

SAFETY DATA SHEET

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

Contact information

General



Par Sterile Products
870 Parkdale Road, Rochester, M.I. 48307
T: +1 (800) 828-9393
F: +1 (201) 829-9222
E-mail: drugsafety@parpharm.com

Emergency telephone number

Chemtrec (24-hour availability):
+1 (800) 424-9300 (USA and Canada)
+1 (703) 527-3887 (International; collect calls accepted)

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| Product identifier | Levothyroxine Sodium for Injection (lyophilized powder) |
| Synonyms | Levothyroxine, L-thyroxine, (-)-Thyroxine; 3,3',5,5'-Tetraiodo-L-thyronine, L-3,5,3',5'-Tetraiodothyronine, L-T4, T4, L-Tyrosine, O-(4-hydroxy-3,5-diodophenyl)-3,5-diiido- |
| Trade names | None identified |
| Chemical family | Mixture containing synthetic thyroid hormone (T4). |
| Relevant identified uses of the substance or mixture and uses advised against | Bulk formulated pharmaceutical mixture/formulated pharmaceutical product packaged in final form for patient use; indicated as a thyroid hormone replacement therapy for the treatment/prevention of hypothyroidism. |
| Note | The physical, chemical, toxicological and ecological properties of this product/mixture has not been fully characterized. This SDS will be revisited as more data become available. |

SECTION 2 - HAZARDS IDENTIFICATION

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| Classification of the substance or mixture | Drugs in the finished state and intended for the final user are not subject to labeling in the US, EU or Canada. Please consult the prescribing/packaging information. The classification and labelling listed below is for bulk levothyroxine sodium for injection. |
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SECTION 2 - HAZARDS IDENTIFICATION ...continued

Globally Harmonized System [GHS]

Corrosive (skin) - Category 1. Corrosive (eye) - Category 1. Specific Target Organ Toxicity (repeated exposure) - Category 1. Reproductive Toxicity - Category 1B.

Label elements**GHS hazard pictogram****GHS signal word**

Danger

GHS hazard statements

H314 - Causes severe skin burns and eye damage. H372 - Can cause damage to thyroid, gastrointestinal tract, cardiovascular system, kidney, and bone through prolonged or repeated exposure. H360FD - May damage fertility. May damage the unborn child.

GHS precautionary statements

P201 - Obtain special instructions before use. P202 - Do not handle until all safety precautions have been read and understood. P260 - Do not breathe dust. P264 - Wash hands thoroughly after handling. P270 - Do not eat, drink or smoke when using this product. P281 - Use personal protective equipment as required. P301 + P330 + P331 - IF SWALLOWED: rinse mouth. Do NOT induce vomiting. P303 + P361 + P353 - If on skin or hair: Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower. P304 + P340 - IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing. P305 + P351 + P338 - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P363 - Wash contaminated clothing before reuse. P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.

Other hazards

Levothyroxine is a synthetic form of a naturally occurring thyroid hormone (T4). Commonly reported adverse effects generally correspond to the symptoms of hyperthyroidism and include fatigue, weight loss, fever, sweating, headache, restlessness/anxiety, tremors, muscle weakness, insomnia, tachycardia, palpitations, arrhythmias, increased blood pressure, chest pain, shortness of breath, gastrointestinal disturbances, flushing, decreased bone mineral density, menstrual irregularities, and fertility impairment. Signs of overdosage include confusion and disorientation.

Note

This mixture is classified as dangerous/hazardous according to Regulation EC No 1272/2008 (EU) and Hazard Communication Standard No. 1910.1200 (US OSHA). See Section 16 for full text of classifications.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

| <u>Ingredient</u> | <u>CAS #</u> | <u>EINECS/ ELINCS#</u> | <u>Amount</u> | <u>GHS Classification</u> |
|---|--------------|----------------------------|---------------|------------------------------|
| Mannitol | 69-65-8 | 200-711-8 | 70 - 80% | Not classified |
| Sodium phosphate, dibasic, anhydrous | 7558-79-4 | 231-448-7 | 10 - 15% | SI2: H315; EI2: H319 |
| Sodium Hydroxide | 1310-73-2 | 215-185-5 | 5 - 10% | SC1: H314 |
| Levothyroxine Sodium | 55-03-8 | 200-221-4 | 1 - 5% | STOT-R1:H372; RT1B:H360FD |

Note The ingredient(s) listed above are considered dangerous/hazardous. The remaining components are non-dangerous/not hazardous and/or present at amounts below reportable limits. See Section 16 for full text of GHS classifications.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures**Immediate Medical Attention Needed**

Yes

Eye Contact

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.

Skin Contact

Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.

Inhalation

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.

Ingestion

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.

Protection of first aid responders

See Section 8 for Exposure Controls/Personal Protection recommendations.

Most important symptoms and effects, both acute and delayed

See Sections 2 and 11.

Indication of immediate medical attention and special treatment needed, if necessary

Contains levothyroxine sodium, a synthetic T4 hormone. Medical conditions aggravated by exposure: thyroid disorders. Treat symptomatically and supportively. If accidental exposure occurs to an individual who is also taking other medication(s), consult the corresponding package or prescribing information for potential drug interactions.

SECTION 5 - FIREFIGHTING MEASURES

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| Extinguishing media | Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials. |
| Specific hazards arising from the substance or mixture | No information identified. May emit toxic fumes of carbon monoxide, carbon dioxide, oxides of nitrogen, phosphate and any sodium-containing compounds. |
| Flammability/Explosivity | No specific information identified for the product/mixture. High concentrations of finely divided airborne particles can potentially explode if ignited. |
| Advice for firefighters | Wear full protective clothing and a self-contained breathing apparatus with a full facepiece operated in the pressure demand or other positive pressure mode. Decontaminate all equipment after use. |

SECTION 6 - ACCIDENTAL RELEASE MEASURES

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| Personal precautions, protective equipment and emergency procedures | If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Do not breathe dust. |
| Environmental precautions | Do not empty into drains. Avoid release to the environment. |
| Methods and material for containment and cleaning up | If vials are crushed or broken, DO NOT RAISE DUST. Surround spill or powder with absorbents and place a damp cloth or towel over the area to minimize entry of powder into the air. Add excess liquid to allow the material to enter into solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container for disposal in accordance with applicable waste disposal regulations (see section 13). Decontaminate the area twice with an appropriate solvent (see section 9). |
| Reference to other sections | See Sections 8 and 13 for more information. |

SECTION 7 - HANDLING AND STORAGE

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| Precautions for safe handling | If vials are crushed or broken, follow recommendations for handling potent pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Wash thoroughly after handling. |
| Conditions for safe storage including any incompatibilities | Protect from light and store unreconstituted product between 20° to 25°C (68° to 77°F). Retain in carton until time of use. Reconstituted drug product is preservative free. Discard any unused portion. |
| Specific end use(s) | No information identified. |

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note Wash hands, face and other potentially exposed areas immediately in the event of physical contact. Dispose of broken vials in a sharps container.

**Control Parameters/
Occupational Exposure
Limit Values**

| <u>Compound</u> | <u>Issuer</u> | <u>Type</u> | <u>OEL</u> |
|--------------------------------------|--|------------------|-----------------------|
| Mannitol | -- | -- | -- |
| Sodium phosphate, dibasic, anhydrous | -- | -- | -- |
| Sodium Hydroxide | ACGIH, Czech Republic, Denmark, Finland, NIOSH, Portugal, Spain, Sweden, Australia, Mexico | Ceiling | 2 mg/m ³ |
| | Austria, Belgium, Bulgaria, Finland, France, Hungary, Lithuania, Slovak Republic, Slovenia, Spain, OSHA | TWA-8 HR | 2 mg/m ³ |
| | Austria | STEL (8 x 5 min) | 4 mg/m ³ |
| | Czech Republic, Estonia, Sweden | TWA-8 HR | 1 mg/m ³ |
| | Hungary, Ireland, Slovenia, Singapore | STEL | 2 mg/m ³ |
| | Latvia, Poland | TWA-8 HR | 0.5 mg/m ³ |
| | NIOSH | IDLH | 10 mg/m ³ |
| | Poland | STEL | 1 mg/m ³ |
| Levothyroxine Sodium | -- | -- | -- |

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION ...continued

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| Exposure/Engineering controls | None required for normal handling of packaged product. If vials are crushed/broken or if handling bulk mixture: Control exposures to below the OEL for the active pharmaceutical ingredient (if available). Otherwise, selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Open handling should not be performed when handling potent substances, or substances of unknown toxicity. Material should be handled inside a closed process, ventilated enclosure, isolator or device of equivalent or better control that is suitable for dusts and/or aerosols. |
| Respiratory protection | None required for normal handling of packaged product. If vials are crushed/broken or if handling bulk mixture: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. For routine powder handling tasks, an approved and properly worn powered air-purifying respirator equipped with HEPA filters or combination filters should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use 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 air purifying respirators may not provide adequate protection. |
| Hand protection | None required for normal handling of packaged product. If vials are crushed/broken or if handling bulk mixture: Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered. When the material is dissolved or suspended in an organic solvent, wear gloves that provide protection against the solvent. |
| Skin protection | Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Base the choice of skin protection on the job activity, potential for skin contact and solvents and reagents in use. |
| Eye/face protection | Wear safety glasses with side shields, chemical splash goggles, or full face shield, if necessary. Base the choice of protection on the job activity and potential for contact with eyes or face. An emergency eye wash station should be available. |
| Environmental Exposure Controls | Avoid release to the environment and operate within closed systems wherever practicable. Air and liquid emissions should be directed to appropriate pollution control devices. In case of spill, do not release to drains. Implement appropriate and effective emergency response procedures to prevent release or spread of contamination and to prevent inadvertent contact by personnel. |
| Other protective measures | Wash hands in the event of contact with this mixture, especially before eating, drinking or smoking. Protective equipment is not to be worn outside the work area (e.g., in common areas or out-of-doors). |

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

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| Appearance | Lyophilized powder |
| Color | White |
| Odor | Odorless |
| Odor threshold | No information identified. |
| pH | 10.0 to 11.4 |
| Melting point/ freezing point | ~ 256°C |
| Initial boiling point and boiling range | No information identified. |
| Flash point | 200°C |
| Evaporation rate | Not applicable. |
| Flammability (solid, gas) | No information identified. |
| Upper/lower flammability or explosive limits | No information identified. |
| Vapor pressure | No information identified |
| Vapor density | No information identified. |
| Relative density | No information identified. |
| Water solubility | Soluble. |
| Solvent solubility | No information identified. |
| Partition coefficient (<i>n</i>-octanol/water) | No information identified. |
| Auto-ignition temperature | No information identified. |
| Decomposition temperature | No information identified. |
| Viscosity | No information identified. |
| Explosive properties | No information identified. |
| Oxidizing properties | No information identified. |

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ...continued

Other information

| | |
|--------------------------|--------------------------|
| Molecular weight | Not applicable (Mixture) |
| Molecular formula | Not applicable (Mixture) |

SECTION 10 - STABILITY AND REACTIVITY

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| Reactivity | No information identified. |
| Chemical stability | Light sensitive |
| Possibility of hazardous reactions | No information identified. |
| Conditions to avoid | Avoid extreme temperatures. |
| Incompatible materials | No information identified. |
| Hazardous decomposition products | No information identified. |

SECTION 11 - TOXICOLOGICAL INFORMATION

Note No toxicology data for the product/mixture were identified. The following data describe the active ingredient and/or the individual ingredients where applicable.

Information on toxicological effects

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

Acute toxicity

| <u>Compound</u> | <u>Type</u> | <u>Route</u> | <u>Species</u> | <u>Dose</u> |
|--------------------------------------|---------------------|--------------|----------------|-------------|
| Mannitol | LD ₅₀ | Oral | Rat | 13.5 g/kg |
| | LD ₅₀ | Oral | Mice | 14 g/kg |
| Sodium phosphate, dibasic, anhydrous | LD ₅₀ | Oral | Rat | 17 g/kg |
| Sodium Hydroxide | -- | -- | -- | -- |
| Levothyroxine Sodium | LD ₅₀ | IP | Rat | 20 mg/kg |
| | LD ₅₀ | IV | Rat | 20 mg/kg |
| | LD ₅₀ | SC | Rat | 50 mg/kg |
| | Minimum Lethal Dose | Oral | Dog | 2400 mg/kg |

Irritation/Corrosion Sodium hydroxide is corrosive to the eye and skin *in vitro* and *in vivo*. Sodium phosphate was considered mildly irritating to rabbit eyes and skin in a standard Draize test.

Sensitization No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION ...continued

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| STOT-single exposure | No information identified. |
| STOT-repeated exposure/Repeat-dose toxicity | Target organs of toxicity in rats and rabbits orally exposed to $\geq 200 \mu\text{g/kg}$ levothyroxine (study duration not specified) include the thyroid, gastrointestinal tract, cardiovascular system and kidney. In a 3-week study with male rats, the same dose cause a decrease in bone mineral density. |
| Reproductive toxicity | No studies identified. |
| Developmental toxicity | Fetal and maternal toxicity were noted in rats and rabbits orally treated with $120 \mu\text{g/kg/day}$ levothyroxine during gestation. Impairment of lens development was noted in rats after daily oral doses of $250\text{-}300 \mu\text{g}$. Drug-related effects on limb and CNS development were seen in teratogenicity studies with mice and chinchillas, respectively (details not specified). No increases in abnormalities were reported in guinea pigs or rabbits (details not specified). |
| Genotoxicity | Levothyroxine was negative for genotoxicity in the Ames bacterial mutagenicity assay and an <i>in vitro</i> micronucleus assay with human lymphocytes. |
| Carcinogenicity | No studies identified. This mixture is not listed by NTP, IARC, ACGIH or OSHA as a carcinogen. |
| Aspiration hazard | No data available. |
| Human health data | See Section 2 - "Other hazards" |

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

| <u>Compound</u> | <u>Type</u> | <u>Species</u> | <u>Concentration</u> |
|--------------------------------------|-------------|-----------------------------------|--|
| Mannitol | -- | -- | -- |
| Sodium phosphate, dibasic, anhydrous | -- | -- | -- |
| Sodium Hydroxide | Toxic range | freshwater fish and invertebrates | 20 to 40 mg/L (data on pH changes unavailable) |
| Levothyroxine Sodium | -- | -- | -- |

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| Persistence and Degradability | Sodium hydroxide rapidly dissolves and dissociates in water. No data were available for other ingredients. |
| 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. |

SECTION 12 - ECOLOGICAL INFORMATION ...continued

Note Aquatic toxicity of sodium hydroxide is related to the effects of pH changes. Sodium hydroxide in neutralized mixtures is not considered toxic to the environment. Because data on other ingredients were not identified, releases into the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Do not send down the drain or flush down the toilet. All wastes containing the material should be properly labeled. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater treatment facility.

SECTION 14 - TRANSPORT INFORMATION

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.

UN proper shipping name None assigned.

Transport hazard classes and packing group None assigned.

Environmental hazards Based on the available data, this mixture is not regulated as an environmental hazard or a marine pollutant.

Special precautions for users Avoid release to the environment.

Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code Not applicable.

SECTION 15 - REGULATORY INFORMATION

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

SECTION 15 - REGULATORY INFORMATION ...continued

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|-----------------------------------|--------------------------------------|
| Chemical safety assessment | Not conducted. |
| WHMIS classification | SC1: H314; STOT-R1:H372; RT1B:H360FD |
| TSCA status | Drugs are exempt from TSCA. |
| SARA section 313 | Not listed. |
| California proposition 65 | Not listed. |
| Additional information | No other information identified. |

SECTION 16 - OTHER INFORMATION

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| Full text of H phrases and GHS classifications | SC1 - Skin corrosion Category 1. H314 - Causes severe skin burns and eye damage. SI2 - Skin irritant Category 2. H315 - Causes skin irritation. EI2 - Eye irritant Category 2. H319 - Causes serious eye irritation. STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. H372 - Can cause damage to thyroid, gastrointestinal tract, cardiovascular system, kidney, and bone through prolonged or repeated exposure. RT1B - Reproductive toxicity Category 1B. H360FD - May damage fertility. May damage the unborn child. |
| Sources of data | Information from published literature and internal company data. |
| 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; CLP - Classification, Labelling, and Packaging of Substances and Mixtures; 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; STOT - Specific Target Organ Toxicity; 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 | 25 June 2015 |

SECTION 16 - OTHER INFORMATION ...continued

Revisions Updated formatting in compliance with General US, EU, and GHS requirements;
Updated storage information in Section 7.

Disclaimer The above information is based on data available to us and is believed to be correct. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions.

No representation, warranty, or guarantee, express or implied (including a warranty of fitness or merchantability for a particular purpose), is made with respect to the materials, the accuracy of this information, the results to be obtained from the use thereof, or the hazards connected with the use of the material. Caution should be used in the handling and use of the material because it is a potent pharmaceutical product. The above information is offered in good faith and with the belief that it is accurate. As of the date of issuance, we are providing all information relevant to the foreseeable handling of the material. However, in the event of an adverse incident associated with this product, this Safety Data Sheet is not, and is not intended to be, a substitute for consultation with appropriately trained personnel.