

SAFETY DATA SHEET

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

Contact information

General



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Product identifier	Orkambi® (lumacaftor/ivacaftor) Tablets (for Adult and Pediatric Use)
Synonyms	VX-809/VX-770 Fixed-dose Tablets For VX-809: Lumacaftor; VRT-826809; VRT-0826809; 3-[6-({[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropyl]carbonyl}amino)-3-methylpyridin-2-yl]benzoic acid For VX-770: Ivacaftor; VRT-813077; N-(2,4-di-tert-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
Trade names	Orkambi®
Chemical family	Mixture
Relevant identified uses of the substance or mixture and uses advised against	Bulk formulated pharmaceutical mixture/formulated pharmaceutical product/mixture packaged in final form for patient use; indicated for the treatment of cystic fibrosis (CF)
Note	This safety data sheet (SDS) is written to address potential worker health and safety issues associated with the handling of the formulated product/mixture.

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 labeling listed below is for bulk drug product.**

Globally Harmonized System [GHS] Not classified

Label elements

GHS hazard pictogram None required

GHS signal word None required

GHS hazard statements None required

GHS precautionary statements None required

Other hazards Orkambi® Tablets contains fixed amounts of VX-770 and VX-809. VX-809 partially restores expression of the CF transmembrane conductance regulator (CFTR) protein, whereas VX-770 improves CFTR functions. Commonly observed adverse effects reported in healthy volunteers given high doses were diarrhea and fatigue. In studies with CF patients, mild to moderate effects including cough, throat pain, difficulty breathing, and increased blood pressure were reported. Menstrual abnormalities have also been reported.

Note This mixture does not meet criteria for classification 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). Nevertheless, it should be handled with caution as it has not yet been fully tested.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

<u>Ingredient</u>	<u>CAS #</u>	<u>EINECS/ ELINCS#</u>	<u>Amount</u>	<u>GHS Classification</u>
VX-809	936727-05-8	N/A	20-45%	Not classified
VX-770	873054-44-5	N/A	20-40%	Not classified
Cellulose	9004-34-6	232-674-9	20-30%	Not classified

Note The ingredients listed above are not considered hazardous, but are listed because they are pharmacologically active. Cellulose (in microcrystalline form) is listed because it has OELs and is present at or above 1%. The remaining components are present at amounts below reportable limits. See Section 16 for full text of GHS classifications.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures

Immediate Medical Attention Needed	No
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: 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 carbon monoxide, carbon dioxide, and oxides of nitrogen and fluoride.
Flammability/Explosivity	No explosivity or flammability data identified. High concentrations of finely divided airborne organic particles can potentially explode if ignited.
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 crush, break or chip tablets.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	If handling bulk material or if tablets 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 tablets are crushed or broken, dust containing drug substance may be released. Minimize dust generation and accumulation. Follow recommendations for handling pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Avoid breathing dust. Wash thoroughly after handling.
Conditions for safe storage including any incompatibilities	Store at $\leq 30^{\circ}\text{C}$ away from incompatible materials.
Specific end use(s)	No information identified.

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**

<u>Compound</u>	<u>Issuer</u>	<u>Type</u>	<u>OEL</u>
VX-809	--	--	--
VX-770	--	--	--

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION ...continued

**Control Parameters/
Occupational Exposure
Limit Values**

...continued

<u>Compound</u>	<u>Issuer</u>	<u>Type</u>	<u>OEL</u>
Cellulose	ACGIH, Australia, Belgium, Estonia, France, Portugal, Romania, Singapore, Spain	TWA-8 HR	10 mg/m ³
	Ireland, United Kingdom	TWA-8 HR	10 mg/m ³ (inhalable dust); 4 mg/m ³ (respirable dust)
	Ireland	STEL	20 mg/m ³ (total inhalable dust)
	Latvia	TWA-8 HR	2 mg/m ³
	Mexico	TWA-8 HR/STEL	10/20 mg/m ³
	NIOSH	TWA-8 HR	10 mg/m ³ (total dust); 5 mg/m ³ (respirable dust)
	OSHA	TWA-8 HR	15 mg/m ³ (total dust); 5 mg/m ³ (respirable fraction)
	United Kingdom	STEL	20 mg/m ³ (inhalable dust); 12 mg/m ³ (respirable dust)

**Exposure/Engineering
controls**

None required for normal handling of coated tablets. If tablets are crushed or broken: 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**

None required for normal handling of coated tablets. If tablets are crushed or 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

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION ...continued

Respiratory protection ...continued	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	None required for normal handling of coated tablets. If tablets are crushed or 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 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	Tablet
Color	Pink
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	Not applicable.
Flash point	No information identified.
Evaporation rate	Not applicable.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ...continued

Flammability (solid, gas)	No information identified.
Upper/lower flammability or explosive limits	No information identified.
Vapor pressure	Not applicable.
Vapor density	Not applicable.
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	Not applicable.
Decomposition temperature	No information identified.
Viscosity	Not applicable.
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	Stable under recommended handling and storage conditions.
Possibility of hazardous reactions	Not expected to occur.
Conditions to avoid	Protect from light and moisture.
Incompatible materials	No information identified.
Hazardous decomposition products	No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note Limited data for this product/mixture were identified. The following data describe the active ingredients where applicable.

Information on toxicological effects

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

Acute toxicity

<u>Compound</u>	<u>Type</u>	<u>Route</u>	<u>Species</u>	<u>Dose</u>
VX-809	--	--	--	--
VX-770	--	--	--	--
Cellulose	LC ₅₀	Inhalation	Rat	>5800 mg/m ³ /4h
	LD ₅₀	Oral	Rat	>5000 mg/kg
	LD ₅₀	Dermal	Rabbit	>2000 mg/kg

Irritation/Corrosion VX-809 and VX-770 are non-irritating to skin, non-corrosive/non-severe eye irritant.

Sensitization VX-809 and VX-770 are not potential skin sensitizers.

STOT-single exposure VX-809
Mouse (single-dose) NOAEL, PO = >2000 mg/kg
Rat (single-dose) NOAEL, PO = 1000 mg/kg (decreased activity, hunched appearance, fur staining at 2000 mg/kg)

VX-770
Single PO doses of 2000 mg/kg in mice and 500 mg/kg in rats were tolerated.

STOT-repeated exposure/Repeat-dose toxicity Rat (3-month) NOAEL, PO = 1000 mg/kg/day VX-809 + 100 mg/kg/day VX-770 (highest dose tested)
Dog (28-day) NOAEL, PO = 600 mg/kg/day VX-809 + 15 mg/kg/day VX-770 (hematological and cardiovascular changes at 600 + 60 mg/kg/day)

Reproductive toxicity VX-809
Rat (reproductive) NOAEL, PO = 1000 mg/kg/day

VX-770
Rat (reproductive) NOAEL, PO = 100 mg/kg/day (female) and 200 mg/kg/day (male) (impaired female fertility at 200 mg/kg/day secondary to maternal toxicity)

Developmental toxicity VX-809
Rat (maternal and developmental) NOAEL, PO = 2000 mg/kg/day
Rabbit (maternal) NOAEL, PO = 50 mg/kg/day (effects at 100 mg/kg/day)
Rabbit (developmental) NOAEL, PO = >200 mg/kg/day

VX-770
Rat (maternal) NOAEL, PO = 50 mg/kg/day
Rat (developmental) NOAEL, PO = 100 mg/kg/day ((decreased fetal body

SECTION 11 - TOXICOLOGICAL INFORMATION ...continued

Developmental toxicity ...continued	weights, skeletal variations at 200 mg/kg/day; no malformations) Rabbit (maternal) NOAEL, PO = 25 mg/kg/day Rabbit (developmental) NOAEL, PO = \geq 100 mg/kg/day
Genotoxicity	VX-809 and VX-770 were negative for genotoxicity in <i>in vitro</i> and <i>in vivo</i> assays.
Carcinogenicity	VX-809 No carcinogenic effects were noted in female and male mice at oral doses up to 1500 and 2000 mg/kg/day, respectively, for 26 weeks. No carcinogenic effects were noted in female and male rats at oral doses up to 1000 mg/kg/day for 2 years. VX-770 No carcinogenic effects were noted in mice and female rats at oral doses up to 200 and 50 mg/kg/day, respectively, for 2 years. None of the components of the mixture 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				
<u>Compound</u>	<u>Type</u>	<u>Species</u>	<u>Concentration</u>	
VX-809	--	--	--	
VX-770	--	--	--	
Cellulose	--	--	--	
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 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 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 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	Not applicable.
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; LD ₅₀ - Median Lethal Dose (50% mortality in group); 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; PO - oral; PNEC - Predicted No Effect Concentration; SARA - Superfund Amendments and Reauthorization Act; SDS - Safety Data Sheet; STOT - Specific Target Organ Toxicity; 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
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SECTION 16 - OTHER INFORMATION ...continued

Disclaimer ...continued

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