



Material Safety Data Sheet

Material Name: Methadone Hydrochloride Injection, USP

*** Section 1 - Chemical Product and Company Identification ***

Manufacturer Information

Bioniche Pharma
272 E Deerpath Road
Suite 304
Lake Forest, IL 60045

Phone: 888-258-4199

Emergency # 888-875-1671

*** Section 2 - Hazards Identification ***

Emergency Overview

FINISHED PHARMACEUTICAL PRODUCT. REFER TO PHYSICIANS' DESK REFERENCE. DRUG ENFORCEMENT ADMINISTRATION STATUS: CONTROLLED SUBSTANCE, SCHEDULE II. ACTIVE INGREDIENT: TOXIC

MAY IRRITATE EYES. AFFECTS RESPIRATORY SYSTEM, CENTRAL NERVOUS SYSTEM, CARDIOVASCULAR SYSTEM. THE MAJOR HAZARDS ARE RESPIRATORY DEPRESSION AND, TO A LESSER DEGREE, SYSTEMIC HYPOTENSION. RESPIRATORY ARREST, SHOCK, CARDIAC ARREST, AND DEATH MAY OCCUR.

SHORT-TERM INGESTION OR INJECTION CAN CAUSE LIGHTEADEDNESS, DIZZINESS, SEDATION, NAUSEA, VOMITING, AND SWEATING. OTHER ADVERSE EFFECTS INCLUDE DROWSINESS, TROUBLED BREATHING, FLUSHED FACE, IRREGULAR HEARTBEAT, CONSTIPATION, WEAKNESS, LOSS OF APPETITE, GENERAL FEELING OF DISCOMFORT, FALSE SENSE OF WELL-BEING, DRY MOUTH, STOMACH CRAMPS, DIFFICULTY OR DECREASED URINATION, CONFUSION, HEADACHE, AND VISUAL DISTURBANCES.

OVERDOSE SYMPTOMS CAN INCLUDE COLD, CLAMMY SKIN, CONFUSION, CONVULSIONS, SEVERE DIZZINESS, DROWSINESS, RESTLESSNESS OR WEAKNESS, PINPOINT PUPILS, SLOW HEARTBEAT, SLOW OR TROUBLED BREATHING AND COMA. CARDIAC ARREST AND DEATH CAN OCCUR. MAY CAUSE DEPENDENCY.

MAY CAUSE SENSITIZATION AND ALLERGIC REACTION BY SKIN ABSORPTION, INGESTION OR INJECTION.

Potential Health Effects: Eyes

Direct contact with this solution may cause eye irritation.

Potential Health Effects: Skin

Direct contact with this solution may cause mild skin irritation. Can be absorbed via skin to cause symptoms described under "Therapeutic Side Effects".

Potential Health Effects: Ingestion

No hazard is expected from normal clinical use. See "Therapeutic Side Effects" for information on side effects by ingestion of therapeutic doses.

Potential Health Effects: Inhalation

No hazard is expected from normal clinical use. Inhalation of mists or sprays of this solution may irritate the respiratory system and cause symptoms described under "Therapeutic Side Effects".

Material Safety Data Sheet

Material Name: Methadone Hydrochloride Injection, USP

Medical Conditions Aggravated by Exposure

Methadone Hydrochloride Injection is contraindicated in patients with a known hypersensitivity to methadone hydrochloride or any other ingredient in Methadone Hydrochloride Injection. Methadone Hydrochloride Injection is contraindicated in any situation where opioids are contraindicated such as: patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute bronchial asthma, active alcoholism, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma, cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia, or hypercarbia, head injury, other intracranial lesions or a pre-existing increase in intracranial pressure.

THERAPEUTIC SIDE EFFECTS: Methadone Hydrochloride is a synthetic opioid analgesic (narcotic) used for the treatment of narcotic addiction and severe pain. The most common dose-dependent adverse effects associated with therapeutic treatments include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. Other adverse effects include drowsiness, troubled breathing, flushed face, irregular heartbeat, constipation, weakness, loss of appetite, general feeling of discomfort, false sense of well-being, dry mouth, stomach cramps, difficulty or decreased urination, confusion, headache, and visual disturbances. A single dose of 50-100 mg can be life threatening. Symptoms of overdose include cold, clammy skin, confusion, convulsions, severe dizziness, drowsiness, restlessness or weakness, pinpoint pupils, slow heartbeat, (slow or troubled breathing), respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), skeletal-muscle flaccidity and extreme somnolence progressing to stupor or, coma. Apnea, circulatory collapse, cardiac arrest and death can occur.

Methadone Hydrochloride can produce drug dependence of the morphine-type and therefore has the potential for being abused, although this is not a typical health hazard for persons handling or administering this product. Caution should be used in handling of the product to avoid potential dependence from skin contact due to skin absorption characteristics of the Chlorobutanol component, which can carry Methadone Hydrochloride with it into the blood stream. Under certain circumstances, inhalation exposure could lead not only to respiratory tract irritation, but also to systemic absorption of methadone. In such a situation, systemic toxic effects would occur in accordance with the dose absorbed.

HMIS Ratings: Health: 2 Fire: 0 HMIS Reactivity 0

Hazard Scale: 0 = Minimal 1 = Slight 2 = Moderate 3 = Serious 4 = Severe * = Chronic hazard

*** Section 3 - Composition / Information on Ingredients ***

CAS #	Component	Percent
1095-90-5	Methadone hydrochloride	99.9
7647-14-5	Sodium chloride	0.9
7732-18-5	Water	Balance
928-51-8	1-Butanol, 4-chloro-	0.05

*** Section 4 - First Aid Measures ***

First Aid: Eyes

Flush with running water for 15 minutes holding eyelids open. Seek medical attention if adverse effect occurs.

First Aid: Skin

Wash contaminated area with soap and water, Seek medical attention if irritation or adverse effect occurs.

First Aid: Ingestion

Flush mouth out with water and get medical attention immediately.

First Aid: Inhalation

No specific treatment is necessary since this product is not likely to be hazardous by inhalation. Move person to fresh air immediately and seek medical attention if irritation or adverse effect occurs.

First Aid: Notes to Physician

Consult the Package Insert for additional information, which can assist with treatment of overexposure. Treatment of opioid analgesic overdose (such as this product) should be symptomatic and supportive and may include the following:

Material Safety Data Sheet

Material Name: Methadone Hydrochloride Injection, USP

1. Empty the stomach, induce vomiting or perform gastric lavage (if product was taken orally). However, treatment of respiratory depression or other potentially life-threatening adverse effects must take precedence.
2. Establish adequate respiratory exchange through provision of a patent airway.
3. Administer opioid antagonist naloxone, preferably intravenously. Naloxone injections may be repeated at two to three minute intervals as needed.
4. Administer intravenous fluids and/or vasopressors and use other supportive measures as needed.
5. Continue to monitor patient (mandatory because the duration of action of the opioid analgesic may exceed that of the antagonist) and administer additional naloxone as needed.
6. Alternatively, initial treatment may be followed by continuous intravenous infusion of naloxone, with the rate of infusion being adjusted according to patient response.

*** Section 5 - Fire Fighting Measures ***

General Fire Hazards

See Section 9 for Flammability Properties.

When involved in a fire, this product may decompose and produce irritating fumes and toxic gases.

Hazardous Combustion Products

Thermal decomposition may result in the emission of carbon monoxide, carbon dioxide, nitrogen oxides and hydrogen chloride.

Extinguishing Media

Use media suitable for fire in surrounding area.

Fire Fighting Equipment/Instructions

Wear full protective clothing and positive pressure self-contained breathing apparatus.

NFPA Ratings: Health: 2 Fire: 0 Reactivity: 0

Hazard Scale: 0 = Minimal 1 = Slight 2 = Moderate 3 = Serious 4 = Severe

*** Section 6 - Accidental Release Measures ***

Containment Procedures

Stop the flow of material, if this is without risk.

Clean-Up Procedures

Using appropriate protective equipment, wipe up and containerize spilled material. Avoid generation of splashes or sprays during cleanup. Avoid contamination of sewers and waterways. Dispose of spilled material according to local regulations.

Evacuation Procedures

Isolate area. Keep unnecessary personnel away.

Special Procedures

None

*** Section 7 - Handling and Storage ***

Handling Procedures

Storage Temperature (Min./Max.): Controlled Room Temperature: 77°F (25°C).

Shelf Life: Two Years

Protect from temperatures below 59°F (15°C) and above 86°F (30°C).

Storage Procedures

Store at recommended temperatures, in original container tightly closed, away from food. Protect from light. Wear appropriate light-weight gloves during use. Because this is a controlled substance, special handling and storage requirements must be observed to assure compliance with Drug Enforcement Administration regulations.

*** Section 8 - Exposure Controls / Personal Protection ***

A: Component Exposure Limits

ACGIH, OSHA, and NIOSH have not developed exposure limits for any of this product's components.

Engineering Controls

Follow requirements under the Bloodborne Pathogen Standard (29 CFR 1910.1030). Precautions should be taken during the following activities:

Material Safety Data Sheet

Material Name: Methadone Hydrochloride Injection, USP

- Withdrawal of needles from drug vials;
 - Drug transfers using syringes and needles or filter straws;
 - Opening ampoules; and,
 - Expulsion of air from drug-filled syringes.
- DO NOT CLIP OR CRUSH NEEDLE WITH WHICH THIS PRODUCT WAS IN CONTACT. Use of this product should meet the following provisions.
- Work should be performed in an appropriate, designated area;
 - Contaminated waste must be properly handled; and,
 - If necessary, work areas must be regularly decontaminated.

PERSONAL PROTECTIVE EQUIPMENT

Personal Protective Equipment: Eyes/Face

Goggles.

Personal Protective Equipment: Skin

Light-weight gloves.

Personal Protective Equipment: Respiratory

Not required under normal conditions of therapeutic administration and use.

Personal Protective Equipment: General

None

* * * Section 9 - Physical & Chemical Properties * * *

Appearance:	Clear, Colorless	Odor:	None
Physical State:	Liquid	pH:	4.5-6.5
Vapor Pressure:	Not Available	Vapor Density:	Not Available
Boiling Point:	Similar to water	Melting Point:	235°C (455°F)
Solubility (H2O):	Complete	Specific Gravity:	Not Available
Freezing Point:	Similar to water	Evaporation Rate:	Not Available
VOC:	Not Available	Octanol/H2O Coeff.:	117 @ 7.4 pH
Flash Point:	Not Applicable	Flash Point Method:	Not Applicable
Upper Flammability Limit (UFL):	Not Applicable	Lower Flammability Limit (LFL):	Not Applicable
Burning Rate:	Not Applicable	Auto Ignition:	Not Applicable

* * * Section 10 - Chemical Stability & Reactivity Information * * *

Chemical Stability

This is a stable material.

Chemical Stability: Conditions to Avoid

Avoid temperatures exceeding 86°F (30°C).

Incompatibility

May react with strong oxidizing agents (e.g., peroxides, permanganates, nitric acid, etc.), strong acids, substances that are incompatible with water.

Hazardous Decomposition

Thermal decomposition may result in the emission of carbon oxides and nitrogen oxides.

Possibility of Hazardous Reactions

Will not occur.

* * * Section 11 - Toxicological Information * * *

Acute Dose Effects

A: General Product Information

For Active ingredient-Human Data: LDLo (Oral-Child) 5 mg/kg; Brain and Coverings: other degenerative changes; Lungs, Thorax, or Respiration: acute pulmonary edema.

Methadone causes effects on the central nervous system, cardiac system and gastrointestinal system. The major hazards of adverse reaction to Methadone treatment are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred.

Material Safety Data Sheet

Material Name: Methadone Hydrochloride Injection, USP

B: Component Analysis - LD50/LC50

Methadone hydrochloride (1095-90-5)

Oral LD50 Rat 30 mg/kg

Sodium chloride (7647-14-5)

Inhalation LC50 Rat >42 g/m³ 1 h; Oral LD50 Rat 3 g/kg; Dermal LD50 Rabbit >10 g/kg

Water (7732-18-5)

Oral LD50 Rat >90 mL/kg

1-Butanol, 4-chloro- (928-51-8)

Oral LD50 Mouse 990 mg/kg

Carcinogenicity

A: General Product Information

Data from published reports of carcinogenicity studies indicate that there was a significant increase in pituitary adenomas in female B6C2F 1 mice consuming 15 mg/kg/day methadone for two years. This dose was approximately 0.6 times a human daily oral dose of 120 mg/day, on a body surface area basis. However, this finding was not seen in mice consuming 60 mg/kg/day (approximately 2.5 times a human daily oral dose of 120 mg/day). Furthermore, in a two-year study of dietary administration of methadone to Fischer 344 rats, there was no clear evidence for treatment related increase in the incidence of neoplasms, at doses as high as 28 mg/kg/day in males and 88 mg/kg/day in females (approximately 2.3 times and 7.1 times, respectively, a human daily oral dose of 120 mg/day) based on body surface area comparison.

B: Component Carcinogenicity

None of this product's components are listed by ACGIH, IARC, OSHA, NIOSH, or NTP.

Mutagenicity

In published reports, methadone tested negative in tests for chromosome breakage and disjunction and sex-linked recessive lethal gene mutations in germ cells of *Drosophila* using feeding and injection procedures. Methadone treatment of male mice increased sex chromosome and autosome univalent chromosomes and translocations in multivalent chromosomes. Methadone tested positive in the *E. coli*, DNA repair system and *Neurospora crassa* and mouse lymphoma forward mutation assays.

Teratogenicity

PREGNANCY CATEGORY C-RISK CANNOT BE RULED OUT, Human evidence is lacking, but animal evidence is positive). There are no controlled studies of methadone use in pregnant women that can be used to establish safety. Methadone has been detected in amniotic fluid and cord plasma at concentrations proportional to maternal plasma and in newborn urine at lower concentrations than corresponding maternal urine.

A retrospective series of 101 pregnant opiate-dependent women who underwent inpatient opiate detoxification with Methadone did not demonstrate any increased risk of miscarriage in the 2nd trimester or premature delivery in the 3rd trimester. Several studies have suggested that infants born to narcotic-addicted women treated with methadone during all or part of pregnancy have been found to have decreased fetal growth with reduced birth weight, length, and/or head circumference compared to controls. The growth deficit does not appear to persist into later childhood. However, children born to women treated with methadone during pregnancy have been shown to demonstrate mild but persistent deficits in performance on psychometric and behavioral tests. Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Material Safety Data Sheet

Material Name: Methadone Hydrochloride Injection, USP

Methadone does not appear to be teratogenic in the rat or rabbit models. However, following large doses, Methadone produced teratogenic effects in the guinea pig, hamster and mouse. One published study found that in hamster fetuses, subcutaneous methadone doses of 31 mg/kg or greater (estimated exposure was approximately 2 times a human daily oral dose of 120 mg/day on a mg/m² basis, or equivalent to a human daily intravenous dose of 120 mg/day) on day 8 of gestation produced exencephaly and neurological effects. Some of the reported effects were observed at doses that were maternally toxic. In another study, a single subcutaneous dose of 22-24 mg/kg Methadone (estimated exposure was approximately equivalent to a human daily oral dose of 120 mg/day on a mg/m² basis; or half a human daily intravenous dose of 120 mg/day) on day 9 of gestation in mice also produced exencephaly in 11% of the embryos. However, no effects were reported in rats and rabbits at oral doses up to 40 mg/kg (estimated exposure was approximately 3 and 6 times, respectively, a human daily oral dose of 120 mg/day on a mg/m² basis; or 1.5 Babies born to mothers who have been taking opioids regularly prior to delivery may be physically dependent. Onset of withdrawal symptoms in infants is usually in the first days after birth but may be delayed for two to four weeks. Withdrawal signs in the newborn include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever.

There are conflicting reports on whether the risk of sudden infant death syndrome (SIDS) is increased in infants born to women treated with Methadone during pregnancy. Abnormal fetal non-stress tests (NSTs) have been reported to occur more frequently when the test is performed 1-2 hours after a maintenance dose of Methadone in late pregnancy compared to controls. Published animal studies suggest that perinatal exposure to opioids including Methadone may alter neuronal development and behavior in the offspring. Perinatal Methadone exposure in rats has been linked to alterations in learning ability, motor activity, thermal regulation, nociception responses and sensitivity to other drugs. Additional animal data demonstrates evidence for neuro-chemical changes in the brains of Methadone-treated offspring, including the cholinergic, dopaminergic, noradrenergic and serotonergic systems. Methadone is secreted into human milk. There is no information on use of parenteral Methadone in breast feeding, or on the safety of the high doses of Methadone typically used in chronic pain treatment. The safety of breastfeeding while taking oral Methadone is also controversial.

*** Section 12 - Ecological Information ***

Ecotoxicity

A: General Product Information

No information available for the product.

B: Component Analysis - Ecotoxicity - Aquatic Toxicity

Sodium chloride (7647-14-5)

Test & Species

96 Hr LC50 Lepomis macrochirus	5560-6080 mg/L [flow-through]	Conditions
96 Hr LC50 Lepomis macrochirus	12946 mg/L [static]	
96 Hr LC50 Pimephales promelas	6020-7070 mg/L [static]	
96 Hr LC50 Pimephales promelas	7050 mg/L [semi- static]	
96 Hr LC50 Pimephales promelas	6420-6700 mg/L [static]	
96 Hr LC50 Oncorhynchus mykiss	4747-7824 mg/L [flow-through]	
48 Hr EC50 Daphnia magna	1000 mg/L	
48 Hr EC50 Daphnia magna	340.7 - 469.2 mg/L [Static]	

Material Safety Data Sheet

Material Name: Methadone Hydrochloride Injection, USP

*** Section 13 - Disposal Considerations ***

US EPA Waste Number & Descriptions

Component Waste Numbers

No EPA Waste Numbers are applicable for this product's components.

Disposal Instructions

Disposal must be in accordance with applicable federal, state, and local laws and regulations. Dispose of any cleanup materials and waste residue according to all applicable laws and regulations.

See Section 7 for Handling Procedures. See Section 8 for Personal Protective Equipment recommendations.

*** Section 14 - Transportation Information ***

US DOT Information

Shipping Name: Medicine, liquid, toxic, n.o.s. (methadone)

UN/NA #: 1851 **Hazard Class:** 6.1 **Packing Group:** II

Required Label(s): Class 6.1 (Toxic)

*** Section 15 - Regulatory Information ***

US Federal Regulations

Component Analysis

None of this products components are listed under SARA Section 302 (40 CFR 355 Appendix A), SARA Section 313 (40 CFR 372.65), or CERCLA (40 CFR 302.4).

State Regulations

Component Analysis - State

None of this product's components are listed on the state lists from CA, MA, MN, NJ, PA, or RI.

Component Analysis - WHMIS IDL

No components are listed in the WHMIS IDL.

Additional Regulatory Information

Component Analysis - Inventory

Component	CAS #	TSCA	CAN	EEC
Methadone hydrochloride	1095-90-5	No	No	EINECS
Sodium chloride	7647-14-5	Yes	DSL	EINECS
Water	7732-18-5	Yes	DSL	EINECS
1-Butanol, 4-chloro-	928-51-8	Yes	DSL	EINECS

*** Section 16 - Other Information ***

Other Information

The information herein is presented in good faith and believed to be accurate as of the effective date given.

However, no warranty, expressed or implied, is given. It is the buyer's responsibility to ensure that its activities comply with Federal, State or provincial, and local laws.

Key/Legend

EPA = Environmental Protection Agency; TSCA = Toxic Substance Control Act; ACGIH = American Conference of Governmental Industrial Hygienists; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration., NJTSR = New Jersey Trade Secret Registry.

End of Sheet