SAFETY DATA SHEET

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

Contact information

General

Alkermes, Inc.
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Waltham, MA 02451
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E-mail: SDScoordinator@alkermes.com

Emergency telephone number

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+1 (800) 424-9300 (USA and Canada)
+1 (703) 527-3887 (International; collect calls accepted)

Product identifier

ARISTADA® (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use

Trade names

ARISTADA®

Chemical family

Phenylpiperazine

Active Ingredient

Aripiprazole lauroxil

Chemical Name of Active Ingredient

(7-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]butoxy}-2-oxo-3,4-dihydro-2H-quinolin-1-yl) methyl dodecanoate

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

Formulated pharmaceutical product packaged in final form for administration to patients; extended release injectable suspension for intramuscular use; approved for use as an antipsychotic drug for the treatment of schizophrenia.

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

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture

Globally Harmonized System [GHS]

Reproductive Toxicity - Category 2. Specific Target Organ Toxicity (repeated exposure) - Category 1. Aquatic toxicity (chronic) - Category 4.

Label elements

GHS hazard pictogram

GHS signal word

Danger

GHS hazard statements

H361fd - Suspected of damaging fertility. Suspected of damaging the unborn child. H372 - Causes damage to the cardiovascular and central nervous systems through prolonged or repeated exposure. H413 - May cause long-lasting harmful effects to aquatic life.

GHS precautionary statements

P201 - Obtain special instructions before use. P260 - Do not breathe mist/vapors/ spray. P273 - Avoid release to the environment. 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.

Other hazards

Following intramuscular injection, ARISTADA is converted to N-hydroxymethyl-aripiprazole, which is subsequently converted to aripiprazole. The most common adverse effect reported with use is akathisia (a state of agitation, distress, and restlessness that is often seen with similar-acting drugs). Other frequently reported effects include headache, insomnia, restlessness, weight changes, and injection site pain. Less frequent adverse effects include dizziness, constipation and dry mouth, weakness, heart palpitations and tachycardia (rapid heart rate), and anxiety. Additional effects reported with oral overdosage of aripiprazole include vomiting, somnolence, and tremor. There is also an increased risk of tardive dyskinesia (involuntary movement disorder), metabolic changes (leading to diabetes), orthostatic hypotension (dizziness upon standing), and white blood cell reduction (leading to increased risk of infection).

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur in association with antipsychotic drugs, including ARISTADA. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ ELINCS#	Amount	GHS Classification
Aripiprazole lauroxil	1259305-29-7	N/A	~24 %	ATO4: H302; RT2: H361fd; STOT-R1: H372; AA4: H413

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 an antipsychotic agent. Medical conditions aggravated by exposure: psychiatric disorders. 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 toxic fumes of carbon monoxide and carbon dioxide, oxides of nitrogen, hydrogen chloride, and other chlorine-containing compounds.
Flammability/ Explosivity	No explosivity or flammability data identified. As product is an aqueous solution, 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 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 mist/vapors/spray.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning	If syringes are crushed or broken, 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. Collect spilled material, absorbent, and rinse water into suitable containers 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	If syringes are crushed or broken, follow recommendations for handling potent pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Avoid breathing vapor or mist. Wash thoroughly after handling.
Conditions for safe storage including any incompatibilities	Store at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F). Keep away from incompatible materials. Store locked up.
Specific end use(s)	No information identified.
Note	Dispose of broken syringes in a sharps container.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Control Parameters/Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Aripiprazole lauroxil	Alkermes	TWA 8-HR	10 µg/m³

Exposure/Engineering controls

None required for normal handling of product. If syringes are broken: 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 potent substances, or substances of unknown toxicity. Material should be handled inside a closed process, ventilated enclosure, isolator or device of equivalent or better control that is suitable for aerosols.

Respiratory protection

None required for normal handling of product. If syringes are broken: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. For routine handling tasks, an approved and properly worn powered air-purifying respirator equipped with appropriate HEPA filters or combination filters should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use 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 air purifying respirators may not provide adequate protection.

Hand protection

None required for normal handling of product. Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered. If a situation arises in which the material is diluted in an organic solvent, wear gloves that provide protection against the solvent.

Skin protection

None required for normal handling of product. 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 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	ARISTADA is an extended-release injectable liquid suspension supplied in a 5-mL pre-filled syringe with safety needles in three available strengths: 441 mg in 1.6 mL, 662 mg in 2.4 mL, and 882 mg in 3.2 mL. The kit contains a 5-mL pre-filled syringe containing ARISTADA sterile aqueous suspension and safety needles.
Color	White to off-white suspension; kits are labeled as follows: Light blue (441-mg strength) Green (662-mg strength) Burgundy (882-mg strength)
Odor	No information identified.
Odor threshold	No information identified.
pH	No information identified.
Melting point/freezing point	81-83°C (M.P. for aripiprazole lauroxil crystalline powder)
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	Practically insoluble (<0.01 mg/mL at 25°C).
Solvent solubility	No information identified.
Partition coefficient (*n-octanol/water*)	5.3 (aripiprazole)
Auto-ignition temp.	No information identified.
Decomposition temp.	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Viscosity No information identified.

Explosive properties No information identified.

Oxidizing properties No information identified.

Other information

Molecular weight 660.7 (aripiprazole lauroxil)

Molecular formula $C_{36}H_{51}Cl_{12}N_3O_4$ (aripiprazole lauroxil)

SECTION 10 - STABILITY AND REACTIVITY

Reactivity No information identified.

Chemical stability No information identified.

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 **No toxicology data for the product were identified. The following data describe aripiprazole (a metabolite of the active moiety, N-hydroxymethyl-aripiprazole).**

Information on toxicological effects

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

Acute toxicity

Compound	Type	Route	Species	Dose
Aripiprazole lauroxil	LD_{50}	Intramuscular (IM)	Rat	>60 mg aripiprazole equivalents
	LD_{50}	IM	Dog	>1,000 mg aripiprazole equivalents
	LD_{50}	Oral	Rat (female)	705 mg/kg (aripiprazole)
	LD_{50}	Oral	Rat (male)	965 mg/kg (aripiprazole)

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Acute toxicity
…continued

Compound	Type	Route	Species	Dose
	LD_{50}	Oral	Monkey	>2000 mg/kg (aripiprazole)

Irritation/Corrosion No data available.

Sensitization No data available.

STOT-single exposure In single-dose IM studies with aripiprazole lauroxil, there were no signs of toxicity observed in rats. Transient and reversible impairment of hindlimb function was seen in some treated dogs.

Clinical findings associated with single oral doses up to 700-950 mg/kg aripiprazole in rats included decreased motor activity, convulsions, incoordination, tremors, and catalepsy (muscle rigidity). Similar effects were noted in monkeys orally treated with single doses up to 2000 mg/kg. Single intravenous (IV) doses up to 2 and 1 mg/kg in rats and monkeys, respectively, did not cause any adverse effects.

STOT-repeated exposure/Repeat-dose toxicity When rats were treated monthly with aripiprazole lauroxil by IM injection for 4 or 6 months, findings were limited to changes in body weight and granuloma formation (a response to foreign material) at the injection sites. Neither of these effects was considered adverse. When similar IM studies were performed using dogs, there were no toxicologically significant findings (observed drug-related effects were limited to granulomatous injection site reactions, plus sporadic and transient decreases in locomotor activity). NOAELs in the longest studies were 70 mg aripiprazole equivalents in rats and 1,400 mg aripiprazole equivalents in dogs, respectively.

Retinal degeneration was observed in albino rats treated with aripiprazole at oral doses >40 mg/kg/day for 26 weeks (about 7 times the maximum recommended human dose (MRHD), based on surface area). This effect was not observed in mice or in monkeys. The relevance of this finding to humans is unknown. Other effects seen in oral rat and monkeys studies (up to 52 weeks) included central nervous system effects and changes to the adrenals (rats only), gallbladder, liver, and reproductive organs (rats only).

Reproductive toxicity Reduced fertility and mating indices in both sexes, and altered estrous cycle with delayed time to mating time in females, were seen in rats treated IM with aripiprazole lauroxil at a dose of 98 mg aripiprazole equivalents. Intramuscular NOAELs of 33 mg aripiprazole equivalents were identified for both sexes, with NOAELs of 98 mg aripiprazole equivalents for general toxicity.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Developmental toxicity No evidence of maternal or fetal toxicity was seen in IM studies of aripiprazole lauroxil using pregnant rats and rabbits, at doses equivalent to 98 and 1,968 mg aripiprazole, respectively. In studies of aripiprazole, developmental toxicity (delayed skeletal ossification, decreased fetal weights, and/ or skeletal abnormalities) was seen in rats and rabbits at oral doses of 10 and 30 mg/kg/day, respectively and embryo-/fetotoxicity was noted at higher, maternally toxic doses in both species. The data suggest that aripiprazole may have a potential to adversely affect fetal development.

Genotoxicity Aripiprazole lauroxil was negative when tested in the Ames bacterial mutagenicity assay and in an *in vitro* chromosomal aberration study using peripheral human lymphocytes. Aripiprazole was also negative in a bacterial DNA repair assay, a forward mutation assay using mouse lymphoma cells, and an *in vivo* unscheduled DNA repair assay in rat hepatocytes. Although positive results were noted in an aripiprazole Ames bacterial mutagenicity assay and an aripiprazole mutation assay with Chinese hamster lung cells (with and without metabolic activation), the overall weight-of-evidence suggests a low genotoxic potential in mammalian cells for aripiprazole.

Carcinogenicity No studies identified for aripiprazole lauroxil. Aripiprazole was negative for carcinogenicity in male rats and mice at oral doses up to 10 and 30 mg/kg/day, respectively, for 2 years. An increased incidence of tumors believed to be prolactin-mediated, benign tumors in the pituitary gland and mammary glands were noted in female mice and rats at 3 and 10 mg/kg/day, respectively. Malignant adrenocortical tumors were also seen in female rats at higher doses. As the relevance of prolactin-mediated endocrine tumors in rodents to human health is not known, the data presented are inconclusive and the carcinogenic potential of aripiprazole to humans is not known. Aripiprazole 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
Aripiprazole lauroxil	--	--	--

Additional toxicity information No data available.

Persistence and Degradability Aripiprazole is not expected to undergo hydrolysis (not inherently biodegradable).

Bioaccumulative potential Based on its log K_{OW} of 5.3 and an estimated bioconcentration factor of 2,400, aripiprazole has a very high potential for bioconcentration in the environment.

Mobility in soil Aripiprazole is expected to be immobile in soil.

SECTION 12 - ECOLOGICAL INFORMATION …continued

Results of PBT and vPvB assessment	Not performed.
Other adverse effects	Aripiprazole is not expected to volatilize from water and moist soil surfaces.
Note	As no ecological information is available on aripiprazole lauroxil, ecological data for aripiprazole (a metabolite of the active moiety, N-hydroxymethyl-aripiprazole) are presented above. 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, 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 listed 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.
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	ATO4 - Acute Toxicity (Oral) Category 4. H302 - Harmful if swallowed. RT2 - Reproductive toxicity Category 2. H361fd - Suspected of damaging fertility. Suspected of damaging the unborn child. STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. H372 - Causes damage to the cardiovascular and central nervous systems through prolonged or repeated exposure. AA4- Acute aquatic toxicity Category 4. H413 - May cause long-lasting harmful effects to aquatic life.
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, Labeling, 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; STOT - Specific Target Organ Toxicity; STEL - Short Term Exposure Limit; TDG -

SECTION 16 - OTHER INFORMATION …continued

Abbreviations …continued

Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act; TWA - Time Weighted Average; WHMIS - Workplace Hazardous Materials Information System

Issue Date

30 March 2016

Revisions

7th. Revised product identifier and associated notes.

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 exposure 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 ARISTADA.