CHEMICAL PRODUCT / COMPANY IDENTIFICATION

Material Identification

Grade: CLINICAL – DEA SCHEDULE II CONTROLLED SUBSTANCE

Trade Names and Synonyms

Oxymorphone Hydrochloride Injection
Oxymorphone Hydrochloride (Active Ingredient)

Company Identification

DISTRIBUTOR:
Endo Pharmaceuticals Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

MANUFACTURER:
DSM Pharmaceuticals Inc.
Greenville, NC 27835

PHONE NUMBERS:
Product Information / Medical Emergency: 1-800-462-3636

COMPOSITION / INFORMATION ON INGREDIENTS

Components

<table>
<thead>
<tr>
<th>Material</th>
<th>CAS Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OXYMORPHONE HYDROCHLORIDE</td>
<td>357-07-3</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>INACTIVE INGREDIENTS</td>
<td></td>
<td>&gt;99.8</td>
</tr>
</tbody>
</table>

HAZARDS IDENTIFICATION

Potential Health Effects

Since OPANA® INJECTION is formulated for human therapeutic use, normal handling should not constitute a hazard. The following information is provided for those circumstances where handling in the workplace may result in uncontrolled exposure.
WARNING: OPANA® Injection is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to that of morphine.

OPANA® Injection, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

In addition to analgesia, other pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis and cough suppression.

As with all potent opioid analgesics, possible adverse effects associated with therapeutic administration include drowsiness, nausea, vomiting, contraction of pupils, itching, confusion, light-headedness and headache. Respiratory depression may occur following overexposure or in individuals with unusual sensitivity to oxymorphone hydrochloride.

The active ingredient, oxymorphone hydrochloride, is harmful if swallowed or absorbed through the skin. Exposure can cause gastrointestinal disturbances and opioid effects. Other symptoms include respiratory depression, cardiovascular disturbances, circulatory failure and coma.

OPANA® Injection should be used with caution during labor. Sinusoidal fetal heart rate patterns may occur with the use of opioid analgesics. Opioid analgesics, including OPANA® Injection, cross the placenta and may cause respiratory depression and psycho-physiologic effects in the newborn. No reports linking the use of oxymorphone hydrochloride with congenital defects have been located.

Carcinogenicity Information

None of the components present in this material at concentrations equal to or greater than 0.1% are listed by IARC, NTP, OSHA or ACGIH as a carcinogen.

FIRST AID MEASURES

First Aid

INHALATION
If vapor or mist is inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Call a physician.

SKIN CONTACT
In case of contact, wash skin with soap and water. Call a physician. Wash contaminated clothing before reuse.
EYE CONTACT
In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Call a physician.

INGESTION
If swallowed, immediately give two glasses of water and induce vomiting. Never give anything to an unconscious person. Call a physician.

Notes to Physicians

OPANA® Injection is indicated for the relief of moderate to severe pain. It is also indicated for preoperative medication, for support of anesthesia, for obstetrical analgesia and for relief of anxiety in patients with dyspnea associated with pulmonary edema secondary to acute left ventricular dysfunction.

In the treatment of OPANA® Injection overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression, which may result from overdosage or unusual sensitivity to opioids including OPANA® Injection. In the presence of hypoventilation or apnea, oxygen should be administered, and respiration should be assisted or controlled as indicated. Nalmefene is an alternative pure opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of OPANA® Injection may exceed that of the antagonist, the patient should be kept under continued surveillance, and repeated doses of the antagonist should be administered according to the antagonist labeling as needed to maintain adequate respiration.

Anaphylactic shock is rare, but may occur in sensitive individuals. It may be managed by appropriate administration of epinephrine and general life-support measures.

The clinical utility of extracorporeal elimination techniques has not been determined.

FIRE FIGHTING MEASURES

Flammable Properties
Not a fire or explosion hazard
Extinguishing Media

Water Spray, Water Fog, Foam, Dry Powder (Sand or Met-L-X), Dry Chemical, CO₂.

Fire Fighting Instructions

Evacuate personnel to a safe area. Keep personnel removed and upwind of fire. Wear self-contained breathing apparatus. Guard against intruders.

ACCIDENTAL RELEASE MEASURES

Safeguards (Personnel)

NOTE: Review FIRE FIGHTING MEASURES and HANDLING (PERSONNEL) sections before proceeding with clean-up. Use appropriate PERSONAL PROTECTION EQUIPMENT during clean-up.

Spill Clean Up

Soak up with sawdust, sand, oil dry or other absorbent material. Recover undamaged and minimally contaminated material for reuse and reclamation.

HANDLING AND STORAGE

Handling (Personnel)

Avoid breathing vapors or mist. Avoid contact with eyes, skin or clothing. Wash thoroughly after handling. Wash clothing after use.

Storage

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F). Store in a dark place (protect from light). Do not store or consume food, drink or tobacco in areas where they may become contaminated with this material. Store in accordance with federal regulations

OPANA® INJECTION is a Schedule II opioid and therefore subject to the Federal Controlled Substances Act; store accordingly.

EXPOSURE CONTROLS / PERSONAL PROTECTION

Personal Protective Equipment

EYE / FACE PROTECTION

Wear safety glasses with side shields. Wear full face protection when it is
judged that the possibility exists for eye and face contact.

**RESPIRATORS**
Wear an appropriate NIOSH/MSHA approved air purifying respirator or positive pressures air-supplied respirator in situations where a respirator is judged appropriate to prevent inhalation.

**SKIN PROTECTION**
Wear impervious clothing such as gloves, lab coat, shoe covers, apron or jumpsuit, as appropriate. Consult the site safety professional for additional guidance, as needed.

**Exposure Guidelines**

**Exposure Limits**

<table>
<thead>
<tr>
<th>Compound</th>
<th>PEL (OSHA)</th>
<th>TLV (ACGIH)</th>
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</thead>
<tbody>
<tr>
<td>OPANA® INJECTION</td>
<td>None Established</td>
<td>None Established</td>
</tr>
</tbody>
</table>

**PHYSICAL AND CHEMICAL PROPERTIES**

**Physical Data**

- Form: Liquid
- Color: Colorless

**How Supplied**

1 mg/mL: 1 mL ampuls (box of 10)

**STABILITY AND REACTIVITY**

**Chemical Stability**

Stable at normal temperatures and storage conditions.

**Incompatibility with Other Materials**

None reasonably foreseeable.

**Decomposition**

Decomposition will not occur if handled and stored properly.
Polymerization

Polymerization will not occur.

TOXICOLOGICAL INFORMATION

Animal Data

The toxicological effects OPANA® INJECTION have not been characterized in animal studies. The adverse effects associated with oxymorphone hydrochloride, the active ingredient, are summarized.

Oxymorphone hydrochloride has not been evaluated for adverse effects in animal studies by the inhalation or ocular route of exposure. Consequently, the potential hazards via these routes are unknown.

Dermal Data

Oxymorphone hydrochloride was found not to be a primary skin irritant when tested as a solution on rabbits. When tested via a transdermal patch, however, it was observed to be a mild to moderate skin irritant in rabbits.

Oxymorphone hydrochloride administered parenterally and orally to animals induced analgesia, decreased motor activity and/or slowed respiratory rate.

Oral Data

LD50: 490 mg/kg (mice, strain undefined)
       140 mg/kg (Wistar rats)

Intravenous Data

LD50: 82 mg/kg (mice, strain undefined)
       95 mg/kg (Wistar rats)

Subcutaneous Data

LD50: 280 mg/kg (mice, strain undefined)
       160 mg/kg (Wistar rats)

LD50 is the median dose at which lethality occurred in 50% of the animals tested following oral exposure or exposure by injection.

Mutagenicity

Oxymorphone hydrochloride was not mutagenic when tested in the in vitro bacterial reverse mutation assay (Ames test) at concentrations of ≤ 5270 mcg/plate, or in an in vitro mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes at concentrations ≤ 5000 mcg/ml with or without metabolic activation. Oxymorphone hydrochloride tested
positive in both the rat and mouse in vivo micronucleus assays. An increase in micronucleated polychromatic erythrocytes occurred in mice given doses of ≥ 250 mg/kg and in rats given doses of 20 and 40 mg/kg. A subsequent study demonstrated that oxymorphone hydrochloride was not aneugenic in mice following administration of up to 500 mg/kg. Additional studies indicate that the increased incidence of micronucleated polychromatic erythrocytes in rats may be secondary to increased body temperature following oxymorphone administration. Doses associated with increased micronucleated polychromatic erythrocytes also produce a marked, rapid increase in body temperature. Pretreatment of animals with sodium salicylate minimized the increase in body temperature and prevented the increase in micronucleated polychromatic erythrocytes after administration of 40 mg/kg oxymorphone.

Reproductive and Developmental Toxicity
Oxymorphone hydrochloride did not affect reproductive function or sperm parameters in male rats at any dose tested (≤ 50 mg/kg/day via oral gavage). In female rats, an increase in the length of the estrus cycle and decrease in the mean number of viable embryos, implantation sites and corpora lutea were observed at doses of oxymorphone ≥ 10 mg/kg/day via oral gavage. The dose of oxymorphone associated with reproductive findings in female rats is 0.8 times a total human daily dose of 120 mg OPANA® based on a body surface area. The dose of oxymorphone that produced no adverse effects on reproductive findings in female rats (i.e., NOAEL) is 0.4 times a total human daily dose of 120 mg OPANA® based on body surface area.

Oxymorphone hydrochloride administration did not cause malformations at any doses evaluated during developmental toxicity studies in rats (≤ 25 mg/kg/day via oral gavage) or rabbits (≤ 50 mg/kg/day via oral gavage). These doses are ~2 times and 8 times a total human daily dose of 120 mg of OPANA® (an immediate-release oral tablet formulation), based on body surface area. There were no developmental effects in rats treated with 5 mg/kg/day or rabbits treated with 25 mg/kg/day. Fetal weights were reduced in rats and rabbits given doses of ≥ 10 mg/kg/day and 50 mg/kg/day, respectively. These doses are ~0.8 and 4 times respectively a total human daily dose of 120 mg of OPANA®, based on body surface area. There were no effects of oxymorphone hydrochloride on intrauterine survival at doses ≤ 25 mg/kg/day in rats, or ≤ 50 mg/kg/day in rabbits. In a study that was conducted prior to the establishment of Good Laboratory Practices (GLP) and not according to current recommended methodology, a single subcutaneous injection of oxymorphone hydrochloride on gestation day 8 was reported to produce malformations in offspring of hamsters that received 10 times a total human daily dose of 120 mg of OPANA®, based on body surface area. This dose also produced 83% maternal lethality.

Oxymorphone hydrochloride administration to female rats during gestation in a pre- and postnatal developmental toxicity study reduced mean litter size (18%) at a dose of 25 mg/kg/day via oral gavage, attributed to an increase in the incidence
of stillborn pups. An increase in neonatal death occurred at doses ≥ 5 mg/kg/day. Post-natal survival of the pups was reduced throughout weaning following treatment of the dams with 25 mg/kg/day. Low pup birth weight and decreased postnatal weight gain occurred in pups born to oxymorphone-treated female rats given a dose of 25 mg/kg/day. This dose is ~2 times a total human daily dose of 120 mg of OPANA®, based on body surface area.

Carcinogenicity
Long-term studies have been completed to evaluate the carcinogenic potential of oxymorphone in both Sprague-Dawley rats and CD-1 mice. Oxymorphone HCl was administered to Sprague-Dawley rats (2.5, 5 and 10 mg/kg/day in males and 5, 10 and 25 mg/kg/day in females) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 10-mg/kg/day dose in male rats was 0.34-fold and at the 25-mg/kg/day dose in female rats was 1.5-fold the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in rats. Oxymorphone HCl was administered to CD-1 mice (10, 25, 75 and 150 mg/kg/day) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 150-mg/kg/day dose in mice was 14.5-fold (in males) and 17.3-fold (in females) times the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in mice.

DISPOSAL CONSIDERATIONS

Waste Disposal

Treatment, storage, transportation and disposal must be in accordance with applicable Federal, State/Provincial, Local and DEA regulations.

TRANSPORTATION INFORMATION

Shipping Information

The known properties of this material do not constitute a hazard as defined by the U.S. Department of Transportation.

OTHER INFORMATION

NFPA, NPCA-HMIS

NFPA Rating
Health : 0
Flammability : 0
Reactivity : 0
NPCA-HMIS Rating
Health : 0
Flammability : 0
Reactivity : 0

Additional Information

OPANA® is a trademark of Endo Pharmaceuticals Inc.

References


The DuPont Merck Pharmaceutical Co. NUMORPHAN® INJECTION MSDS (#DMP03225) dated 10/24/95.


The data in this Material Safety Data Sheet relates only to the specific material designated herein and does not relate to use in combination with any other material or in any process.

Responsibility of MSDS: Medical Affairs Department
Endo Pharmaceuticals Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

Telephone 800-462-3636

End of MSDS