



TECHNICAL DATA PACKAGE

BENFOTIAMINE

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SUANFARMA

PRODUCT SPECIFICATION SHEET

REVISION 1.2019

<u>IDENTIFICATION</u>	
NAME	BENFOTIAMINE
SYNONYMS	<i>s-benzoylthiamine-o-monophosphate</i>
PRODUCT CODE	BEN
SHELF LIFE	24 Months
COUNTRY OF ORIGIN	China

<u>PHYSICAL & CHEMICAL ANALYSIS</u>	
<u>PARAMETER</u>	<u>SPECIFICATION</u>
1. APPEARANCE COLOR	Crystalline powder White to Light Yellow
2. IDENTIFICATION	A. Positive to IR Reference Standard B. Retention time of major peak corresponds with that of the reference standard
3. CLARITY OF SOLUTION	Colorless to light yellow clear solution
4. LOSS ON DRYING	NMT 1.5%
5. CHLORIDE	NMT 0.053%
6. SULPHATE	NMT 0.011%
7. HEAVY METALS	NMT 20 ppm
8. ASSAY	NLT 99.0%
9. RELATED SUBSTANCES	
BENZOIC ACID	NMT 0.15%
THIAMINE	NMT 0.15%
TOTAL IMPURITIES	NMT 1.0%

STORAGE CONDITIONS: PRESERVE IN TIGHTLY-SEALED CONTAINERS UNDER COOL, DRY CONDITIONS. AVOID EXCESSIVE EXPOSURE TO SUNLIGHT.
MANUFACTURING SITE: THIS MATERIAL HAS BEEN CUSTOM MADE AND PROCESSED AT NO.1, BADU ROAD, TIANTAI INDUSTRIAL PARK, TIANTAI, ZHEJIANG, 317200, CHINA TO MEET SUAN FARMA, INC. SPECIFICATIONS.

Julianna Chedid

Julianna Chedid, QA/QC Assistant
DATE PRINTED: September 25, 2019



ALLERGEN STATEMENT

We, Suan Farma, Inc., hereby declare that Benfotiamine (product code: BEN) is free of allergens, including but not limited to the following:

- Egg or egg derivatives (e.g. from chicken, turkey, egg yolks, egg whites, etc.)
- Milk or Dairy Products
- Fish (e.g. bass, flounder, or cod)
- Peanuts
- Shellfish, including crustaceans, mollusks and their derivatives (e.g. crab, lobster, shrimp, scallops)
- Soybean or soybean derivatives
- Tree nuts (e.g. almonds, pecans, or walnuts)
- Wheat or wheat derivatives
- Alcohol (e.g. ethanol, methanol, isopropyl)
- Animal or Animal-sourced ingredients
- Artificial color
- Artificial flavor
- Artificial preservative
- Artificial sweeteners (e.g. aspartame, saccharin, sucralose)
- Barley or barley derivatives
- Benzoates
- BHA / BHT or related compounds
- Celery
- Coal tar dyes
- Corn or corn derivatives (e.g. maltodextrin, corn starch, corn syrup)
- Fruit or fruit derivatives
- Gluten (e.g. from wheat, oats, barley, spelt, millet, amaranth, or rye grain)
- Lactose
- Lupins
- MSG
- Mustard
- Natural latex
- Oat or oat derivatives
- Rice or rice derivatives
- Sesame seeds and derivatives
- Sugar (e.g. fructose, sucrose, dextrose)
- Sugar alcohols (e.g. sorbitol, mannitol)
- Sulphites, metaspulphites or sulfur dioxide
- Vegetables or vegetable derivatives
- Yeast or yeast derivatives
- Yellow 5

This material has been custom made and processed at No. 1 Badu Road, Tiantai Industrial Park, Tiantai, Zhejiang, China to meet Suan Farma, Inc. specifications.

Regards,

Julianna Chedid

Julianna Chedid
QA/QC Assistant
November 2019

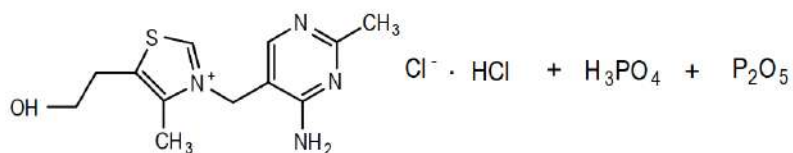
MANUFACTURING PROCESS FLOW CHART

Product Name: Benfotiamine

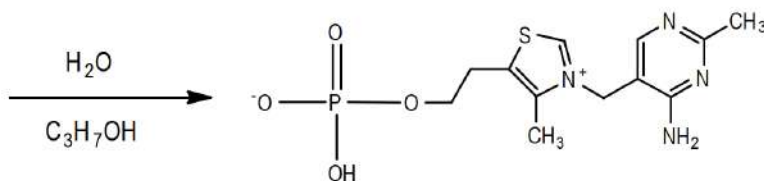
Product Code: BEN

Synthetic Route of Benfotiamine:

Step 1: Synthetic route of 3-((4-amino-2-methylpyrimidin-5-yl) methyl)-4-methyl-5-(2-(phosphonoxy)ethyl)thiazol-3-ium (TMP) Esterification reaction

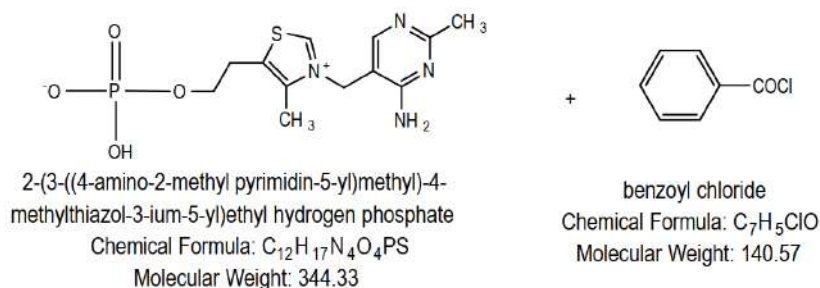


Thiamine Hydrochloride
Chemical Formula: $C_{12}H_{18}Cl_2N_4OS$
Molecular Weight: 337.27



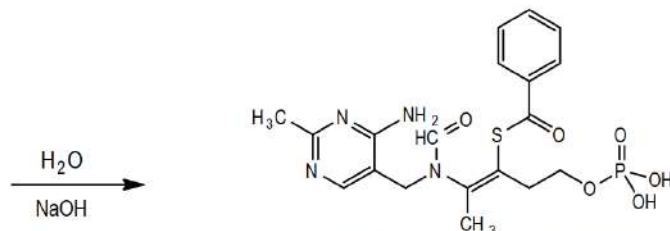
2-(3-((4-amino-2-methylpyrimidin-5-yl)methyl)-4-methylthiazol-3-ium-5-yl)ethyl hydrogen phosphate
Chemical Formula: $C_{12}H_{17}N_4O_4PS$
Molecular Weight: 344.33

Step 2: Synthetic route of Crude benfotiamine Acylation reaction



2-(3-((4-amino-2-methyl pyrimidin-5-yl)methyl)-4-methylthiazol-3-ium-5-yl)ethyl hydrogen phosphate
Chemical Formula: $C_{12}H_{17}N_4O_4PS$
Molecular Weight: 344.33

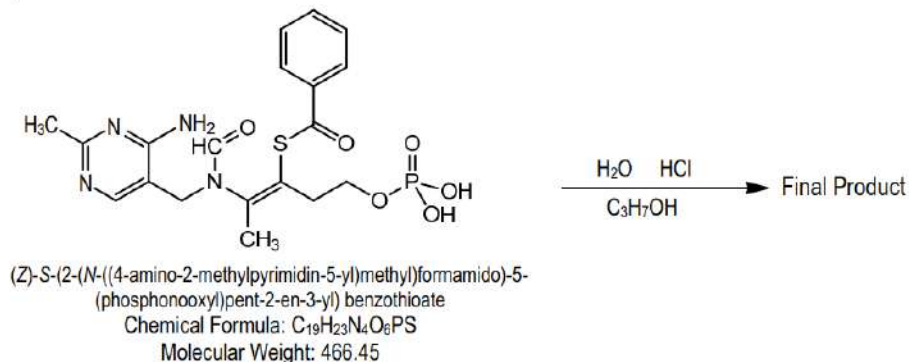
benzoyl chloride
Chemical Formula: C_7H_5ClO
Molecular Weight: 140.57



(Z)-S-(2-(N-((4-amino-2-methylpyrimidin-5-yl)methyl)formamido)-5-(phosphonoxy)pent-2-en-3-yl) benzothioate
Chemical Formula: $C_{19}H_{23}N_4O_6PS$
Molecular Weight: 466.45

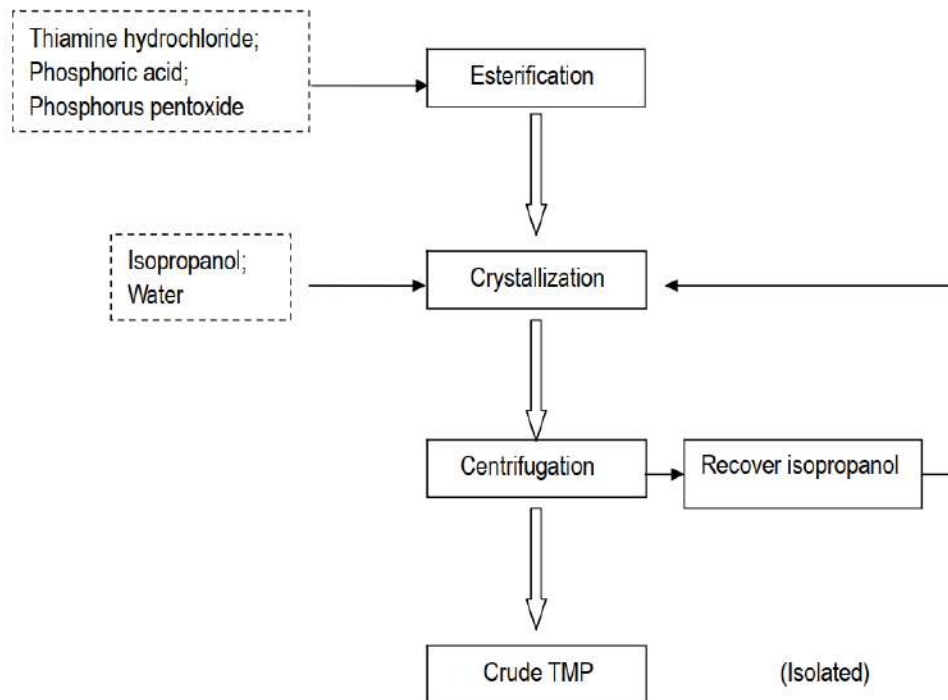
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Step 3: Purification of benfotiamine

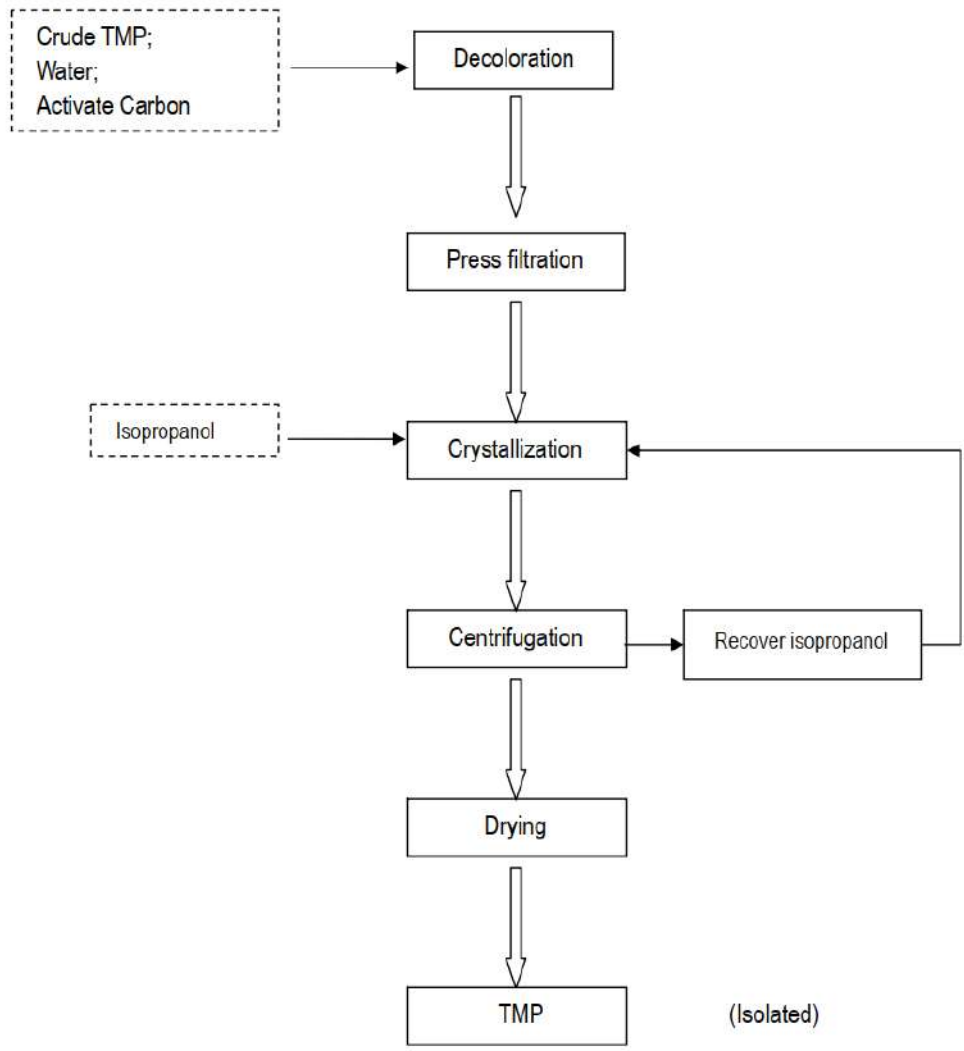


Benfotiamine Flow Diagram:

Step 1: Synthetic route of 3-((4-amino-2-methylpyrimidin-5-yl)methyl)-4-methyl-5-(2-(phosphonoxy)ethyl)thiazol-3-ium (TMP) Esterification reaction

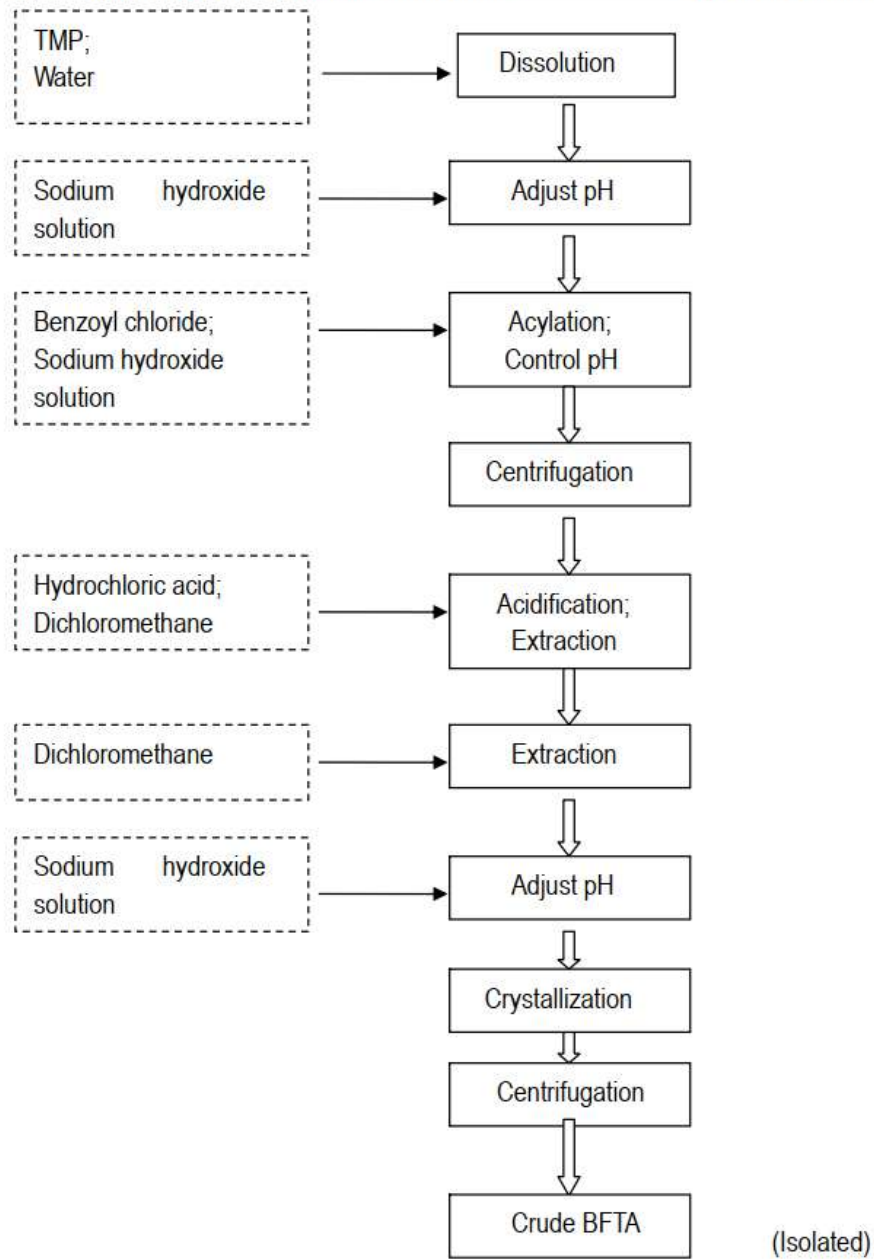


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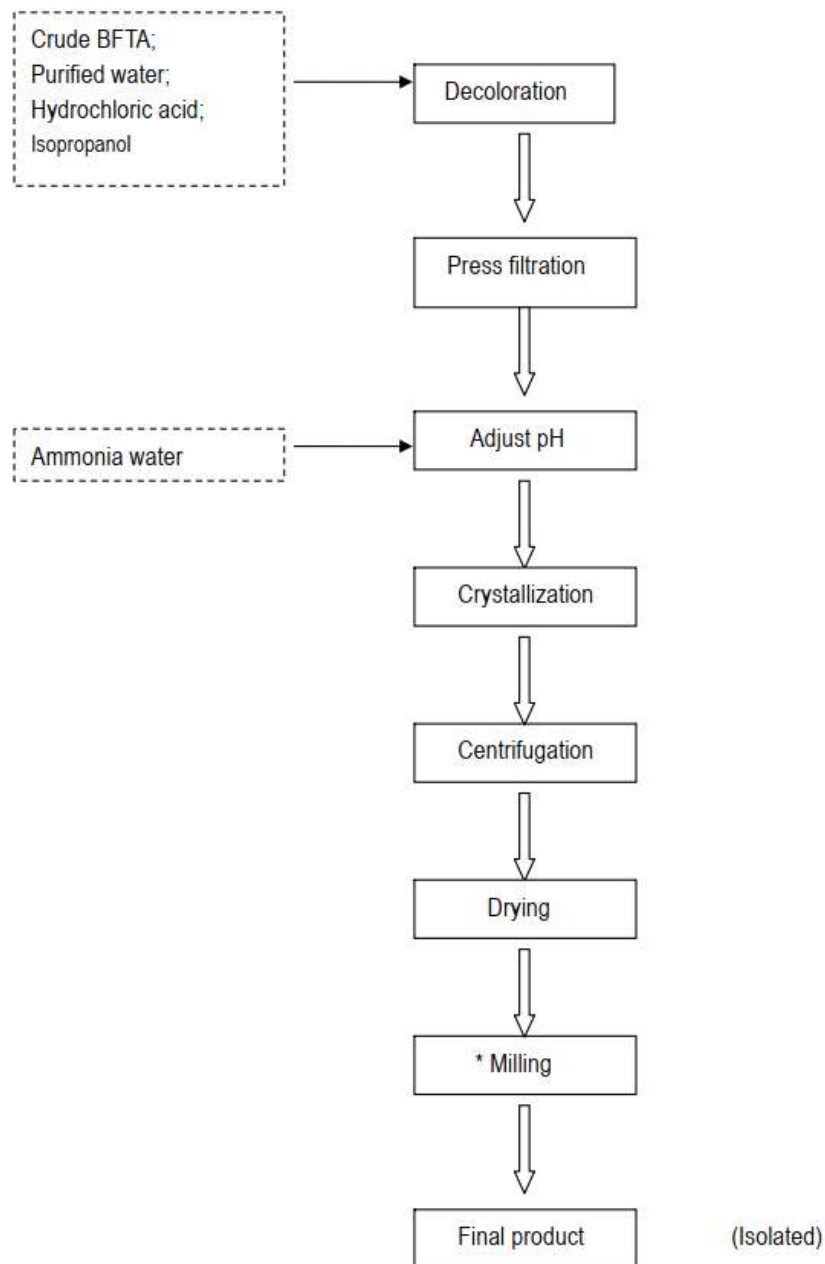


Step 2: Synthetic route of Crude benfotiamine

Acylation reaction



Step 3: Purification of benfotiamine



* the milling step depend on customer's needs and the medicinal product the API is used for

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SECTION 1: PRODUCT & COMPANY IDENTIFICATION

Product identifier:

Substance name: BENFOTIAMINE
Chemical Name: N-((4-Amino-2-methyl-5-pyrimidinyl)methyl)-N-(4-hydroxy-2-mercapto-1-methyl-1 butenyl)formamide-S-benzoate dihydrogen phosphate
EC Number: Not available
REACH Registration Number: None
CAS Number: 22457-89-2

Relevant identified uses of the substance or mixture and uses advised against:

Relevant identified uses: pharmaceutical active ingredient
Uses advised against: None

Supplier Name:

Suan Farma, Inc.
17-09 Zink Place, Unit 7 Fair Lawn, NJ 07410
Phone: 201-343-1188
FAX: 201-343-1102
E-mail: adminus@suanfarma.com

Emergency Phone Number: CHEMTREC (24-hr Access) 800-424-9300;
International CHEMTREC, call: 703-527-3887

SECTION 2: HAZARD(S) IDENTIFICATION

Classification of the substance or mixture

Classification according to Regulation (EC) No 1272/2008 [CLP]: Eye Irritation Cat 2
Classification according to Directive 67/548/EEC: Not available
Additional information: None

Label elements

Labelling according to Regulation (EC) No 1272/2008 [CLP]

Hazard pictogram(s):



Signal word:

Warning

Hazard statements:

H318: Causes serious eye damage.

Precautionary statements:

P 201: Obtain special instructions before use.
P 280: Wear protective gloves/protective clothing/eye protection/face protection.
P 260: Do not breathe dust/fume/gas/mist/vapors/spray.
P 305 + P 351 + P 338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P 309 + P 311: IF exposed or if you feel unwell: call a POISON CENTER or doctor/physician.
P 501: Dispose of contents/container to the collection point of hazardous or special waste.



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SECTION 3: COMPOSITION/INFORMATION ON INGREDIENTS

Substances:

Product identifier type in accordance with Article 18(2) of Regulation (EC) No 1272/2008	Identifier number	Identification name	Weight % content (or range)	EC Number
CAS number 22457-89-2	Not available	Not available	> 98	278-488-1

Mixtures:

Not applicable.

SECTION 4: FIRST AID MEASURES

Description of first aid measures:

General notes:

Following inhalation: If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.

Following skin contact: In case of contact, immediately wash skin with soap and plenty of water.

Following eye contact: In case of contact, immediately flush eyes with plenty of water for 15 minutes at least.

Following ingestion: If swallowed, wash out mouth with water provided person is conscious. Call a physician.

Most important symptoms and effects, both acute and delayed:

Not available

Indication of any immediate medical attention and special treatment needed:

Not available

SECTION 5: FIRE FIGHTING MEASURES

Extinguishing media:

Suitable extinguishing media: Water spray. Carbon dioxide, dry chemical or foam apropiad.

Special hazards arising from the substance or mixture:

Hazardous combustion products: Emits toxic fumes under fire.

Advice for firefighters:

Use self contained breathing apparatus and protective clothing to prevent contact with skin and eyes.

SECTION 6: ACCIDENTAL RELEASE MEASURES.

Personal precautions, protective equipment and emergency procedures:

Wear a respirator, chemical safety goggles, rubber boots and heavy rubber gloves

Environmental precautions:

None

Methods and material for containment and cleaning up:

Place in a bag and hold for waste disposal. Avoid raising dust. Ventilate area and wash the place where the product has been spilled once removed completely.

Reference to other sections:

None



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SECTION 7: HANDLING AND STORAGE

Precautions for safe handling:

Protective measures: Avoid inhalation. Avoid contact with eyes, skin or clothing.
Advice on protection against fire and explosion: Avoid prolonged or repeated exposure.

Conditions for safe storage, including any incompatibilities:

Technical measures and storage conditions: Keep tightly closed. Store in cool, dry place.
Packaging materials: Not applicable
Requirements for storage rooms and vessels: Not applicable
Storage class: Not applicable
Further information on storage conditions: Not applicable

Specific end use(s):

Not applicable

SECTION 8: EXPOSURE CONTROLS/PERSONAL PROTECTION

Exposure controls:

Appropriate engineering controls:

Safety shower and eye bath. A compulsory mechanical exhaust fumes.

Personal protection equipment:

Eye and face protection: Chemical goggles.
Skin protection: None
Hand protection: Gloves compatible chemical resistant.
Other skin protection: None
Respiratory protection: Use respirators and components tested and approved under appropriate government standards.
Thermal hazards: None

Environmental exposure controls:

Substance/mixture related measures to prevent exposure: None
Instruction measures to prevent exposure: None
Organizational measures to prevent exposure: None
Technical measures to prevent exposure: None

SECTION 9: PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance: White powder
Odor: Odorless
pH: Not available
Melting point / freezing point: Not available
Initial boiling point and boiling range: Not available
Flash point: Not available
Evaporation rate: Not available
Flammability (solid, gas): Not available
Upper/lower flammability or explosive limits: Not available
Vapor pressure: Not available
Vapor density: Not available



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Relative density:	Not available
Solubility(ies):	Soluble in ethanol
Partition coefficient: n-octanol/water:	Not available
Auto-ignition temperature:	Not available
Decomposition temperature:	Not available
Viscosity:	Not available
Explosive properties:	Not available
Oxidizing properties:	Not available

SECTION 10: STABILITY AND REACTIVITY

Reactivity:	None
Chemical stability:	Stable
Possibility of hazardous reactions:	None
Conditions to avoid:	None
Incompatible materials:	Strong oxidizing agents.
Hazardous decomposition products:	Carbon monoxide, carbon dioxide, nitrogen oxides, sulfur oxides.

SECTION 11: TOXICOLOGY INFORMATION

Information on toxicological effects:

Acute toxicity:	Not available
Skin corrosion/irritation:	May cause skin irritation
Serious eye damage/irritation:	May cause eye irritation
Respiratory or skin sensitization:	Not available
Germ cell mutagenicity:	Not applicable
Carcinogenicity:	Not applicable
Reproductive toxicity:	Not applicable
Summary of evaluation of the CMR properties:	Not applicable
STOT-single exposure:	Not applicable
STOT-repeated exposure:	Not applicable
Aspiration hazard:	Not applicable

SECTION 12: ECOLOGICAL INFORMATION

Toxicity:

Acute (short-term) toxicity:	Not available
Fish:	Not available
Crustacea:	Not available
Algae/aquatic plants:	Not available
Other organisms:	Not available
Chronic (long-term) toxicity:	Not available
Fish:	Not available
Crustacea:	Not available
Algae/aquatic plants:	Not available
Other organisms:	Not available

Persistence and degradability:

Abiotic Degradation:	Not available
Physical and photo-chemical	

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elimination:	Not available
Biodegradation:	Not available
Bioaccumulative potential:	
Partition coefficient	
n-octanol /water (log Kow):	Not available
Bioconcentration factor (BCF):	Not available
Mobility in soil:	
Known or predicted distribution to environmental compartments:	Not available
Surface tension:	Not available
Adsorption/Desorption:	Not available
Results of PBT and vPvB assessment:	
Not available	
Other adverse effects:	
Not available	
Additional information:	
Not available	

SECTION 13: DISPOSAL CONSIDERATIONS

Waste treatment methods:

Product/Packaging disposal:

Dissolve or mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber. Observe all federal, state and local environmental protection.

Waste treatment-relevant information: Not available

Sewage disposal-relevant information: Not available

Other disposal recommendations: Not available

SECTION 14: TRANSPORT INFORMATION

UN number:	Not applicable
UN proper shipping name:	Not applicable
Transport hazard class(es):	Not applicable
Packing group:	Not applicable
Environmental hazards:	Not applicable
Special precautions for user:	Not applicable
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:

Not available

Chemical Safety Assessment:

None



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SECTION 16: OTHER INFORMATION

Text of R phrases mentioned in Section 3:

R41: Risk of serious damage to eyes

Text of Hazard statements "H" referred to in section 3:

H318: Causes serious eye damage.

Further information

This information is based upon the present state of our knowledge. This SDS had been compiled and is solely intended for this product.

Notice to reader

Employers should use this information only as a supplement to other information gathered by them and should make independent judgement of suitability of this information to ensure proper use and protect the health and safety of employees. This information is furnished without warranty and any use of the product not in conformance with this Safety Data Sheet or in combination with any other product or process is the responsibility of the user.

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information and we assume no liability resulting from its use, users should make their own investigations to determine the suitability of the information for their purposes. In no way shall the company be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if the company has been advised of the possibility of such damages.



ADDITIONAL INFORMATION

We, Suan Farma, Inc., hereby declare that **Benfotiamine** (product code: **BEN**) is manufactured in accordance with the following guidelines:

- The above material has not been genetically modified or exposed to genetically modified organisms during the production process and is therefore GMO free.
- No animal derived products have been used in the manufacture of the above material, making it free from components which can cause Bovine Spongiform Encephalopathy (BSE) or Transmissible Spongiform Encephalopathy (TSE).
- Elemental impurities in the above material comply with limits set forth in ICH Q3D.
- The above material is synthetically produced. No botanical or animal products are used in this material. Therefore, it is suitable for vegetarian and vegan consumption.

Analytical methods for the above material are as follows:

Item	Specification	Test Method
Appearance	Light yellow or almost white power	Visual observation
Identification	(1) IR spectrum accordance with reference spectrum (2) The retention time of the major peak corresponds with that of the reference standard	(1) Infrared absorption spectrophotometry in accordance with reference spectrum (2) The retention time of major peak corresponds with that of the reference standard in HPLC.
Solution color and clearness	Colorless to pale-yellow clear solution	Accurately weigh 0.5g of sample and dissolve it in 10ml of dilute hydrochloric acid.
Chloride	Not more than 0.053%	Test solution: take 0.1575g of sample to be test in 25ml volumetric flask, add water to scale.
Sulphate	Not more than 0.011%	Sample solution: take 1.81g of sample to be test in a comparison tube, add 2ml hydrochloric acid, then add water to 20ml. Transfer 15ml of sample solution in a comparison tube, add 2.5ml mixture solution (3ml barium chloride solution and 4.5ml of standard potassium sulphate solution, shake up, place for 1min), then add 0.5ml glacial acetic acid, shake up.
Heavy metals	Not more than 0.002%	Determine on 1.0g of sample
Loss on drying	Not more than 1.5%	Accurately weigh 1.0g of the substance, dry at 105°C to constant weight.
Related substances	Benzoic acid: NMT 0.1%	Preparation of Solution Dilute solution: weigh 3.6g NaH ₂ PO ₄ and dissolve it into 1L of water, adjust pH to 2.5 with dilute phosphoric acid. Measure 800ml of above solution, add 200ml of Methanol. Test solution: Accurately weigh 20mg of sample to be examined, dilute to 100ml with dilute solution. Reference solution 2: Accurately weigh 20mg of Benfotiamine standard substance, dilute to 100mL with dilute solution.
	Thiamine: NMT 0.1%	Reference solution 1: Take 1ml of reference solution 2 and dilute to 100ml with dilute solution. System suitability solution: take 6mg of amide, 3mg of TMP, 3mg of Benzoic acid, 3mg of thiamine in 100ml volumetric flask, add dilute solution to scale, as resolution stock solution. Accurate weigh 20mg of benfotiamine working reference substance into 100ml of volumetric flask, then measure 1ml of resolution stock solution into above volumetric flask, dilute to scale with dilute solution, shake. Chromatographic condition:

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	<p>Total impurities: NMT 1.0%</p>	<p>Column: C18, 4.6×250mm, 5µm Detection wavelength: UV 243nm Column temperature: 45°C Flow rate: 0.8ml/min Inject volume: 20µl Running time: 50min Mobile phase: Weigh 1.98g of NaH₂PO₄ and 0.64g of Sodium 1-octanesulfonate, dissolve with 550ml of water, adjust pH to 2.5 with dilute phosphoric acid to get buffer solution, and mix with methanol (buffer solution: methanol = 54: 46), filter with organic membrane.</p>
<p>Purity (Assay)</p>	<p>≥ 99.0%</p>	<p>Calculate the content of impurity in sample according to the following formula: Content = $(A_i \times M_{st} / A_{st} \times M_i) \times 1/100 \times 100\%$ In the formula: A_i: peak area of each impurity peak in test solution A_{st}: peak area of Benfotiamine in reference solution M_{st}: mass of Benfotiamine standard substance M_i: mass of sample</p>

Regards,

Julianna Chedid

Julianna Chedid
 QA/QC Assistant
 Suan Farma, Inc.
 May 2020