SAFETY DATA SHEET

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

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Product identifier	Letairis®, Ambrisentan Tablets
Synonyms	(S)-2-(4,6-dimethyl-pyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropanoic acid
Trade names	Letairis®, Volibris®
Chemical family	Mixture
Relevant identified uses of the substance or mixture and uses advised against	Endothelin receptor antagonist approved for the treatment of pulmonary arterial hypertension (PAH), to improve exercise ability and delay clinical worsening.
Note	This SDS is written to address potential worker health and safety issues associated with the handling of the formulated product. This SDS will be revisited if more data become available.
Issue Date	17 February 2015

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 drug product.**
Regulation (EC) 1272/2008 [GHS]	Reproductive Toxicity - Category 1B.
Directive 67/548/EEC or 1999/45/EC	T - R61 (Repr. Cat 2)

Label elements

SECTION 2 - HAZARDS IDENTIFICATION …continued

CLP/GHS hazard pictogram	
CLP/GHS signal word	Danger
CLP/GHS hazard statements	H360DF - May damage fertility or the unborn child.
CLP/GHS precautionary statements	P201 - Obtain special instructions before use. P202 - Do not handle until all safety precautions have been read and understood. P281 - Use personal protective equipment as required. 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.
EU symbol/indication of danger	 T- Toxic.
Risk (R) Phrase(s)	R60 - May impair fertility. R61 - May cause harm to the unborn child.
Safety Advice	S2 - Keep out of reach of children. S13 - Keep away from food, drink, and animal feeding stuffs. S22 - Do not breathe dust. S24/25 - Avoid contact with skin and eyes. S36 - Wear suitable protective clothing. S53 - Avoid exposure - Obtain special instructions before use.
Other hazards	In human clinical use, the most frequently reported adverse effects following repeat dose in healthy individuals included headache, fatigue, dizziness, feeling hot, photophobia, and nasal congestion. There may be a drug-related decrease in blood hemoglobin concentrations associated with chronic use. Frequently reported adverse effects in PAH patients included: peripheral edema, nasal congestion, sinusitis, flushing, nasopharyngitis, abdominal pain, constipation, palpitations, dyspnea, and headache. Decreased sperm counts have also been observed in human and animal studies with other endothelin receptor antagonists.
US Signal word	Warning
US Hazard overview	Pharmaceutical product for prescription use only. If tablets are crushed or broken and contacted, exposure may occur. Possible reproductive/developmental hazard - contains ambrisentan, an endothelin receptor antagonist which may cause adverse reproductive effects or may adversely affect the developing fetus.
Note	This product/mixture is classified as hazardous according to Directive 1999/45/EC, Regulation EC No 1272/2008 (EU-CLP), and applicable US regulations. The CLP/ GHS classifications are based on Regulation (EC) 1272/2008.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ELINCS#	Amount	EU Classification	GHS Classification
Cellulose	9004-34-6	232-674-9	20-30%	Not classified	Not classified
Ambrisentan	177036-94-1	N/A	3-8%	Toxic - T: R60, R61	RT1B: H360DF

Note The ingredient(s) listed above are considered hazardous and/or are the active ingredient. The remaining components are non-hazardous and/or present at amounts below reportable limits. See Section 16 for full text of EU and GHS classifications. The EU classification is based on Directive 1999/45/EC 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 If swallowed, call a physician immediately. 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 toxic gases of carbon monoxide, carbon dioxide, and oxides of nitrogen.
Flammability/Explosivity	No flammability information was identified. Ambrisentan is extremely sensitive to ignition from an electrostatic source if dispersed as finely divided particles in a dust cloud at high concentrations (based on its explosive properties; See Section 9). Avoid generating dust; fine dust dispersed in air in sufficient concentrations, and in the presence of an ignition source, is a potential dust explosion hazard.
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.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	For small spills (such as in a laboratory), soak up material with absorbent, e.g., damp paper towel, and wash spill area thoroughly with soap and water. For large spills in manufacturing, do not raise dust. Surround spill or powder with absorbents and place a damp cloth or towel over the area to minimize powder from entering the air. Add excess liquid to allow for the material to enter solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container suitable for disposal. Decontaminate area a second time. Dispose of material in a manner that is compliant with federal, state and local laws.
Reference to other sections	See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling	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 temperature of 25 °C, excursions from 15 °C - 30 °C permitted. Store in sturdy containers or use an unbreakable outer container. Keep container tightly closed when not in use. Keep out away from direct sunlight.

SECTION 7 - HANDLING AND STORAGE …continued

Specific end use(s) No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Control Parameters/Occupational Exposure Limit Values

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

Exposure/Engineering controls None required for normal handling of packaged product. If handling bulk tablets or if tablets are crushed or broken: Control exposures to below the OEL. Selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Open handling should not be performed when handling powders, wet solids or aerosolized solutions of this compound (either alone or mixed with excipients). Material should be handled inside a closed process, ventilated enclosure, isolator or device of equivalent or better control that is suitable for dusts and/or aerosols. Emphasis is to be placed on closed material transfer systems and process containment, without 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.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION …continued

Respiratory protection	None required for normal handling of packaged product. If handling bulk tablets or if tablets are crushed or broken: Choice of respiratory protection should be appropriate to the task and 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.
Hand protection	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). Decontaminate all protective equipment following use.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance	Tablet
Color	Pale pink and deep pink
Odor	No information identified.
Odor threshold	No information identified.
pH	Not applicable

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Melting point/freezing point	No information identified.
Initial boiling point and boiling range	Not applicable
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	Ambrisentan is extremely sensitive to ignition from an electrostatic source and has the potential to explode at high dust concentrations based on the following data: Minimum Ignition Energy (MIE): < 3 mJ (DIN EN 13821-Mike 3 apparatus)
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.

SECTION 10 - STABILITY AND REACTIVITY …continued

Chemical stability Stable

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

Information on toxicological effects

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

Acute toxicity

Compound	Type	Route	Species	Dose
Cellulose	LC_{50}	Inhalation	Rat	>5800 mg/m /4h
	LD_{50}	Oral	Rat	>5000 mg/kg
	LD_{50}	Dermal	Rabbit	>2000 mg/kg
Ambrisentan	LD_{50}	Oral	Rat (male)	4640 mg/kg
	LD_{50}	Oral	Rat (female)	3160 mg/kg

Irritation/Corrosion No information identified.

Sensitization No information identified.

STOT-single exposure No information identified.

STOT-repeated exposure/Repeat-dose toxicity After 26 weeks of daily doses, female dogs showed slight gastric fundic gland atrophy at 900 mg/kg/day, and rats exhibited nasal osseus hyperplasia and inflammation at 100 and 500 mg/day, respectively. In rats, nasal effects were severe enough in some animals to fully obstruct the airways, resulting in death after 15 weeks or longer exposure

Reproductive toxicity The development of testicular tubular atrophy and sterility has been linked to the chronic administration of endothelin receptor antagonists to rodents. Testicular tubular atrophy was observed in oral fertility studies with male rats dosed with ambrisentan. However, no consistent effects on sperm count, sperm motility, mating performance, or fertility were observed. Testicular tubular atrophy (focal/ multifocal or diffuse) was also observed in repeat dose studies in rats and mice. No testicular changes were observed in dog studies of up to 39 weeks duration at an exposure 35-fold that seen in humans based on area-under-the-curve (AUC) plasma concentrations.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Developmental toxicity The effect of ambrisentan on embryo-fetal development has been assessed in rats and rabbits after oral dose administration on gestation days 6-17. In both species, abnormalities of the lower jaw, tongue, and/or palate were consistently observed at all doses. Additionally, interventricular septal defects, trunk vessel defects, thyroid and thymus abnormalities, ossification of the basisphenoid bone, and an increased incidence of left umbilical artery closure were observed in the rat study.

Genotoxicity The genotoxicity of ambrisentan was assessed in a comprehensive battery of *in vitro* and *in vivo* studies. Ambrisentan was clastogenic when tested at high concentrations in mammalian cells *in vitro*. Ambrisentan was not mutagenic to bacteria, and produced no evidence of genotoxicity in two *in vivo* rodent studies.

Carcinogenicity There was no evidence of carcinogenic potential in two-year oral daily dosing studies in rats and mice. There was a small increase in mammary fibroadenomas, a benign tumor, in male rats at the highest dose only. This mixture is not 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
Cellulose	--	--	--
Ambrisentan	--	--	--

Persistence and Degradability No data identified.

Bioaccumulative potential No data identified.

Mobility in soil No data identified.

Results of PBT and vPvB assessment No data identified.

Other adverse effects No data identified.

Note The environmental characteristics of this product/mixture have not been fully investigated. 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	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	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 US, EU and GHS (EU-CLP - Regulation EC No 1272/2008) guidelines. Consult your local or regional authorities for more information.
Chemical safety assessment	Not conducted.

SECTION 15 - REGULATORY INFORMATION …continued

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: If tablets are crushed or broken: Possible reproductive/developmental hazard - contains ambrisentan, an endothelin receptor antagonist which may cause adverse reproductive effects or may adversely affect the developing fetus.
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	T - Toxic. R60 - May impair fertility. R61 - May cause harm to the unborn child.
Full text of H phrases, P phrases and GHS classification	RT1B - Reproductive toxicity Category 1B. H360DF - May damage fertility or the unborn child.
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

SECTION 16 - OTHER INFORMATION …continued

Abbreviations …continued	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 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.