



## SAFETY DATA SHEET

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

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<b>Product identifier</b>	ISIS 766720 Liquid Drug Product
<b>Synonyms</b>	IONIS-GHR-L <sub>Rx</sub> , GalNAc Conjugated Liquid Drug Product, Ligand Conjugated Antisense (LICA)
<b>Trade names</b>	Not applicable
<b>Chemical family</b>	GalNAc conjugated 2'-O-methoxyethyl modified phosphorothioate oligonucleotide
<b>Relevant identified uses of the substance or mixture and uses advised against</b>	Bulk formulated pharmaceutical mixture designed to treat Acromegaly
<b>Note</b>	The physical, chemical, toxicological and ecological properties of this mixture and/ or its ingredients have not been fully characterized. This SDS will be revisited as more data become available.

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### SECTION 2 - HAZARDS IDENTIFICATION

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#### Classification of the substance or mixture

<b>Globally Harmonized System [GHS]</b>	Mixture not yet fully tested
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#### Label elements

<b>GHS hazard pictogram</b>	None required
<b>GHS signal word</b>	None required
<b>GHS hazard statements</b>	None required

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**SECTION 2 - HAZARDS IDENTIFICATION ...continued**

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**GHS  
precautionary  
statements**                      None required

**Other hazards**                      Mixture contains oligonucleotides, which are molecules composed of approximately 16 to 20 covalently linked naturally-occurring nucleotides on a phosphodiester and/or phosphorothioate backbone. Based on their intended diagnostic or therapeutic use, engineered oligonucleotides vary in nucleotide sequence to match and bind with a specific target genetic sequence. In clinical trials, modified oligonucleotides were generally well-tolerated. Although non-specific binding of oligonucleotides to other RNA sequences may occur, the drug candidates are designed to avoid this interaction. No genotoxic, reproductive (males or females) and/or developmental effects are expected, based on epidemiological and non-clinical data.

The hazardous properties of oligonucleotides have not been fully investigated and the potential health hazards associated with exposure/handling are unknown, but these compounds are generally not irritating and are not absorbed directly through skin or oral exposure routes. While chemical modification of oligonucleotides increases their stability in the body *via* parenteral routes, the likelihood of systemic effects following accidental ingestion or inhalation in a workplace setting is low, due to their rapid breakdown in the digestive tract and low bioavailability *via* inhalation.

**Note**                                      This substance 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 care because it is pharmacologically active and has not yet been fully tested.

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**SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS**

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<u>Ingredient</u>	<u>CAS #</u>	<u>EINECS/ ELINCS#</u>	<u>Amount</u>	<u>GHS Classification</u>
Oligonucleotides	N/A	N/A	1-30 %	Not classified
Sodium phosphate, dibasic, anhydrous	7558-79-4	231-448-7	1-2 %	SI2: H315; EI2: H319
Sodium phosphate, monobasic	7558-80-7	231-449-2	≤1 %	SI2: H315; EI2: H319
Sodium chloride	7647-14-5	231-598-3	≤1 %	Not classified

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**SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS ...continued**

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**Note** The substance(s) listed above are considered dangerous/hazardous or are active ingredients. The remaining component is water, which is non-hazardous. See Section 16 for full text of EU and GHS classifications. See Section 16 for full text of EU and EU-CLP/GHS classifications. The EU classification is based on Directive 67/548/EEC and the GHS classification is based on Regulation (EC) 1272/2008.

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**SECTION 4 - FIRST AID MEASURES**

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**Description of first aid measures**

<b>Immediate Medical Attention Needed</b>	Yes
<b>Eye Contact</b>	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.
<b>Skin Contact</b>	Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.
<b>Inhalation</b>	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.
<b>Ingestion</b>	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.
<b>Protection of first aid responders</b>	No extraordinary precautions required.
<b>Most important symptoms and effects, both acute and delayed</b>	See Sections 2 and 11
<b>Indication of immediate medical attention and special treatment needed, if necessary</b>	Medical conditions aggravated by exposure: None known or reported. Treat symptomatically and supportively.

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**SECTION 5 - FIREFIGHTING MEASURES**

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<b>Extinguishing media</b>	Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.
<b>Specific hazards arising from the substance or mixture</b>	No information identified. May emit toxic fumes of carbon monoxide, carbon dioxide, and oxides of nitrogen, sulfur, phosphorus.

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**SECTION 5 - FIREFIGHTING MEASURES ...continued**

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<b>Flammability/ Explosivity</b>	No explosivity or flammability data available. As mixture is an aqueous solution, it is not expected to be flammable or explosive.
<b>Advice for firefighters</b>	Wear full protective clothing and a self-contained breathing apparatus with a full face piece operated in the pressure demand or other positive pressure mode. Decontaminate all surfaces and equipment which may have come into contact with this substance, using an appropriate agent.

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**SECTION 6 - ACCIDENTAL RELEASE MEASURES**

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<b>Personal precautions, protective equipment and emergency procedures</b>	If material is released or spilled, cordon off spill area. 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.
<b>Environmental precautions</b>	Do not empty into drains. Avoid release to the environment.
<b>Methods and material for containment and cleaning up</b>	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.
<b>Reference to other sections</b>	See Sections 8 and 13 for more information.

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**SECTION 7 - HANDLING AND STORAGE**

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<b>Precautions for safe handling</b>	Avoid contact with eyes, skin and other mucous membranes. Wash thoroughly after handling. Use only with adequate local exhaust ventilation. Avoid breathing mist/spray.
<b>Conditions for safe storage including any incompatibilities</b>	Store in a refrigerator between 2-8° C, away from incompatible materials. Keep container tightly closed when not in use. Keep out of reach of children. Avoid extreme temperatures.
<b>Specific end use(s)</b>	No information identified.

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**SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION**

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**Control****Parameters/Occupational****Exposure Limit Values**

<u>Compound</u>	<u>Issuer</u>	<u>Type</u>	<u>OEL</u>
Oligonucleotides	--	--	--
Sodium chloride	Latvia, Lithuania, Russia	TWA-8 HR	5 mg/m <sup>3</sup>

**Exposure/Engineering controls**

Control exposures to below the OEL (if available). Otherwise, selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Use local exhaust and/or enclosure at aerosol/ mist-generating points. Emphasis is to be placed on closed material transfer systems and process containment, with limited open handling. High-energy operations should be done within an approved emission control or containment system.

**Respiratory protection**

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 fitted air purifying respirator should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use a powered air-purifying respirator equipped with appropriate 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.

**Skin protection**

Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely, e.g., during clean up of large spill. Base the choice of skin protection on the job activity and potential for skin contact.

**Eye/face protection**

Wear safety glasses with side shields if eye contact is likely, e.g., during cleanup of large spill). Base the choice of protection on the job activity and potential for contact with eyes and face. An emergency eyewash station should be available.

**Environmental Exposure Controls**

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 this substance, especially before eating, drinking or smoking.

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**SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES**

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**Information on basic physical and chemical properties**

<b>Appearance</b>	Liquid
<b>Color</b>	Clear; Colorless to yellow

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**SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ...continued**

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<b>Odor</b>	Odorless
<b>Odor threshold</b>	No information identified.
<b>pH</b>	6.5 to 8.5
<b>Melting point/freezing point</b>	Similar to water
<b>Initial boiling point and boiling range</b>	Similar to water
<b>Flash point</b>	No information identified.
<b>Evaporation rate</b>	Similar to water
<b>Flammability (solid, gas)</b>	No information identified.
<b>Upper/lower flammability or explosive limits</b>	No information identified.
<b>Vapor pressure</b>	No information identified.
<b>Vapor density</b>	No information identified.
<b>Relative density</b>	No information identified.
<b>Water solubility</b>	Soluble in water
<b>Solvent solubility</b>	No information identified.
<b>Partition coefficient (<i>n</i>-octanol/water)</b>	<1.0
<b>Auto-ignition temperature</b>	No information identified.
<b>Decomposition temperature</b>	No information identified.
<b>Viscosity</b>	No information identified.
<b>Explosive properties</b>	No information identified.
<b>Oxidizing properties</b>	No information identified.
<b>Other information</b>	
<b>Molecular weight</b>	Not applicable (Mixture)
<b>Molecular formula</b>	Contains C, N, P, O, H and S atoms

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**SECTION 10 - STABILITY AND REACTIVITY**

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<b>Reactivity</b>	No information identified.
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**SECTION 10 - STABILITY AND REACTIVITY ...continued**

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<b>Chemical stability</b>	Stable
<b>Possibility of hazardous reactions</b>	Not expected to occur.
<b>Conditions to avoid</b>	Avoid extreme temperatures.
<b>Incompatible materials</b>	Strong acids and bases, and materials incompatible with water.
<b>Hazardous decomposition products</b>	No information identified.

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**SECTION 11 - TOXICOLOGICAL INFORMATION**

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**Note** No data for the mixture were identified. The following data describe oligonucleotides, in general, and other ingredients, where applicable.

**Information on toxicological effects**

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

**Acute toxicity**

<u>Compound</u>	<u>Type</u>	<u>Route</u>	<u>Species</u>	<u>Dose</u>
Oligonucleotides	--	--	--	--
Sodium phosphate, dibasic, anhydrous	LD50	Oral	Rat	17 g/kg
Sodium phosphate, monobasic	LD50	Oral	Rabbit	8290 mg/kg
	LD50	Intramuscular	Rat	250 mg/kg
Sodium chloride	LD50	Oral	Rat	3000 mg/kg
	LD50	Dermal	Rabbit	>10,000 mg/kg
	LC50	Inhalation	Rat	>42 g/m <sup>3</sup> (1-hr)
	LD50	Oral	Mouse	4000 mg/kg

**Additional acute toxicity information** Acute IV exposure of monkeys to moderate/high doses of various oligonucleotides led to transient inhibition of the blood clotting cascade.

**Irritation/Corrosion** Sodium phosphate (dibasic and monobasic) was considered mildly irritating to rabbit eyes and skin in Standard Draize tests.

**Sensitization** No data available.

**STOT-single exposure** No data available.

**STOT-repeated exposure/Repeat-dose toxicity** Repeated parenteral exposure of mice and rats to moderate doses of various oligonucleotides led to pro-inflammatory effects. Such effects were not reported in monkeys in similar studies.

**Reproductive toxicity** No data available.

**Developmental toxicity** There is no evidence that oligonucleotides adversely affect embryos or fetal development.

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**SECTION 11 - TOXICOLOGICAL INFORMATION** ...continued

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<b>Genotoxicity</b>	Oligonucleotide drug candidates have been negative for genotoxicity in the Ames bacterial mutagenicity assay, <i>in vitro</i> chromosomal aberration assay, and <i>in vivo</i> mouse bone marrow micronucleus test.
<b>Carcinogenicity</b>	No data available. This substance is not listed by NTP, IARC, ACGIH or OSHA as a carcinogen.
<b>Aspiration hazard</b>	No data available.
<b>Human health data</b>	No data available.

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**SECTION 12 - ECOLOGICAL INFORMATION**

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**Toxicity**

<u>Compound</u>	<u>Type</u>	<u>Species</u>	<u>Concentration</u>
Oligonucleotides	--	--	--
Sodium chloride	EC50/96h	Fish (various species)	>4,700 mg/L
	EC50/48h	Daphnia magna	340-1000 mg/L

**Persistence and Degradability** No data identified.

**Bioaccumulative potential** No data identified.

**Mobility in soil** No data identified.

**Results of PBT and vPvB assessment** Not performed.

**Other adverse effects** No data identified.

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

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**SECTION 13 - DISPOSAL CONSIDERATIONS**

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**Waste treatment methods** Mixture should be disposed of according to applicable local waste disposal 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 with prescribed local guidelines. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater facility.

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**SECTION 14 - TRANSPORT INFORMATION**

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**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.



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**SECTION 14 - TRANSPORT INFORMATION ...continued**

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<b>UN proper shipping name</b>	None assigned.
<b>Transport hazard classes and packing group</b>	None assigned
<b>Environmental hazards</b>	Based on the available data, this mixture is not regulated as an environmental hazard or a marine pollutant.
<b>Special precautions for users</b>	No special precautions needed.
<b>Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code</b>	Not applicable.

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**SECTION 15 - REGULATORY INFORMATION**

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<b>Safety, health and environmental regulations/legislation specific for the substance or mixture</b>	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.
<b>Chemical safety assessment</b>	Not conducted.
<b>TSCA status</b>	Not listed
<b>SARA section 313</b>	Not listed.
<b>California proposition 65</b>	Not listed.
<b>Additional information</b>	No other information identified.

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**SECTION 16 - OTHER INFORMATION**

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<b>Full text of H phrases, and GHS classification</b>	Not applicable.
<b>Sources of data</b>	Internal company data

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**SECTION 16 - OTHER INFORMATION ...continued**

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**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; 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

**Issue Date** 12 April 2019

**Revisions**

- 1.0 New Document
- 1.1 Product identifier and synonyms updated
- 2.0 Company name changed to Ionis
- 2.1 Section 2 updated
- 2.2 Removed reference to EU CLP, US Signal word; issue date moved to section 16.

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