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## **Pfizer Ireland Pharmaceuticals**

Enforcement Team B,  
Office of Environmental Enforcement,  
South/Southwest Region,  
Environmental Protection Agency,  
Inniscarra,  
Co. Cork,  
P31 XV59

**20-October-2022**

**Ref: IE Licence register number P0013-05**

**Re: Revised Follow Up to INCI024029 reported on 04-Oct-2022 : Abatement partially offline :  
Emission Point A2-18 (V18) OSP4 : panel filter and HEPA filter not in place during PK-2445  
milling**

### **Root Causes and Preventative Actions**

We refer to incident ref. INCI024029 reported on 04-Oct-2022 in which a panel filter and HEPA filter were found to be not in place on emission point A2-18 (V18) during a milling operation on mill PK-2445 in the OSP4 building.

The material being milled was Ziprasidone Hydrochloride which is an active pharmaceutical ingredient (API) in solid form. Ziprasidone Hydrochloride is an antipsychotic medication which is used to treat schizophrenia and bipolar disorder. The API was being milled on mill no. PK-2445 in order to bring the particle size of the material into a specified range for quality purposes. The Safety Data Sheet (SDS) for Ziprasidone Hydrochloride is provided in the Appendix.

The investigation into the incident has progressed. The root causes have now been identified and corrective/preventative actions have been developed.

## Root Causes

1. Prior to the commencement of a milling campaign, a specialist contractor HVAC company is engaged to install a new HEPA filter and associated panel filter on the mill vent line. The HVAC service engineers install the HEPA and panel filters, and then conduct DOP (Dispersed Oil Particulate) verification testing to confirm that the filter is installed and functioning correctly.

In this case the HVAC service engineer normally covering the site was on annual leave at the time. The replacement HVAC engineer assigned to the job notified OSP4 operations that DOP testing was complete. However the subsequent investigation found that the filters were not in place on the equipment prior to the commencement of the milling campaign. The investigation with the contractor company to establish the lower-level root cause is ongoing.

2. An associated root cause is that site procedures currently do not independently confirm the installation of the HEPA filter prior to a campaign. The installation of the HEPA is currently confirmed by the notification by the contract company that DOP verification testing is complete, since DOP testing confirms both the correct installation and the integrity of the filter. In this case the notification by the contract company was erroneous and there was no independent check that the filters were in place.

## Preventative Actions

1. The DOP raw data test sheet used by the contract HVAC company will be revised to include a signature by appropriate site personnel. This will confirm that the HEPA filter on the correct equipment has been DOP tested.
2. Site procedures will be revised to require that the installation of the HEPA filter has to be physically confirmed by site personnel. This physical check will happen prior to and independently of completion of the DOP verification test.

We also confirm that a full check has been carried out of other HEPA filters units serviced by the HVAC company in question and all are installed as normal. We are confident that the actions described above will prevent a recurrence of the incident.

We trust that this is to the satisfaction of the Agency.

Yours Sincerely,

### **Pfizer Ireland Pharmaceuticals**

Ringaskiddy Active Pharmaceutical Ingredient Plant

### **Edward O'Sullivan**

Environment, Health and Safety Department

# Appendix

## Safety Data Sheet for Ziprasidone Hydrochloride



# SAFETY DATA SHEET

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## 1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND THE COMPANY/UNDERTAKING

### Product Identifier

**Material Name:** Ziprasidone hydrochloride monohydrate

**Trade Name:** Not applicable  
**Compound Number:** CP-88,059-01  
**Chemical Family:** Benzisothiazol derivative

**Relevant Identified Uses of the Substance or Mixture and Uses Advised Against Intended Use:** Pharmaceutical active

### Details of the Supplier of the Safety Data Sheet

Pfizer Global Manufacturing  
Pfizer Inc  
235 East 42nd Street  
New York, NY 10017  
1-800-879-3477

Pfizer Ltd  
Ramsgate Road  
Sandwich, Kent  
CT13 9NJ  
United Kingdom  
+00 44 (0)1304 616161

**Emergency telephone number:**  
1-212-573-2222

**Emergency telephone number:**  
International CHEMTREC (24 hours): +1-703-527-3887

**Hours of Operation - 24 Hours**

**Contact E-Mail:** pfizer-MSDS@pfizer.com

## 2. HAZARDS IDENTIFICATION

### Classification of the Substance or Mixture

#### GHS - Classification

Skin Sensitization: Category 1  
Specific target organ systemic toxicity (repeated exposure): Category 2

#### EU Classification:

EU Indication of danger: Xi - Irritant  
Xn - Harmful

#### EU Risk Phrases:

R43 - May cause sensitization by skin contact.  
R48/22 - Harmful: danger of serious damage to health by prolonged exposure if swallowed.

### Label Elements

**Signal Word:** Warning  
**Hazard Statements:** H317 - May cause an allergic skin reaction  
H373 - May cause damage to organs through prolonged or repeated exposure: liver

**Precautionary Statements:** P260 - Do not breathe dust/fume/gas/mist/vapors/spray  
P272 - Contaminated work clothing should not be allowed out of the workplace  
P280 - Wear protective gloves/protective clothing/eye protection/face protection  
P302+ P352 - IF ON SKIN: Wash with plenty of soap and water  
P333 + P313 - If skin irritation or rash occurs: Get medical advice/attention  
P314 - Get medical attention/advice if you feel unwell

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**Other Hazards**  
**Australian Hazard Classification (NOHSC):**

No data available  
Hazardous Substance. Non-Dangerous Goods.

**Note:** This document has been prepared in accordance with standards for workplace safety, which requires the inclusion of all known hazards of the product or its ingredients regardless of the potential risk. The precautionary statements and warning included may not apply in all cases. Your needs may vary depending upon the potential for exposure in your workplace.

### 3. COMPOSITION / INFORMATION ON INGREDIENTS

#### Hazardous

Ingredient	CAS Number	EU EINECS/ELINCS List	EU Classification	GHS Classification	%
Ziprasidone hydrochloride	138982-67-9	Not Listed	Xi;R43 Xn;R48/22	Skin Sens.1 (H317) STOT RE.2 (H373)	100

**Additional Information:** Ingredient(s) indicated as hazardous have been assessed under standards for workplace safety.

**For the full text of the R phrases and CLP/GHS abbreviations mentioned in this Section, see Section 16**

### 4. FIRST AID MEASURES

#### Description of First Aid Measures

**Eye Contact:** Flush with water while holding eyelids open for at least 15 minutes. Seek medical attention immediately.

**Skin Contact:** Remove contaminated clothing. Flush area with large amounts of water. Use soap. Seek medical attention. For information on potential delayed effects, see Section 2 - Hazards Identification and/or Section 11 - Toxicological Information.

**Ingestion:** Never give anything by mouth to an unconscious person. Wash out mouth with water. Do not induce vomiting unless directed by medical personnel. Seek medical attention immediately.

**Inhalation:** Remove to fresh air and keep patient at rest. Seek medical attention immediately.

#### Most Important Symptoms and Effects, Both Acute and Delayed

**Symptoms and Effects of Exposure:** For information on potential signs and symptoms of exposure, See Section 2 - Hazards Identification and/or Section 11 - Toxicological Information.

**Medical Conditions Aggravated by Exposure:** None known

#### Indication of the Immediate Medical Attention and Special Treatment Needed

**Notes to Physician:** None

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### 5. FIRE FIGHTING MEASURES

**Extinguishing Media:** Use carbon dioxide, dry chemical, or water spray.

**Special Hazards Arising from the Substance or Mixture**

**Hazardous Combustion Products:** Emits toxic fumes of carbon monoxide, carbon dioxide, nitrogen oxides, sulfur oxides, hydrogen chloride and other chlorine- and sulfur-containing compounds.

**Fire / Explosion Hazards:** Fine particles (such as dust and mists) may fuel fires/explosions.

**Advice for Fire-Fighters**

During all fire fighting activities, wear appropriate protective equipment, including self-contained breathing apparatus.

**Additional Information:** This material is not expected to support combustion

### 6. ACCIDENTAL RELEASE MEASURES

**Personal Precautions, Protective Equipment and Emergency Procedures**

Personnel involved in clean-up should wear appropriate personal protective equipment (see Section 8). Minimize exposure.

**Environmental Precautions**

Place waste in an appropriately labeled, sealed container for disposal. Care should be taken to avoid environmental release.

**Methods and Material for Containment and Cleaning Up**

**Measures for Cleaning / Collecting:** Contain the source of spill if it is safe to do so. Collect spilled material by a method that controls dust generation. A damp cloth or a filtered vacuum should be used to clean spills of dry solids. Clean spill area thoroughly.

**Additional Consideration for Large Spills:** Non-essential personnel should be evacuated from affected area. Report emergency situations immediately. Clean up operations should only be undertaken by trained personnel.

### 7. HANDLING AND STORAGE

**Precautions for Safe Handling**

Ground and bond all bulk transfer equipment. Avoid open handling. Minimize dust generation. Use local exhaust ventilation or perform work under fume hood/fume cupboard. Avoid inhalation and contact with skin, eye, and clothing. When handling, use appropriate personal protective equipment (see Section 8). Wash hands and any exposed skin after removal of PPE. Releases to the environment should be avoided. Review and implement appropriate technical and procedural waste water and waste disposal measures to prevent occupational exposure or environmental releases. Potential points of process emissions of this material to the atmosphere should be controlled with dust collectors, HEPA filtration systems or other equivalent controls.

**Conditions for Safe Storage, Including any Incompatibilities**

**Storage Conditions:** Store at room temperature in properly labeled containers. Keep away from heat, sparks and flames.

**Incompatible Materials:** As a precautionary measure, keep away from strong oxidizers.

**Specific end use(s):** Pharmaceutical active

### 8. EXPOSURE CONTROLS / PERSONAL PROTECTION

**Control Parameters**

Ziprasidone hydrochloride  
Pfizer OEL TWA-8 Hr:

90µg/m<sup>3</sup>, Sensitizer

**Analytical Method:** Analytical method available. Contact Pfizer Inc for further information.  
**Exposure Controls**

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### 8. EXPOSURE CONTROLS / PERSONAL PROTECTION

<b>Engineering Controls:</b>	Engineering controls should be used as the primary means to control exposures. Use process containment, local exhaust ventilation, or other engineering controls to maintain airborne levels within the OEB range.
<b>Personal Protective Equipment:</b>	Refer to applicable national standards and regulations in the selection and use of personal protective equipment (PPE).
<b>Hands:</b>	Wear impervious gloves to prevent skin contact.
<b>Eyes:</b>	Wear safety glasses as minimum protection.
<b>Skin:</b>	Wear impervious protective clothing to prevent skin contact - consider use of disposable clothing where appropriate.
<b>Respiratory protection:</b>	If the applicable Occupational Exposure Limit (OEL) is exceeded, wear an appropriate respirator with a protection factor sufficient to control exposures to below the OEL.

### 9. PHYSICAL AND CHEMICAL PROPERTIES

<b>Physical State:</b>	Powder	<b>Color:</b>	White to light pink
<b>Odor:</b>	No data available.	<b>Odor Threshold:</b>	No data available.
<b>Molecular Formula:</b>	C <sub>21</sub> H <sub>21</sub> ClN <sub>4</sub> OS•HCl•H <sub>2</sub> O	<b>Molecular Weight:</b>	467.4

<b>Solvent Solubility:</b>	Methanol (1.46 mg/ml); Tetrahydrofuran (0.002 mg/ml)
<b>Water Solubility:</b>	No data available
<b>Solubility:</b>	Insoluble: Water
<b>pH:</b>	No data available.
<b>Melting/Freezing Point (°C):</b>	308 - 311
<b>Boiling Point (°C):</b>	No data available.
<b>Partition Coefficient: (Method, pH, Endpoint, Value)</b>	
<b>Ziprasidone hydrochloride</b>	
Measured Log P	3.44

**Decomposition Temperature (°C):** No data available.

<b>Evaporation Rate (Gram/s):</b>	No data available
<b>Vapor Pressure (kPa):</b>	No data available
<b>Vapor Density (g/ml):</b>	No data available
<b>Relative Density:</b>	No data available
<b>Viscosity:</b>	No data available

#### Flammability:

<b>Autoignition Temperature (Solid) (°C):</b>	No data available
<b>Flammability (Solids):</b>	No data available
<b>Flash Point (Liquid) (°C):</b>	No data available
<b>Upper Explosive Limits (Liquid) (% by Vol.):</b>	No data available
<b>Lower Explosive Limits (Liquid) (% by Vol.):</b>	No data available

**Dust Explosivity:** This material presents a weak to moderate dust explosion hazard (K<sub>st</sub> = 151 bar-m/s) and has a low sensitivity to ignition (100 - 500 mJ).

<b>Max. Explosion Pressure (bar):</b>	8.1
<b>Max. Rate of Pressure Rise (bar/sec):</b>	555
<b>K<sub>st</sub> Value (bar*m/s):</b>	151
<b>St Class:</b>	St 1
<b>Min. Ignition Energy (mJ):</b>	100 - 300
<b>Min. Ignition Temperature (°C):</b>	640 - 660
<b>Limiting Oxygen Concentration (% vol):</b>	12 - 15%
<b>Min. Explosion Concentration (g/m<sup>3</sup>):</b>	95 g/m <sup>3</sup>

#### Electrostatic Risk:

<b>Charge Relaxation Time:</b>	
Ambient Humidity:	Hours
Low Humidity:	Hours

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Chargability: Ambient Humidity: 8E12  
Low Humidity: 1E14

Polymerization: Will not occur

### 10. STABILITY AND REACTIVITY

**Reactivity:** No data available  
**Chemical Stability:** Stable under normal conditions of use.  
**Possibility of Hazardous Reactions**  
**Oxidizing Properties:** No data available  
**Conditions to Avoid:** Fine particles (such as dust and mists) may fuel fires/explosions.  
**Incompatible Materials:** As a precautionary measure, keep away from strong oxidizers.  
**Hazardous Decomposition Products:** No data available

### 11. TOXICOLOGICAL INFORMATION

#### Information on Toxicological Effects

**Short Term:** Antipsychotic drug: causes central nervous system effects. Drugs of this class have been associated with rare, but potentially serious cardiac events. These events have not been observed from occupational exposures, however, those with preexisting cardiovascular illnesses may be at increased risk from exposure.

**Known Clinical Effects:** This drug is prescribed for antipsychotic therapy and can depress central nervous system function. The most common adverse effect associated with the clinical use of ziprasidone was somnolence.

#### Acute Toxicity: (Species, Route, End Point, Dose)

##### Ziprasidone hydrochloride

Rat Oral LD50 > 2000 mg/kg  
Rat IP LD50 > 2000mg/kg  
Mouse Oral LD50 > 2000mg/kg  
Mouse IP LD50 500-1000mg/kg  
Rabbit Dermal LD50 > 2000mg/kg

**Acute Toxicity Comments:** A greater than symbol (>) indicates that the toxicity endpoint being tested was not achievable at the highest dose used in the test.

#### Irritation / Sensitization: (Study Type, Species, Severity)

##### Ziprasidone hydrochloride

Eye Irritation Rabbit Non-irritating  
Skin Irritation Rabbit Non-irritating  
Skin Sensitization - GPMT Guinea Pig Positive

#### Repeated Dose Toxicity: (Duration, Species, Route, Dose, End Point, Target Organ)

##### Ziprasidone hydrochloride

6 Month(s) Rat Oral 40 mg/kg/day LOAEL Central nervous system, Liver  
6 Month(s) Dog Oral 40 mg/kg/day LOAEL Central Nervous System, Liver  
1 Month(s) Rat Oral 160 mg/kg/day NOAEL Central Nervous System  
12 Month(s) Dog Oral 10 mg/kg/day NOAEL Central Nervous System

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### 11. TOXICOLOGICAL INFORMATION

#### Reproduction & Developmental Toxicity: (Study Type, Species, Route, Dose, End Point, Effect(s))

##### **Ziprasidone hydrochloride**

Reproductive & Fertility	Rat	Oral 40 mg/kg/day	NOAEL	Negative
Peri-/Postnatal Development	Rat	5 mg/kg/day	NOAEL	Embryotoxicity, Fetotoxicity
Embryo / Fetal Development	Rat	Oral 10 mg/kg/day	NOAEL	Not Teratogenic
Embryo / Fetal Development	Rabbit	Oral 30 mg/kg/day	NOAEL	Not Teratogenic

#### Genetic Toxicity: (Study Type, Cell Type/Organism, Result)

##### **Ziprasidone hydrochloride**

<i>In Vitro</i>	Human Lymphocytes	Negative
<i>In Vivo</i>	Mouse Bone Marrow	Negative
<i>In Vitro</i> Bacterial Mutagenicity (Ames)	<i>Salmonella</i>	Negative
<i>In Vitro</i> Mammalian Cell Mutagenicity	Mouse Lymphoma	Negative

#### Carcinogenicity: (Duration, Species, Route, Dose, End Point, Effect(s))

##### **Ziprasidone hydrochloride**

2 Year(s)	Rat	Oral 12 mg/kg/day	Not carcinogenic
2 Year(s)	Mouse	Oral 200 mg/kg/day	Not carcinogenic

**Carcinogen Status:** Not listed as a carcinogen by IARC, NTP or US OSHA.

### 12. ECOLOGICAL INFORMATION

**Environmental Overview:** This substance was not acutely toxic to aquatic organisms at its maximum solubility. See aquatic toxicity data below.

#### **Toxicity:**

#### Aquatic Toxicity: (Species, Method, End Point, Duration, Result)

##### **Ziprasidone hydrochloride**

<i>Daphnia magna</i> (Water Flea)	OECD	EC50	48 Hours	> 0.048 mg/L
<i>Pimephales promelas</i> (Fathead Minnow)	TAD	LC50	96 Hours	> 0.035 mg/L
<i>Selenastrum capricornutum</i> (Green Alga)	OECD	ErC50	72 Hours	> 0.12 mg/L
<i>Daphnia magna</i> (Water Flea)	OECD	NOEC	21 Days	0.005 mg/L
<i>Ceriodaphnia dubia</i> (Daphnids)	OECD	NOEC	7 Days	0.021 mg/L

**Aquatic Toxicity Comments:** A greater than (>) symbol indicates that acute ecotoxicity was not observed at the maximum solubility. Since the substance is insoluble in aqueous solutions above this concentration, an acute ecotoxicity value (i.e. LC/EC50) is not achievable.

#### Bacterial Inhibition: (Inoculum, Method, End Point, Result)

##### **Ziprasidone hydrochloride**

Activated sludge	OECD	EC50	> 1000 mg/L
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#### **Persistence and Degradability:**

#### Biodegradation: (Method, Inoculum, Biodeg Study, Result, Endpoint, Duration, Classification)

<b>Ziprasidone hydrochloride</b>	Ready	36% After	28 Day(s)	Not Ready
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**Bio-accumulative Potential:**  
**Partition Coefficient: (Method, pH, Endpoint, Value)**

Ziprasidone hydrochloride  
Measured Log P 3.44

**Mobility in Soil:** No data available

### 13. DISPOSAL CONSIDERATIONS

**Waste Treatment Methods:** Dispose of waste in accordance with all applicable laws and regulations. Member State specific and Community specific provisions must be considered. Considering the relevant known environmental and human health hazards of the material, review and implement appropriate technical and procedural waste water and waste disposal measures to prevent occupational exposure and environmental release. It is recommended that waste minimization be practiced. The best available technology should be utilized to prevent environmental releases. This may include destructive techniques for waste and wastewater.

### 14. TRANSPORT INFORMATION

The following refers to all modes of transportation unless specified below.

Not regulated for transport under USDOT, EUADR, IATA, or IMDG regulations.

### 15. REGULATORY INFORMATION

Safety, Health and Environmental Regulations/Legislation Specific for the Substance or Mixture

**Canada - WHMIS: Classifications**

**WHMIS hazard class:**

Class D, Division 2, and Subdivision B.



**Ziprasidone hydrochloride**

CERCLA/SARA 313 Emission reporting

Not Listed

California Proposition 65

Not Listed

EU EINECS/ELINCS List

Not Listed

### 16. OTHER INFORMATION

Text of R phrases and GHS Classification abbreviations mentioned in Section 3

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Sensitization, skin-Cat.1; H317 - May cause an allergic skin reaction  
Specific target organ toxicity, repeated exposure-Cat.2; H373 - May cause damage to organs through prolonged or repeated exposure

Xi - Irritant  
Xn - Harmful

R43 - May cause sensitization by skin contact.  
R48/22 - Harmful: danger of serious damage to health by prolonged exposure if swallowed.

**Data Sources:** Pfizer proprietary drug development information.

**Reasons for Revision:** Updated Section 2 - Hazard Identification. Updated Section 11 - Toxicology Information.

**Revision date:** 12-Jun-2014

**Prepared by:** Product Stewardship Hazard Communication  
Pfizer Global Environment, Health, and Safety Operations

Pfizer Inc believes that the information contained in this Material Safety Data Sheet is accurate, and while it is provided in good faith, it is without warranty of any kind, expressed or implied. If data for a hazard are not included in this document there is no known information at this time.

**End of Safety Data Sheet**