

# Nebivolol hydrochloride

sc-204122



The Power is Question

Material Safety Data Sheet

Hazard Alert Code Key: **EXTREME** **HIGH** **MODERATE** **LOW**

## Section 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

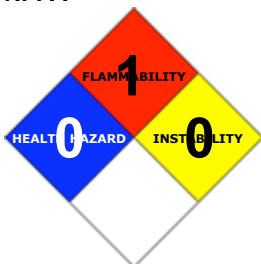
### PRODUCT NAME

Nebivolol hydrochloride

### STATEMENT OF HAZARDOUS NATURE

CONSIDERED A HAZARDOUS SUBSTANCE ACCORDING TO OSHA 29 CFR 1910.1200.

### NFPA



### SUPPLIER

Santa Cruz Biotechnology, Inc.  
2145 Delaware Avenue  
Santa Cruz, California 95060  
800.457.3801 or 831.457.3800

### EMERGENCY:

ChemWatch  
Within the US & Canada: 877-715-9305  
Outside the US & Canada: +800 2436 2255  
(1-800-CHEMCALL) or call +613 9573 3112

### SYNONYMS

C22-H25-F2-N-O4.HCl, "(alphaR, alpha' R, 2R, 2' S)-rel-alpha, a' -[Iminobis(methylene)]bis[6-, "fluoro-3, 4-dihydro-2H-1-benzopyran-2-methanol] hydrochloride", "alpha, alpha' -(iminodimethylene)bis[6-fluoro-2-chromanmethanol]", hydrochloride, "(+/-)-[2R\*(1S\*5S\*(S\*))]-a, a' -[Iminobis(methylene)bis(6-fluoro-3, 4-), "dihydro-2H-1-benzopyran-2-methanol] hydrochloride", "dl-nebivolol hydrochloride", "narbivolol hydrochloride", R-67555, Bystolic, Lobivon, Nebilet, Nebilox, "beta-adrenergic blocker," beta-blocker, antihypertensive, "aryloxypropanolamine derivatives", "vasodilator (peripheral)."

## Section 2 - HAZARDS IDENTIFICATION

### CHEMWATCH HAZARD RATINGS

|               | Min | Max |
|---------------|-----|-----|
| Flammability: | 1   |     |
| Toxicity:     | 2   |     |
| Body Contact: | 2   |     |
| Reactivity:   | 1   |     |
| Chronic:      | 2   |     |

Min/Nil=0  
Low=1  
Moderate=2  
High=3  
Extreme=4



### CANADIAN WHMIS SYMBOLS



## EMERGENCY OVERVIEW

### RISK

Possible risk of impaired fertility.  
Possible risk of harm to the unborn child.

### POTENTIAL HEALTH EFFECTS

#### ACUTE HEALTH EFFECTS

#### SWALLOWED

- Accidental ingestion of the material may be damaging to the health of the individual.
- Side effects from beta-blocking agents include nausea, vomiting, disturbance of the gastrointestinal tract, fatigue and dizziness. The nervous system may be involved, causing depression, delirium, stoppage of breathing, confusion, psychosis, motor abnormalities, coma, visual disturbance and insomnia.

#### EYE

- Eye absorption of beta blockers can reduce the pressure in the eye and causes systemic toxicity.
- This material can cause eye irritation and damage in some persons.

#### SKIN

- Skin contact is not thought to have harmful health effects, however the material may still produce health damage following entry through wounds, lesions or abrasions.
- Open cuts, abraded or irritated skin should not be exposed to this material.
- Entry into the blood-stream, through, for example, cuts, abrasions or lesions, may produce systemic injury with harmful effects. Examine the skin prior to the use of the material and ensure that any external damage is suitably protected.
- This material can cause inflammation of the skin on contact in some persons.

#### INHALED

- Persons with impaired respiratory function, airway diseases and conditions such as emphysema or chronic bronchitis, may incur further disability if excessive concentrations of particulate are inhaled.
- The material can cause respiratory irritation in some persons. The body's response to such irritation can cause further lung damage.

#### CHRONIC HEALTH EFFECTS

■ Ample evidence from experiments exists that there is a suspicion this material directly reduces fertility.  
Results in experiments suggest that this material may cause disorders in the development of the embryo or fetus, even when no signs of poisoning show in the mother.  
Limited evidence suggests that repeated or long-term occupational exposure may produce cumulative health effects involving organs or biochemical systems.  
Long term exposure to high dust concentrations may cause changes in lung function i.e. pneumoconiosis; caused by particles less than 0.5 micron penetrating and remaining in the lung.  
Prolonged use of beta blockers can result in dry mouth, taste distortion, heartburn, stomach pain, nausea, vomiting, loss of appetite, bloating, flatulence, and diarrhea or constipation. The nervous system may be affected by fatigue, headache, dizziness, lethargy, depression, "pins and needles", reduced or increased sensation, anxiety, nervousness, poor concentration, sleep loss and nightmares or bizarre dreams.

## Section 3 - COMPOSITION / INFORMATION ON INGREDIENTS

| NAME                    | CAS RN      | %   |
|-------------------------|-------------|-----|
| nebivolol hydrochloride | 152520-56-4 | >98 |
| carvedil                |             |     |

## Section 4 - FIRST AID MEASURES

#### SWALLOWED

· If swallowed do NOT induce vomiting. · If vomiting occurs, lean patient forward or place on left side (head-down position, if possible) to maintain open airway and prevent aspiration.

#### EYE

■ If this product comes in contact with the eyes: · Wash out immediately with fresh running water. · Ensure complete irrigation of the eye by keeping eyelids apart and away from eye and moving the eyelids by occasionally lifting the upper and lower lids.

#### SKIN

■ If skin contact occurs: · Immediately remove all contaminated clothing, including footwear · Flush skin and hair with running water (and

soap if available).

### **INHALED**

· If fumes or combustion products are inhaled remove from contaminated area. · Other measures are usually unnecessary.

### **NOTES TO PHYSICIAN**

■ Treat symptomatically.

Following a recent overdose with a beta-blocker the stomach should be emptied by gastric lavage. Emesis should not be used.

## **Section 5 - FIRE FIGHTING MEASURES**

|                             |               |
|-----------------------------|---------------|
| Vapour Pressure (mmHG):     | Negligible    |
| Upper Explosive Limit (%):  | Not Available |
| Specific Gravity (water=1): | Not Available |
| Lower Explosive Limit (%):  | Not Available |

### **EXTINGUISHING MEDIA**

- Foam.
- Dry chemical powder.

### **FIRE FIGHTING**

- Alert Emergency Responders and tell them location and nature of hazard.
- Wear breathing apparatus plus protective gloves.

When any large container (including road and rail tankers) is involved in a fire, consider evacuation by 100 metres in all directions.

### **GENERAL FIRE HAZARDS/HAZARDOUS COMBUSTIBLE PRODUCTS**

- Combustible solid which burns but propagates flame with difficulty.
- Avoid generating dust, particularly clouds of dust in a confined or unventilated space as dusts may form an explosive mixture with air, and any source of ignition, i.e. flame or spark, will cause fire or explosion. Dust clouds generated by the fine grinding of the solid are a particular hazard; accumulations of fine dust may burn rapidly and fiercely if ignited.

Combustion products include: carbon monoxide (CO), carbon dioxide (CO<sub>2</sub>), hydrogen chloride, phosgene, hydrogen fluoride, nitrogen oxides (NO<sub>x</sub>), phosphorus oxides (PO<sub>x</sub>), other pyrolysis products typical of burning organic material.

### **FIRE INCOMPATIBILITY**

■ Avoid contamination with oxidizing agents i.e. nitrates, oxidizing acids, chlorine bleaches, pool chlorine etc. as ignition may result.

### **PERSONAL PROTECTION**

Glasses:  
Chemical goggles.  
Gloves:  
Respirator:  
Particulate

## **Section 6 - ACCIDENTAL RELEASE MEASURES**

### **MINOR SPILLS**

- Environmental hazard - contain spillage.
- Clean up waste regularly and abnormal spills immediately.
- Avoid breathing dust and contact with skin and eyes.
- Wear protective clothing, gloves, safety glasses and dust respirator.
- Use dry clean up procedures and avoid generating dust.
- Vacuum up or sweep up. NOTE: Vacuum cleaner must be fitted with an exhaust micro filter (HEPA type) (consider explosion-proof machines designed to be grounded during storage and use).
- Dampen with water to prevent dusting before sweeping.
- Place in suitable containers for disposal.

### **MAJOR SPILLS**

- Environmental hazard - contain spillage.
- Moderate hazard.
- CAUTION: Advise personnel in area.
- Alert Emergency Responders and tell them location and nature of hazard.

## **Section 7 - HANDLING AND STORAGE**

### **PROCEDURE FOR HANDLING**

- Avoid all personal contact, including inhalation.
  - Wear protective clothing when risk of exposure occurs.
- Empty containers may contain residual dust which has the potential to accumulate following settling. Such dusts may explode in the

presence of an appropriate ignition source.

- Do NOT cut, drill, grind or weld such containers.
- In addition ensure such activity is not performed near full, partially empty or empty containers without appropriate workplace safety authorisation or permit.

### RECOMMENDED STORAGE METHODS

- Glass container.
- Polyethylene or polypropylene container.
- Check all containers are clearly labelled and free from leaks.

### STORAGE REQUIREMENTS

- Observe manufacturer's storing and handling recommendations.

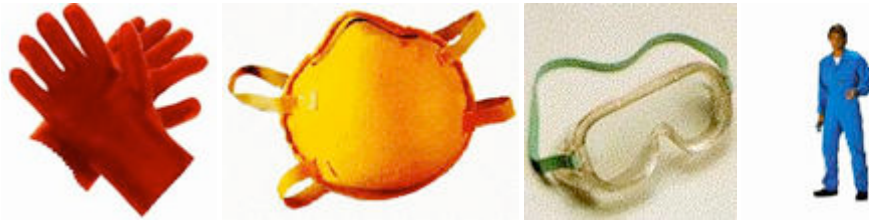
## Section 8 - EXPOSURE CONTROLS / PERSONAL PROTECTION

### EXPOSURE CONTROLS

The following materials had no OELs on our records

- neбиволol hydrochloride: CAS:152520-56-4

### PERSONAL PROTECTION



### RESPIRATOR

Particulate

Consult your EHS staff for recommendations

### EYE

- When handling very small quantities of the material eye protection may not be required.

For laboratory, larger scale or bulk handling or where regular exposure in an occupational setting occurs:

- Chemical goggles
- Face shield. Full face shield may be required for supplementary but never for primary protection of eyes
- Contact lenses may pose a special hazard; soft contact lenses may absorb and concentrate irritants. A written policy document, describing the wearing of lens or restrictions on use, should be created for each workplace or task. This should include a review of lens absorption and adsorption for the class of chemicals in use and an account of injury experience. Medical and first-aid personnel should be trained in their removal and suitable equipment should be readily available. In the event of chemical exposure, begin eye irrigation immediately and remove contact lens as soon as practicable. Lens should be removed at the first signs of eye redness or irritation - lens should be removed in a clean environment only after workers have washed hands thoroughly. [CDC NIOSH Current Intelligence Bulletin 59].

### HANDS/FEET

- Suitability and durability of glove type is dependent on usage. Important factors in the selection of gloves include: such as:

- frequency and duration of contact,
- chemical resistance of glove material,
- glove thickness and
- dexterity

Select gloves tested to a relevant standard (e.g. Europe EN 374, US F739).

- When prolonged or frequently repeated contact may occur, a glove with a protection class of 5 or higher (breakthrough time greater than 240 minutes according to EN 374) is recommended.
- When only brief contact is expected, a glove with a protection class of 3 or higher (breakthrough time greater than 60 minutes according to EN 374) is recommended.
- Contaminated gloves should be replaced.

Gloves must only be worn on clean hands. After using gloves, hands should be washed and dried thoroughly. Application of a non-perfumed moisturiser is recommended.

- Rubber gloves (nitrile or low-protein, powder-free latex). Employees allergic to latex gloves should use nitrile gloves in preference.
- Double gloving should be considered.
- PVC gloves.
- Protective shoe covers.
- Head covering.

Experience indicates that the following polymers are suitable as glove materials for protection against undissolved, dry solids, where abrasive particles are not present.

- polychloroprene
- nitrile rubber
- butyl rubber

- fluorocautchouc
- polyvinyl chloride

Gloves should be examined for wear and/ or degradation constantly.

#### OTHER

- For quantities up to 500 grams a laboratory coat may be suitable.
- For quantities up to 1 kilogram a disposable laboratory coat or coverall of low permeability is recommended. Coveralls should be buttoned at collar and cuffs.
- For quantities over 1 kilogram and manufacturing operations, wear disposable coverall of low permeability and disposable shoe covers.
- For manufacturing operations, air-supplied full body suits may be required for the provision of advanced respiratory protection.
- Eye wash unit.
- Ensure there is ready access to an emergency shower.
- For Emergencies: Vinyl suit.

#### ENGINEERING CONTROLS

- Enclosed local exhaust ventilation is required at points of dust, fume or vapor generation.
- HEPA terminated local exhaust ventilation should be considered at point of generation of dust, fumes or vapors.

## Section 9 - PHYSICAL AND CHEMICAL PROPERTIES

### PHYSICAL PROPERTIES

|                           |                |                                |                 |
|---------------------------|----------------|--------------------------------|-----------------|
| State                     | Divided Solid  | Molecular Weight               | 441.90          |
| Melting Range (°F)        | 428- 431.6     | Viscosity                      | Not Applicable  |
| Boiling Range (°F)        | Not Applicable | Solubility in water (g/L)      | Partly Miscible |
| Flash Point (°F)          | Not Available  | pH (1% solution)               | Not Applicable  |
| Decomposition Temp (°F)   | Not Available  | pH (as supplied)               | Not Applicable  |
| Autoignition Temp (°F)    | Not Available  | Vapour Pressure (mmHG)         | Negligible      |
| Upper Explosive Limit (%) | Not Available  | Specific Gravity (water=1)     | Not Available   |
| Lower Explosive Limit (%) | Not Available  | Relative Vapor Density (air=1) | Not Applicable  |
| Volatile Component (%vol) | Negligible     | Evaporation Rate               | Not Applicable  |

### APPEARANCE

White to almost white powder; does not mix well with water. Soluble in methanol, dimethylsulfoxide and N,N-dimethylformamide. Prep as racemic mixture of (R,S,S,S)- and (S,R,R,R)-enantiomers.

## Section 10 - CHEMICAL STABILITY

### CONDITIONS CONTRIBUTING TO INSTABILITY

- Presence of incompatible materials.
- Product is considered stable.

### STORAGE INCOMPATIBILITY

- Avoid reaction with oxidizing agents.

For incompatible materials - refer to Section 7 - Handling and Storage.

## Section 11 - TOXICOLOGICAL INFORMATION

NEBIVOLOL HYDROCHLORIDE

### TOXICITY AND IRRITATION

#### NEBIVOLOL HYDROCHLORIDE:

- unless otherwise specified data extracted from RTECS - Register of Toxic Effects of Chemical Substances.

■ Contact allergies quickly manifest themselves as contact eczema, more rarely as urticaria or Quincke's edema. The pathogenesis of contact eczema involves a cell-mediated (T lymphocytes) immune reaction of the delayed type.

Asthma-like symptoms may continue for months or even years after exposure to the material ceases. This may be due to a non-allergenic condition known as reactive airways dysfunction syndrome (RADS) which can occur following exposure to high levels of highly irritating compound. Key criteria for the diagnosis of RADS include the absence of preceding respiratory disease, in a non-atopic individual, with abrupt onset of persistent asthma-like symptoms within minutes to hours of a documented exposure to the irritant. A reversible airflow pattern, on spirometry, with the presence of moderate to severe bronchial hyperreactivity on methacholine challenge testing and the lack of minimal lymphocytic inflammation, without eosinophilia, have also been included in the criteria for diagnosis of RADS. RADS (or asthma) following an irritating inhalation is an infrequent disorder with rates related to the concentration of and duration of exposure to the irritating substance. Industrial bronchitis, on the other hand, is a disorder that occurs as result of exposure due to high

concentrations of irritating substance (often particulate in nature) and is completely reversible after exposure ceases. The disorder is characterised by dyspnea, cough and mucus production.

No significant acute toxicological data identified in literature search.

In extensive metabolisers (most of the population) and at doses less than or equal to 10 mg, nebivolol is preferentially beta1 selective. In poor metabolisers and at higher doses, nebivolol inhibits both beta1 - and beta2 - adrenergic receptors. Nebivolol lacks intrinsic sympathomimetic and membrane stabilizing activity at therapeutically relevant concentrations. At clinically relevant doses, it does not demonstrate alpha1-adrenergic receptor blockade activity. Various metabolites, including glucuronides, contribute to beta-blocking activity

**Carcinogenesis:** In a two-year study of nebivolol in mice, a statistically significant increase in the incidence of testicular Leydig cell hyperplasia and adenomas was observed at 40 mg/kg/day (5 times the maximally recommended human dose of 40 mg on a mg/m2 basis). Similar findings were not reported in mice administered doses equal to approximately 0.3 or 1.2 times the maximum recommended human dose. No evidence of a tumorigenic effect was observed in a 24-month study in Wistar rats receiving doses of nebivolol 2.5, 10 and 40 mg/kg/day (equivalent to 0.6, 2.4, and 10 times the maximally recommended human dose). Co-administration of dihydrotestosterone reduced blood LH levels and prevented the Leydig cell hyperplasia, consistent with an indirect LH-mediated effect of nebivolol in mice and not thought to be clinically relevant in man.

**Reproductive toxicity:** A randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male volunteers was conducted to determine the effects of nebivolol on adrenal function, luteinizing hormone, and testosterone levels. This study demonstrated that 6 weeks of daily dosing with 10 mg of nebivolol had no significant effect on ACTH-stimulated mean serum cortisol AUC0-120 min, serum LH, or serum total testosterone.

Effects on spermatogenesis were seen in male rats and mice at .40 mg/kg/day (10 and 5 times the MRHD, respectively). For rats the effects on spermatogenesis were not reversed and may have worsened during a four week recovery period. The effects of nebivolol on sperm in mice, however, were partially reversible.

**Developmental toxicity:** Decreased pup body weights occurred at 1.25 and 2.5 mg/kg in rats, when exposed during the perinatal period (late gestation, parturition and lactation). At 5 mg/kg and higher doses (1.2 times the MRHD), prolonged gestation, dystocia and reduced maternal care were produced with corresponding increases in late fetal deaths and stillbirths and decreased birth weight, live litter size and pup survival. Insufficient numbers of pups survived at 5 mg/kg to evaluate the offspring for reproductive performance.

In studies in which pregnant rats were given nebivolol during organogenesis, reduced fetal body weights were observed at maternally toxic doses of 20 and 40 mg/kg/day (5 and 10 times the MRHD), and small reversible delays in sternal and thoracic ossification associated with the reduced fetal body weights and a small increase in resorption occurred at 40 mg/kg/day (10 times the MRHD). No adverse effects on embryo-fetal viability, sex, weight or morphology were observed in studies in which nebivolol was given to pregnant rabbits at doses as high as 20 mg/kg/day (10 times the MRHD).

**Genotoxicity:** Nebivolol was not genotoxic when tested in a battery of assays (Ames, in vitro mouse lymphoma TK+/-, in vitro human peripheral lymphocyte chromosome aberration, in vivo Drosophila melanogaster sex-linked recessive lethal, and in vivo mouse bone marrow micronucleus tests).

## Section 12 - ECOLOGICAL INFORMATION

This material and its container must be disposed of as hazardous waste.

## Section 13 - DISPOSAL CONSIDERATIONS

### Disposal Instructions

All waste must be handled in accordance with local, state and federal regulations.

‡ Legislation addressing waste disposal requirements may differ by country, state and/ or territory. Each user must refer to laws operating in their area. In some areas, certain wastes must be tracked.

A Hierarchy of Controls seems to be common - the user should investigate:

- Reduction
- Reuse
- Recycling
- Disposal (if all else fails)

This material may be recycled if unused, or if it has not been contaminated so as to make it unsuitable for its intended use. Shelf life considerations should also be applied in making decisions of this type. Note that properties of a material may change in use, and recycling or reuse may not always be appropriate.

DO NOT allow wash water from cleaning equipment to enter drains. Collect all wash water for treatment before disposal.

- Recycle wherever possible.
- Consult manufacturer for recycling options or consult Waste Management Authority for disposal if no suitable treatment or disposal facility can be identified.

## Section 14 - TRANSPORTATION INFORMATION



DOT:

Symbols: G Hazard class or Division: 9

Identification Numbers: UN3077 PG: III

Label Codes: 9 Special provisions: 8, 146,

335, B54,

IB8, IP3,

N20, T1,

TP33

Packaging: Exceptions: 155 Packaging: Non- bulk: 213

Packaging: Exceptions: 155 Quantity limitations: No limit

Passenger aircraft/rail:

Quantity Limitations: Cargo No limit Vessel stowage: Location: A  
aircraft only:

Vessel stowage: Other: None

Hazardous materials descriptions and proper shipping names:

Environmentally hazardous substance, solid, n.o.s

#### **Air Transport IATA:**

ICAO/IATA Class: 9 ICAO/IATA Subrisk: None

UN/ID Number: 3077 Packing Group: III

Special provisions: A97

Cargo Only

Packing Instructions: 911 Maximum Qty/Pack: 400 kg

Passenger and Cargo Passenger and Cargo

Packing Instructions: 911 Maximum Qty/Pack: 400 kg

Passenger and Cargo Limited Quantity Passenger and Cargo Limited Quantity

Packing Instructions: Y911 Maximum Qty/Pack: 30 kg G

Shipping Name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID,

N.O.S. \*(CONTAINS NEBIVOLOL HYDROCHLORIDE)

#### **Maritime Transport IMDG:**

IMDG Class: 9 IMDG Subrisk: None

UN Number: 3077 Packing Group: III

EMS Number: F-A , S-F Special provisions: 179 274 335 909

Limited Quantities: 5 kg Marine Pollutant: Yes

Shipping Name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S.

## **Section 15 - REGULATORY INFORMATION**

**No data for nebivolol hydrochloride (CAS: , 152520-56-4)**

## **Section 16 - OTHER INFORMATION**

*Reasonable care has been taken in the preparation of this information, but the author makes no warranty of merchantability or any other warranty, expressed or implied, with respect to this information. The author makes no representations and assumes no liability for any direct, incidental or consequential damages resulting from its use. For additional technical information please call our toxicology department on +800 CHEMCALL.*

■ Classification of the preparation and its individual components has drawn on official and authoritative sources as well as independent review by the Chemwatch Classification committee using available literature references.

A list of reference resources used to assist the committee may be found at:

[www.chemwatch.net/references](http://www.chemwatch.net/references).

■ The (M)SDS is a Hazard Communication tool and should be used to assist in the Risk Assessment. Many factors determine whether the reported Hazards are Risks in the workplace or other settings. Risks may be determined by reference to Exposures Scenarios. Scale of use, frequency of use and current or available engineering controls must be considered.

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