SECTION 1. PRODUCT AND COMPANY IDENTIFICATION

Product name: Buprenorphine Solid Formulation

Manufacturer or supplier’s details
Company name of supplier: MSD
Address: Avenida 16 de Septiembre No. 301
Xaltocan - Xochimilco Mexico 16090
Telephone: 52 55 57284444
Telefax: 908-735-1496
Emergency telephone: 1-908-423-6000
E-mail address: EHSDATASTEWARD@msd.com

Recommended use of the chemical and restrictions on use
Recommended use: Pharmaceutical

SECTION 2. HAZARDS IDENTIFICATION

GHS Classification
Reproductive toxicity: Category 1A

GHS label elements
Hazard pictograms: ☢️

Signal Word: Danger

Hazard Statements: H360Df May damage the unborn child. Suspected of damaging fertility.

Precautionary Statements:
Prevention:
P201 Obtain special instructions before use.
P202 Do not handle until all safety precautions have been read and understood.
P280 Wear protective gloves/ protective clothing/ eye protection/ face protection.

Response:
P308 + P313 IF exposed or concerned: Get medical advice/ attention.

Storage:
P405 Store locked up.

Disposal:
P501 Dispose of contents/ container to an approved waste disposal plant.
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Version 2.3  Revision Date: 23.03.2020  SDS Number: 918708-00008  Date of last issue: 13.09.2019  Date of first issue: 03.10.2016

Other hazards
Dust contact with the eyes can lead to mechanical irritation.
Contact with dust can cause mechanical irritation or drying of the skin.
May form explosive dust-air mixture during processing, handling or other means.

SECTION 3. COMPOSITION/INFORMATION ON INGREDIENTS

Substance / Mixture: Mixture

Components

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>CAS-No.</th>
<th>Concentration (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starch</td>
<td>9005-25-8</td>
<td>&gt;= 10 - &lt; 20</td>
</tr>
<tr>
<td>Buprenorphine Hydrochloride</td>
<td>53152-21-9</td>
<td>&gt;= 1 - &lt; 5</td>
</tr>
<tr>
<td>Citric acid</td>
<td>77-92-9</td>
<td>&gt;= 1 - &lt; 5</td>
</tr>
</tbody>
</table>

SECTION 4. FIRST AID MEASURES

General advice: In the case of accident or if you feel unwell, seek medical advice immediately.
When symptoms persist or in all cases of doubt seek medical advice.

If inhaled: If inhaled, remove to fresh air.
Get medical attention.

In case of skin contact: In case of contact, immediately flush skin with soap and plenty of water.
Remove contaminated clothing and shoes.
Get medical attention.
Wash clothing before reuse.
Thoroughly clean shoes before reuse.

In case of eye contact: If in eyes, rinse well with water.
Get medical attention if irritation develops and persists.

If swallowed: If swallowed, DO NOT induce vomiting.
Get medical attention.
Rinse mouth thoroughly with water.

Most important symptoms and effects, both acute and delayed: May damage the unborn child. Suspected of damaging fertility.
Contact with dust can cause mechanical irritation or drying of the skin.
Dust contact with the eyes can lead to mechanical irritation.

Protection of first-aiders: First Aid responders should pay attention to self-protection, and use the recommended personal protective equipment when the potential for exposure exists (see section 8).

Notes to physician: Treat symptomatically and supportively.

SECTION 5. FIRE-FIGHTING MEASURES

Suitable extinguishing media: Water spray
Alcohol-resistant foam
Carbon dioxide (CO2)
Dry chemical

Unsuitable extinguishing media: None known.

Specific hazards during fire: Exposure to combustion products may be a hazard to health.
fighting
Hazardous combustion products: Carbon oxides
Nitrogen oxides (NOx)
Specific extinguishing methods: Use extinguishing measures that are appropriate to local circumstances and the surrounding environment. Use water spray to cool unopened containers. Remove undamaged containers from fire area if it is safe to do so. Evacuate area.
Special protective equipment for fire-fighters: In the event of fire, wear self-contained breathing apparatus. Use personal protective equipment.

SECTION 6. ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures: Use personal protective equipment. Follow safe handling advice and personal protective equipment recommendations.
Environmental precautions: Discharge into the environment must be avoided. Prevent further leakage or spillage if safe to do so. Retain and dispose of contaminated wash water. Local authorities should be advised if significant spillages cannot be contained.
Methods and materials for containment and cleaning up: Sweep up or vacuum up spillage and collect in suitable container for disposal. Avoid dispersal of dust in the air (i.e., clearing dust surfaces with compressed air). Dust deposits should not be allowed to accumulate on surfaces, as these may form an explosive mixture if they are released into the atmosphere in sufficient concentration. Local or national regulations may apply to releases and disposal of this material, as well as those materials and items employed in the cleanup of releases. You will need to determine which regulations are applicable. Sections 13 and 15 of this SDS provide information regarding certain local or national requirements.

SECTION 7. HANDLING AND STORAGE

Technical measures: Static electricity may accumulate and ignite suspended dust causing an explosion. Provide adequate precautions, such as electrical grounding and bonding, or inert atmospheres.
Local/Total ventilation: If sufficient ventilation is unavailable, use with local exhaust ventilation.
Advice on safe handling: Do not get on skin or clothing. Do not breathe dust. Do not swallow. Avoid contact with eyes. Handle in accordance with good industrial hygiene and safety practice, based on the results of the workplace exposure assessment.
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Keep container tightly closed.
Minimize dust generation and accumulation.
Keep container closed when not in use.
Keep away from heat and sources of ignition.
Take precautionary measures against static discharges.
Take care to prevent spills, waste and minimize release to the environment.

Hygiene measures:
If exposure to chemical is likely during typical use, provide eye flushing systems and safety showers close to the working place.
When using do not eat, drink or smoke.
Wash contaminated clothing before re-use.
The effective operation of a facility should include review of engineering controls, proper personal protective equipment, appropriate degowning and decontamination procedures, industrial hygiene monitoring, medical surveillance and the use of administrative controls.

Conditions for safe storage:
Keep in properly labeled containers.
Store locked up.
Keep tightly closed.
Store in accordance with the particular national regulations.

Materials to avoid:
Do not store with the following product types:
Strong oxidizing agents
Organic peroxides
Explosives
Gases

SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Ingredients with workplace control parameters

<table>
<thead>
<tr>
<th>Components</th>
<th>CAS-No.</th>
<th>Value type (Form of exposure)</th>
<th>Control parameters / Permissible concentration</th>
<th>Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starch</td>
<td>9005-25-8</td>
<td>VLE-PPT</td>
<td>10 mg/m³</td>
<td>NOM-010-STPS-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TWA</td>
<td>10 mg/m³</td>
<td>ACGIH</td>
</tr>
<tr>
<td>Buprenorphine Hydrochloride</td>
<td>53152-21-9</td>
<td>TWA</td>
<td>0.2 µg/m³ (OEB 5)</td>
<td>Internal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wipe limit</td>
<td>2 µg/100 cm²</td>
<td>Internal</td>
</tr>
</tbody>
</table>

Engineering measures:
Use closed processing systems or containment technologies to control at source (e.g., glove boxes/isolators) and to prevent leakage of compounds into the workplace.
All engineering controls should be implemented by facility design and operated in accordance with GMP principles to protect products, workers, and the environment.
No open handling permitted.
Totally enclosed processes and materials transport systems are required.
Operations require the use of appropriate containment technology designed to prevent leakage of compounds into the workplace.
Personal protective equipment

Respiratory protection: If adequate local exhaust ventilation is not available or exposure assessment demonstrates exposures outside the recommended guidelines, use respiratory protection.

Filter type: Particulates type

Hand protection: Chemical-resistant gloves

Remarks: Consider double gloving.

Eye protection: Wear safety glasses with side shields or goggles. If the work environment or activity involves dusty conditions, mists or aerosols, wear the appropriate goggles. Wear a faceshield or other full face protection if there is a potential for direct contact to the face with dusts, mists, or aerosols.

Skin and body protection: Work uniform or laboratory coat. Additional body garments should be used based upon the task being performed (e.g., sleevelets, apron, gauntlets, disposable suits) to avoid exposed skin surfaces. Use appropriate degowning techniques to remove potentially contaminated clothing.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance: solid
Color: white
Odor: No data available
Odor Threshold: No data available
pH: No data available
Melting point/freezing point: No data available
Initial boiling point and boiling range: No data available
Flash point: Not applicable
Evaporation rate: Not applicable
Flammability (solid, gas): May form explosive dust-air mixture during processing, handling or other means.
Flammability (liquids): No data available
Upper explosion limit / Upper flammability limit: No data available
Lower explosion limit / Lower flammability limit: No data available
### Vapor pressure
- Not applicable

### Relative vapor density
- Not applicable

### Relative density
- No data available

### Density
- No data available

### Solubility(ies)
- Water solubility: No data available

### Partition coefficient: n-octanol/water
- Not applicable

### Autoignition temperature
- No data available

### Decomposition temperature
- No data available

### Viscosity
- Viscosity, kinematic: Not applicable

### Explosive properties
- Not explosive

### Oxidizing properties
- The substance or mixture is not classified as oxidizing.

### Particle size
- No data available

### SECTION 10. STABILITY AND REACTIVITY

#### Reactivity
- Not classified as a reactivity hazard.

#### Chemical stability
- Stable under normal conditions.

#### Possibility of hazardous reactions
- May form explosive dust-air mixture during processing, handling or other means.
- Can react with strong oxidizing agents.

#### Conditions to avoid
- Heat, flames and sparks.
- Avoid dust formation.

#### Incompatible materials
- Oxidizing agents

#### Hazardous decomposition products
- No hazardous decomposition products are known.

### SECTION 11. TOXICOLOGICAL INFORMATION

#### Information on likely routes of exposure

<table>
<thead>
<tr>
<th>Route of Exposure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation</td>
<td></td>
</tr>
<tr>
<td>Skin contact</td>
<td></td>
</tr>
<tr>
<td>Ingestion</td>
<td></td>
</tr>
<tr>
<td>Eye contact</td>
<td></td>
</tr>
</tbody>
</table>

#### Acute toxicity
- Not classified based on available information.

**Product:***

<table>
<thead>
<tr>
<th>Toxicity Type</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute oral toxicity</td>
<td>&gt; 5,000 mg/kg</td>
</tr>
</tbody>
</table>
Method: Calculation method

**Components:**

**Starch:**
- **Acute oral toxicity**: LD50 (Rat): > 5,000 mg/kg
- **Acute dermal toxicity**: LD50 (Rabbit): > 2,000 mg/kg

**Buprenorphine Hydrochloride:**
- **Acute oral toxicity**: LD50 (Mouse): 261 mg/kg
  - LD50 (Rat): 600 mg/kg
- **Acute inhalation toxicity**: Remarks: No data available
- **Acute dermal toxicity**: Remarks: No data available
- **Acute toxicity (other routes of administration)**:
  - LD50 (Rat): 31 mg/kg
  - Application Route: Intravenous
  - LD50 (Mouse): 24 mg/kg
  - Application Route: Intravenous

**Citric acid:**
- **Acute oral toxicity**: LD50 (Mouse): 5,400 mg/kg
- **Acute dermal toxicity**:
  - LD50 (Rat): > 2,000 mg/kg
  - Method: OECD Test Guideline 402
  - Assessment: The substance or mixture has no acute dermal toxicity

**Skin corrosion/irritation**
Not classified based on available information.

**Components:**

**Buprenorphine Hydrochloride:**
- **Remarks**: No data available

**Citric acid:**
- **Species**: Rabbit
- **Method**: OECD Test Guideline 404
- **Result**: No skin irritation

**Serious eye damage/eye irritation**
Not classified based on available information.

**Components:**

**Starch:**
- **Species**: Rabbit
Result

**Buprenorphine Hydrochloride:**
Remarks : No data available

**Citric acid:**
Species : Rabbit
Result : Irritation to eyes, reversing within 21 days
Method : OECD Test Guideline 405

**Respiratory or skin sensitization**

**Skin sensitization**
Not classified based on available information.

**Respiratory sensitization**
Not classified based on available information.

**Components:**

**Starch:**
Test Type : Maximization Test
Routes of exposure : Skin contact
Species : Guinea pig
Result : negative

**Buprenorphine Hydrochloride:**
Remarks : No data available

**Germ cell mutagenicity**
Not classified based on available information.

**Components:**

**Starch:**
Genotoxicity in vitro : Test Type: Bacterial reverse mutation assay (AMES)
Result: negative

**Buprenorphine Hydrochloride:**
Genotoxicity in vitro : Test Type: Bacterial reverse mutation assay (AMES)
Result: equivocal
Test Type: Chromosomal aberration
Result: negative
Test Type: DNA damage and repair, unscheduled DNA synthesis in mammalian cells (in vitro)
Result: positive

**Germ cell mutagenicity - Assessment** : Weight of evidence does not support classification as a germ cell mutagen.
Citric acid:
Genotoxicity in vitro:
Test Type: Bacterial reverse mutation assay (AMES)
Result: negative
Test Type: in vitro micronucleus test
Result: positive
Test Type: Bacterial reverse mutation assay (AMES)
Result: negative

Genotoxicity in vivo:
Test Type: Mutagenicity (in vivo mammalian bone-marrow cytogenetic test, chromosomal analysis)
Species: Rat
Application Route: Ingestion
Result: negative

Carcinogenicity
Not classified based on available information.

Components:
Buprenorphine Hydrochloride:
Species: Rat
Application Route: Oral
Exposure time: 27 Months
LOAEL: 56 mg/kg body weight
Result: positive
Target Organs: Testes
Remarks: The significance of these findings for humans is not certain.

Species: Mouse
Application Route: Oral
Exposure time: 86 weeks
NOAEL: 100 mg/kg body weight
Result: negative

Carcinogenicity - Assessment: Weight of evidence does not support classification as a carcinogen

Reproductive toxicity
May damage the unborn child. Suspected of damaging fertility.

Components:
Buprenorphine Hydrochloride:
Effects on fertility:
Test Type: Fertility
Species: Rat
Application Route: Oral
Fertility: NOAEL: 80 mg/kg body weight
Result: No effects on fertility.

Test Type: Fertility
Species: Rat
Application Route: Subcutaneous
Fertility: NOAEL: 5 mg/kg body weight
Result: No effects on fertility.

Test Type: Fertility
Species: Rabbit
Application Route: Oral
Fertility: LOAEL: 1 mg/kg body weight
Result: Preimplantation loss.

Test Type: Fertility
Species: Rabbit
Application Route: Intravenous
Fertility: LOAEL: 0.2 mg/kg body weight
Result: Postimplantation loss.

Effects on fetal development:

Test Type: Development
Species: Rat
Application Route: Subcutaneous
Developmental Toxicity: LOAEL: 5 mg/kg body weight
Result: Embryo-fetal toxicity., No teratogenic effects., Skeletal malformations.

Test Type: Development
Species: Rat
Application Route: Oral
Developmental Toxicity: NOAEL: 160 mg/kg body weight
Result: No effects on fetal development.

Test Type: Development
Species: Rat
Application Route: Subcutaneous
Developmental Toxicity: LOAEL: 0.1 mg/kg body weight
Result: Effects on newborn.

Test Type: Development
Species: Rabbit
Application Route: Intramuscular
Developmental Toxicity: LOAEL: 5 mg/kg body weight
Result: Embryo-fetal toxicity., Skeletal malformations.

Test Type: Development
Species: Rabbit
Application Route: Oral
Developmental Toxicity: LOAEL: 1 mg/kg body weight
Result: Embryo-fetal toxicity., Skeletal malformations.

Reproductive toxicity - Assessment:

May damage the unborn child. Suspected of damaging fertility.

Citric acid:

Effects on fetal development:

Test Type: One-generation reproduction toxicity study
Species: Rat
Application Route: Ingestion
Result: negative
STOT-single exposure
Not classified based on available information.

Components:
Buprenorphine Hydrochloride:
Assessment: May cause drowsiness or dizziness.

STOT-repeated exposure
Not classified based on available information.

Repeated dose toxicity

Components:
Starch:
Species: Rat
NOAEL: >= 2,000 mg/kg
Application Route: Skin contact
Exposure time: 28 Days
Method: OECD Test Guideline 410

Citric acid:
Species: Rat
NOAEL: 4,000 mg/kg
LOAEL: 8,000 mg/kg
Application Route: Ingestion
Exposure time: 10 Days

Aspiration toxicity
Not classified based on available information.

Experience with human exposure

Components:
Buprenorphine Hydrochloride:
Inhalation: Target Organs: Central nervous system
Symptoms: Drowsiness, sedation, Headache, Nausea, Vomiting, Dizziness, Vertigo, Sweating, constipation, insomnia, Pain, respiratory depression, constriction of pupils, decrease in heart rate, Lowered blood pressure
Remarks: May cause neonatal withdrawal

SECTION 12. ECOLOGICAL INFORMATION

Ecotoxicity

Components:
Buprenorphine Hydrochloride:
Toxicity to algae/aquatic plants: EC50 (Pseudokirchneriella subcapitata (green algae)): 6.25 mg/l
## Toxicity to fish (Chronic toxicity)
- NOEC (Pimephales promelas (fathead minnow)): 0.137 mg/l  
  Exposure time: 28 d  
  Method: OECD Test Guideline 210

## Toxicity to daphnia and other aquatic invertebrates (Chronic toxicity)
- NOEC (Daphnia magna (Water flea)): 0.883 mg/l  
  Exposure time: 21 d  
  Method: OECD Test Guideline 211

## Toxicity to microorganisms
- EC50: 588 mg/l  
  Exposure time: 3 h  
  Test Type: Respiration inhibition  
  Method: OECD Test Guideline 209

## Citric acid:
- LC50 (Pimephales promelas (fathead minnow)): > 100 mg/l  
  Exposure time: 96 h

- EC50 (Daphnia magna (Water flea)): 1,535 mg/l  
  Exposure time: 24 h

### Persistence and degradability

#### Components:

**Buprenorphine Hydrochloride:**  
Biodegradability: Result: Not readily biodegradable.

**Citric acid:**  
Biodegradability: Result: Readily biodegradable.  
Biodegradation: 97%  
Exposure time: 28 d  
Method: OECD Test Guideline 301B
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Bioaccumulative potential

Components:

Buprenorphine Hydrochloride:

Bioaccumulation:
Species: Oncorhynchus mykiss (rainbow trout)
Bioconcentration factor (BCF): 0.4
Method: OECD Test Guideline 305

Partition coefficient: n-octanol/water:
log Pow: 3.11

Citric acid:
Partition coefficient: n-octanol/water:
log Pow: -1.72

Mobility in soil

Components:

Buprenorphine Hydrochloride:
Distribution among environmental compartments:
log Koc: 4.11

Other adverse effects:
No data available

SECTION 13. DISPOSAL CONSIDERATIONS

Disposal methods:
Waste from residues:
Dispose of in accordance with local regulations.
Contaminated packaging:
Empty containers should be taken to an approved waste handling site for recycling or disposal.
If not otherwise specified: Dispose of as unused product.

SECTION 14. TRANSPORT INFORMATION

International Regulations

UNRTDG
Not regulated as a dangerous good

IATA-DGR
Not regulated as a dangerous good

IMDG-Code
Not regulated as a dangerous good

Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code
Not applicable for product as supplied.

Domestic regulation

NOM-002-SCT
Not regulated as a dangerous good

Special precautions for user
Not applicable
SECTION 15. REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture

Federal Law for the control of chemical precursors, essential chemical products and machinery for producing capsules, tablets and pills.

The ingredients of this product are reported in the following inventories:

- AICS: not determined
- DSL: not determined
- IECSC: not determined

SECTION 16. OTHER INFORMATION

Full text of other abbreviations

- ACGIH: USA. ACGIH Threshold Limit Values (TLV)
- ACGIH / TWA: 8-hour, time-weighted average
- NOM-010-STPS-2014 / VLE-PPT: Time weighted average limit value

AICS - Australian Inventory of Chemical Substances; ANTT - National Agency for Transport by Land of Brazil; ASTM - American Society for the Testing of Materials; bw - Body weight; CMR - Carcinogen, Mutagen or Reproductive Toxicant; DIN - Standard of the German Institute for Standardisation; DSL - Domestic Substances List (Canada); ECx - Concentration associated with x% response; ELx - Loading rate associated with x% response; EmS - Emergency Schedule; ENCS - Existing and New Chemical Substances (Japan); ErCx - Concentration associated with x% growth rate response; ERG - Emergency Response Guide; GHS - Globally Harmonized System; GLP - Good Laboratory Practice; IARC - International Agency for Research on Cancer; IATA - International Air Transport Association; IBC - International Code for the Construction and Equipment of Ships carrying Dangerous Chemicals in Bulk; IC50 - Half maximal inhibitory concentration; ICAO - International Civil Aviation Organization; IECSC - Inventory of Existing Chemical Substances in China; IMDG - International Maritime Dangerous Goods; IMO - International Maritime Organization; ISHL - Industrial Safety and Health Law (Japan); ISO - International Organization for Standardization; KECI - Korea Existing Chemicals Inventory; LC50 - Lethal Concentration to 50 % of a test population; LD50 - Lethal Dose to 50% of a test population (Median Lethal Dose); MARPOL - International Convention for the Prevention of Pollution from Ships; n.o.s. - Not Otherwise Specified; Nch - Chilean Norm; NO(A)EC - No Observed (Adverse) Effect Concentration; NO(A)EL - No Observed (Adverse) Effect Level; NOELR - No Observable Effect Loading Rate; NOM - Official Mexican Norm; NTP - National Toxicology Program; NZIoC - New Zealand Inventory of Chemicals; OECD - Organization for Economic Co-operation and Development; OPPTS - Office of Chemical Safety and Pollution Prevention; PBT - Persistent, Bioaccumulative and Toxic substance; PICCS - Philippines Inventory of Chemicals and Chemical Substances; (Q)SAR - (Quantitative) Structure Activity Relationship; REACH - Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals; SADT - Self-Accelerating Decomposition Tempera-
SAFETY DATA SHEET

Buprenorphine Solid Formulation

Version 2.3  Revision Date: 23.03.2020  SDS Number: 918708-00008  Date of last issue: 13.09.2019
Date of first issue: 03.10.2016

Sources of key data used to compile the Material Safety Data Sheet:

Revision Date: 23.03.2020

The information is considered as correct, but not exhaustive, and will be used only as a guide, which is based in the current knowledge of the substance or mixture, and is applicable to proper safety precautions for the product.

MX / Z8