of danger, R Phrases and Safety Advice are based on Directive 1999/45/EC.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ELINCS#	Amount	EU Classification	GHS Classification
Tenofovir Disoproxil Fumarate	202138-50-9	N/A	25-35%	Irritant - Xi: R41	EI1: H318
Emtricitabine	143491-57-0	N/A	15-25%	Not classified	Not classified
Cellulose	9004-34-6	232-674-9	25-35%	Not classified	Not classified
Starch	9005-25-8	232-679-6	4-6%	Not classified	Not classified
Magnesium Stearate	557-04-0	209-150-3	1-2%	Not classified	Not classified

Note The ingredients listed above are considered hazardous. Emtricitabine and Tenofovir Disoproxil Fumarate are pharmacologically active. Microcrystalline cellulose ("Cellulose"), Pregelatinized Starch ("Starch"), and Magnesium Stearate are listed because they have OELs. The remaining components are non-hazardous and/or present at amounts below reportable limits. The EU classification is based on Directive 67/ 548/EEC and the CLP/GHS classification is based on Regulation (EC) 1272/2008.

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

SECTION 4 - FIRST AID MEASURES …continued

Indication of immediate medical attention and special treatment needed, if necessary	Medical conditions aggravated by exposure: None known or reported. 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.

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 gases of carbon monoxide, carbon dioxide, oxides of nitrogen, magnesium-containing compounds, and phosphorus-containing compounds.
Flammability/Explosivity	No information identified.
Advice for firefighters	In case of fire in the surroundings: use the appropriate extinguishing agent. Wear full protective clothing and an approved, positive pressure, self-contained breathing apparatus. Decontaminate all equipment after use.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures	If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	If tablets are spilled, scoop up and dispose of in a manner that is compliant with federal, state or local laws. If tablets are broken or crushed, DO NOT RAISE DUST. Surround spill or powder with absorbents and place a damp cloth or towel over the area to minimize entry of powder into the air. Add excess liquid to allow the material to enter into solution. Capture remaining liquid onto spill adsorbents. Place spill materials into a leak-proof container for disposal in accordance with applicable waste disposal regulations (see section 13). Decontaminate the area twice with an appropriate solvent (see section 9).
Reference to other sections	See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling

If tablets are crushed or broken, dust containing drug substance may be released. Minimize dust generation and accumulation. Follow recommendations for handling bulk formulated/packaged pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Wash thoroughly after handling. Avoid contact with eyes, skin and other mucous membranes. Avoid breathing dust.

Conditions for safe storage including any incompatibilities

Protect from moisture. Store at 25°C (77 °F), excursions permitted to 15-30°C (59- 86°F). Keep container tightly closed; store in original container only.

Specific end use(s)

No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Control Parameters/Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Tenofovir Disoproxil Fumarate	Gilead	TWA-8 HR	200 µg/m³
Emtricitabine	Gilead	TWA-8 HR	1 mg/m³
Cellulose	ACGIH, Australia, Belgium, Estonia, France, Portugal, Romania, Singapore, Spain	TWA-8 HR	10 mg/m³
	Ireland, United Kingdom	TWA-8 HR	10 mg/m³ (inhalable dust); 4 mg/m³ (respirable dust)
	Ireland	STEL	20 mg/m³ (total inhalable dust)
	Latvia	TWA-8 HR	2 mg/m³
	Mexico	TWA-8 HR/STEL	10/20 mg/m³
	NIOSH	TWA-8 HR	10 mg/m³ (total dust); 5 mg/m³ (respirable dust)
	OSHA	TWA-8 HR	15 mg/m³ (total dust); 5 mg/m³ (respirable fraction)
	United Kingdom	STEL	20 mg/m³ (inhalable dust); 12 mg/m³ (respirable dust)

Control Parameters/Occupational Exposure Limit Values
…continued

Compound	Issuer	Type	OEL
Starch	ACGIH, Belgium, Bulgaria, Portugal, Spain, Singapore	TWA-8 HR	10 mg/m³
	Czech Republic, Slovak Republic	TWA-8 HR	4 mg/m³
	Greece, NIOSH	TWA-8 HR	10 mg/m³ (inhalable fraction); 5 mg/m³ (respirable fraction)
	Ireland, United Kingdom	TWA-8 HR	10 mg/m³ (inhalable fraction); 4 mg/m³ (respirable fraction)
	OSHA	TWA-8 HR	15 mg/m³ (total dust); 5 mg/m³ (respirable fraction)
	United Kingdom	STEL	30 mg/m³ (inhalable fraction); 12 mg/m³ (respirable fraction)
	NIOSH	TWA-10 HR	10 mg/m³ (total dust); 5 mg/m³ (respirable fraction)
Magnesium Stearate	ACGIH	TWA-8 HR	10 mg/m³ (stearates)
	Lithuania	TWA-8 HR	3 mg/m³
	Sweden	TWA-8 HR	5 mg/m³

Exposure/Engineering controls

None required for normal handling of packaged product. If handling bulk tablets or tablets are crushed or broken: control exposures to below the OEL (where available). The objective of containment, controls and work practices should be to maintain worker breathing zone concentrations below the respective OEL for each task or operation. In general, the handling practices below are capable of achieving the OELs. However, verification of the acceptability of these recommended containment, controls and work practices to meet OELs through industrial hygiene monitoring of tasks or operations is recommended. 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.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION …continued

Exposure/Engineering controls …continued	High-energy operations such as milling, particle sizing, spraying or fluidizing should be done within an approved emission control or containment system.
Respiratory protection	None required for normal handling of packaged product. If while handling, bulk tablets or tablets are crushed or broken: the choice of respiratory protection should be appropriate to the task, considering 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. The assigned protection factor (APF) of the selected PAPR should be at least 1000.
Hand protection	None required for normal handling of packaged product. Wear nitrile or other impervious gloves if skin contact with tablets is possible.
Skin protection	Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Base the choice of skin protection on the job activity, potential for skin contact and solvents and reagents in use.
Eye/face protection	Wear safety glasses with side shields, chemical splash goggles, or full face shield, if necessary. Base the choice of protection on the job activity and potential for contact with eyes or face. An emergency eye wash station should be available.
Environmental Exposure Controls	Should not be required during normal handling of material. In case of spill, do not release to drains. Avoid release to the environment.
Other protective measures	Wash hands in the event of contact with the tablets, 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	Blue, capsule-shaped, film-coated tablet
Color	Blue
Odor	No information identified.
Odor threshold	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

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	No information identified.
Solvent solubility	No information identified.
Partition coefficient (*n-octanol/water*)	No information identified.
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	No information identified.
Oxidizing properties	No information identified.

Other information

Molecular weight	Not applicable (Mixture)
Molecular formula	Not applicable (Mixture)

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	No information identified.
Chemical stability	Stable

SECTION 10 - STABILITY AND REACTIVITY …continued

Possibility of hazardous reactions Not expected to occur.

Conditions to avoid No information identified.

Incompatible materials No information identified.

Hazardous decomposition products No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note The following data describe the active ingredient and/or the individual ingredients where applicable.

Information on toxicological effects

Route of entry May be absorbed by ingestion. Absorption by inhalation or skin contact is not likely for packaged product, but may occur if tablets are crushed/broken.

Acute toxicity

Compound	Type	Route	Species	Dose
Tenofovir Disoproxil Fumarate	NOEL	Oral	Rat	>1500 mg/kg
Emtricitabine	LD_{50}	Oral	Rat/Mouse	>4000 mg/kg
Cellulose	LC_{50}	Inhalation	Rat	>5800 mg/m³/4h
	LD_{50}	Oral	Rat	>5000 mg/kg
	LD_{50}	Dermal	Rabbit	>2000 mg/kg
Starch	--	--	--	--
Magnesium Stearate	LC_{50}	Inhalation	Rat	>2000 mg/m³

Additional acute toxicity information Administration of non-degraded or degraded TDF/FTC by once daily oral gavage was well tolerated in rats at levels of 30/20, 100/67 and 300/200 mg/kg/day for 14 days. The NOAEL was considered to be 300/200 mg/kg/day for both non-degraded and degraded TDF/FTC. No differences in toxicity were observed between non- degraded and degraded material.

Irritation/Corrosion Tenofovir disoproxil fumarate was a severe eye irritant and a slight skin irritant in rabbits. No information identified for emtricitabine.

Sensitization Tenofovir disoproxil fumarate was not a contact sensitizer in guinea pigs. No information identified for emtricitabine.

STOT-single exposure Oral NOELs of >1,500 and >30 mg/kg were reported in rats and dogs, respectively, following single oral doses of tenofovir disoproxil fumarate.

STOT-repeated exposure/Repeat-dose toxicity NOELs associated with repeat doses were <30 and <3 mg/kg/day tenofovir disoproxil fumarate in rats and dogs, respectively. Target organs of toxicity included the bone and kidney. Oral NOELs of 500, 600 and 200 mg/kg/day emtricitabine were identified in repeat-dose toxicity studies in mice (6-month), rats (3-month) and monkeys (12-month), respectively.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Reproductive toxicity An oral reproductive NOEL of 300 mg/kg/day tenofovir disoproxil fumarate was identified in rats. No effects on fertility were observed in mice and rats treated with oral doses up to >1000 and 750 mg/kg/day emtricitabine, respectively.

Developmental toxicity Reproduction studies performed in rats and rabbits revealed no evidence of harm to the fetus due to tenofovir disoproxil fumarate. The incidence of fetal variations/ malformations was not increased in the offspring of mice or rabbits treated orally with emtricitabine at doses 60- and 120-fold higher, respectively, than those used in humans (based on exposure levels).

Genotoxicity Tenofovir disoproxil fumarate was mutagenic in the *in vitro* mouse lymphoma assay, but was negative in both the Ames bacterial mutagenicity test and an *in vivo* mouse micronucleus assay. Emtricitabine was negative in the Ames bacterial mutagenicity assay, a mutation assay in mouse lymphoma cells and an *in vivo* mouse micronucleus assay.

Carcinogenicity None of the 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. In long-term oral carcinogenicity studies, no evidence of carcinogenicity was observed in rats at doses up to 5 times the recommended therapeutic dose of tenofovir disoproxil fumarate in humans. In similar studies with mice, an increase in duodenal tumors was noted in female mice at 600 mg/kg/day; however, this was likely related to high local concentrations in the gastrointestinal tract. No drug-related increases in tumor incidence were observed in mice or rats treated with oral doses as high as 750 and 600 mg/kg/day emtricitabine, respectively.

Aspiration hazard No data available.

Human health data See "Section 2 - Other Hazards".

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
Tenofovir Disoproxil Fumarate	EC_{50}/72h	Freshwater green algae	47 mg/L
	EC_{50}/48h	Daphnia magna	>98 mg/L
	LC_{50}/96h	Rainbow trout	>92 mg/L
	NOEC/21 days reproduction	Daphnia magna	13 mg/L
	Early Life Cycle NOEC	Fathead minnow	1.9 mg/L
Emtricitabine	EC_{50}/72h	Freshwater green algae	>110 mg/L
	EC_{50}/48h	Daphnia magna	>110 mg/L
	LC_{50}/96h	Rainbow trout	>110 mg/L
	NOEC/21 days reproduction	Daphnia magna	110 mg/L

SECTION 12 - ECOLOGICAL INFORMATION …continued

Toxicity …continued

Compound	Type	Species	Concentration
	Early Life Cycle NOEC	Fathead minnow	6.1 mg/L
Cellulose	--	--	--
Starch	--	--	--

Additional toxicity information EC_{50}s of 940 and >1000 mg a.i./L were identified for tenofovir disoproxil fumarate and emtricitabine, respectively, in a respiratory inhibition study.

Persistence and Degradability Tenofovir disoproxil fumarate and emtricitabine are not readily biodegradable.

Bioaccumulative potential Tenofovir disoproxil fumarate and emtricitabine are unlikely to bioaccumulate, based on their respective log K_{OW} values.

Mobility in soil Tenofovir disoproxil fumarate and emtricitabine are not expected to partition into the sediment.

Adsorption coefficient (Koc) Log K_{oc} values of 1.3 and 21.1-45.6 were identified for tenofovir disoproxil fumarate and emtricitabine, respectively.

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. The above data are for the active ingredient(s) and/or other ingredient(s) where applicable. 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. 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 - 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.

SECTION 14 - TRANSPORT INFORMATION …continued

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 complies with the requirements under US, EU and GHS (EU CLP - Regulation EC No 1272/2008) guidelines. Consult your local/regional authorities for more information.
Chemical safety assessment	Not conducted.
OSHA Hazardous	**Drugs packaged in their finished state and intended for final users are not subject to labeling in the US or under GHS.** If handling the bulk formulation, the following labels apply: Warning - Causes eye irritation.
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.
WHMIS symbol(s)	None required
TSCA status	Drugs are exempt from TSCA.
SARA section 313	Not listed.
California proposition 65	Not listed.

SECTION 16 - OTHER INFORMATION

Full text of R phrases and EU Classifications	X_i - Irritant. R41 - Risk of serious damage to eyes.
Full text of H phrases, P phrases and GHS classification	EI1 - Eye irritant Category 1. H318 - Causes serious eye damage.
Sources of data	Information from published literature 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;
Revisions	This is the third 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.