

Revised: June 2012 (8<sup>th</sup> version, Change of trade name)  
Revised: October 2010

Activator for Neural and Muscle Function  
**SHIGMABITAN® COMBINATION CAPSULES B25**  
(Benfotiamine, Pyridoxine Hydrochloride, Cyanocobalamin combination capsules)

**Storage:**

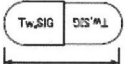
Store in an air-tight container at room temperature.

**Expiration date:**

Indicated on the package and label.

Standard Commodity Classification No. of Japan 873179	
Approval No.	22300AMX01223
Date of listing in the NHI reimbursement price	June 2012
Date of initial marketing in Japan	July 1990
Date of reevaluation (quality)	January 2008

**DESCRIPTION**

Active ingredient per capsule	Benfotiamine ..... 34.58 mg (as Thiamine Chloride Hydrochloride 25 mg) Pyridoxine Hydrochloride (JP) ..... 25 mg Cyanocobalamin (JP) ..... 0.25 mg	
Inactive ingredients	Lactose Hydrate, Cellulose, Magnesium Stearate Capsule shell: Red No.3, Yellow No. 5, Blue No. 1, Titanium Oxide, Sodium Lauryl Sulfate, Gelatin	
Product description	An opaque hard capsule consisting of a red cap and pale-yellowish red body, containing pink powder	
Identification code	Capsule	Tw. SIG
	Package	
Appearance Length Size	 About 15.8mm (No.3 Capsule)	
Weight (mg)	About 237	

**INDICATIONS**

- Vitamin supplementation in patients whose requirements for vitamins contained in this product are increasing and who cannot take adequate vitamins through oral intake of foods (e.g., wasting disease, women during pregnancy or lactation)
  - In any of the following conditions in which deficiencies or metabolic disorders of vitamins contained in this product are estimated to be involved:  
Neuralgia, myalgia/arthritis, peripheral neuritis/nerve palsy
- For patients showing no response, Shigmabitan should not be administered unthoughtfully over a number of months.

**DOSAGE AND ADMINISTRATION**

The usual adult dosage for oral use is 3-4 capsules daily. The dosage may be adjusted according to the patient's age and symptoms.

**PRECAUTIONS****1. Drug Interactions**

Precautions for coadministration (Shigmabitan Combination Capsules B25 should be administered with care when coadministered with the following drugs.

Drugs	Signs, Symptoms and Treatment	Mechanism and Risk Factors
Antiparkinson drug Levodopa	Coadministration of Shigmabitan with levodopa may lead to decreased effects of levodopa.	Pyridoxine hydrochloride contained in this product is a coenzyme for decarboxylase of levodopa. Coadministration of this product with levodopa accelerates the peripheral decarboxylation of levodopa, which is considered to decrease the amount of levodopa delivered to the sites of its action in the brain.

**2. Adverse Reactions**

No investigation such as a drug use investigation clearly showing the incidence of adverse reactions has been conducted.

	Incidence unknown
Hypersensitivity *)	Rash, pruritus
Gastrointestinal	Anorexia, stomach discomfort, nausea/vomiting, diarrhea

\*) Administration of this product should be discontinued.

**3. Precautions Concerning Use**

Precautions regarding dispensing:

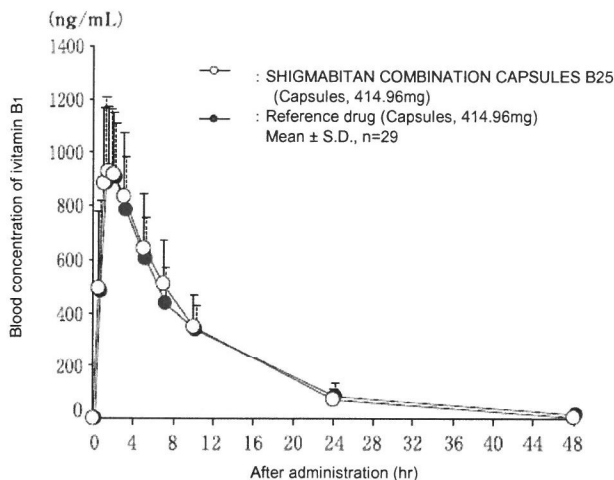
For drugs that are dispensed in a PTP (press-through package) sheet, instruct the patient to remove the drug from the package prior to use. (It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, causing perforation and resulting in severe complications such as mediastinitis.)

**PHARMACOKINETICS****1. Bioequivalence test**

In a cross-over study, single doses of 12 capsules of Shigmabitan Combination Capsules B25 and 12 capsules of a reference drug (equivalent to 414.96 mg of benfotiamine, 300 mg of pyridoxine hydrochloride, and 3 mg of cyanocobalamin) were orally administered to healthy adult men under fasting conditions; blood vitamin B<sub>1</sub> concentrations, plasma vitamin B<sub>6</sub> concentrations, and serum vitamin B<sub>12</sub> concentrations were measured and data obtained on pharmacokinetic parameters (AUC, C<sub>max</sub>) were statistically analyzed. The analysis results confirmed the bioequivalence of these drugs (based on PAB Notification No. 718 dated May 30, 1980).<sup>1)</sup>

(Note) Oral administration of 12 capsules/dose is beyond the approved dosage of Shigmabitan.

1) Benfotiamine (n=29)

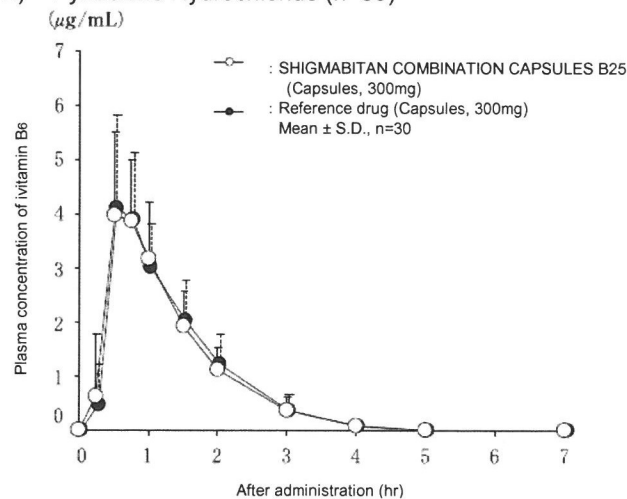


	Determined parameter		Reference parameter	
	AUC <sub>0-8</sub> (ng·hr/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)
SHIGMABITAN COMBINATION CAPSULES B25 (Capsules, 414.96mg)	9996.8±2948.6	1080.3±218.3	1.6±0.7	6.7±2.2
Reference drug (Capsules, 414.96mg)	9899.3±2479.7	1068.3±224.5	1.5±0.7	8.2±3.6

(Mean ± S.D., n=29)

Blood concentration and parameters such as AUC and C<sub>max</sub> may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

2) Pyridoxine Hydrochloride (n=30)

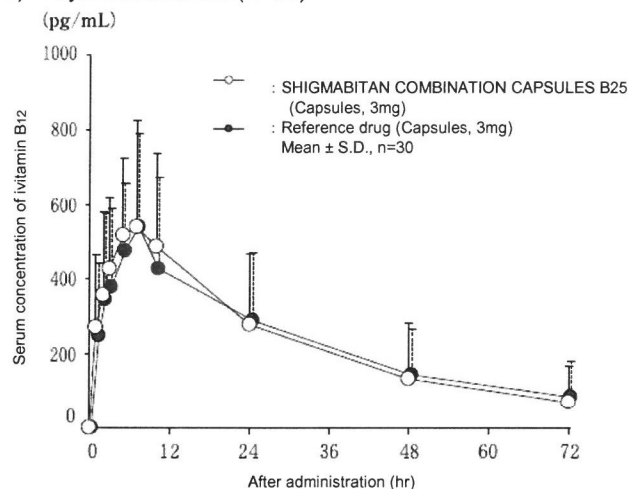


	Determined parameter		Reference parameter	
	AUC <sub>7</sub> (µg·hr/mL)	C <sub>max</sub> (µg/mL)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)
SHIGMABITAN COMBINATION CAPSULES B25 (Capsules, 300mg)	5.55±1.27	4.70±1.13	0.62±0.16	0.59±0.18
Reference drug (Capsules, 300mg)	5.65±1.15	4.70±1.21	0.72±0.31	0.55±0.10

(Mean ± S.D., n=30)

Plasma concentration and parameters such as AUC and C<sub>max</sub> may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

3) Cyanocobalamin (n=30)



	Determined parameter		Reference parameter	
	AUC <sub>0-8</sub> (pg·hr/mL)	C <sub>max</sub> (pg/mL)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)
SHIGMABITAN COMBINATION CAPSULES B25 (Capsules, 3mg)	17103±11209	625±262	6±2	24±16
Reference drug (Capsules, 3mg)	17052±8886	595±260	6±2	34±34

(Mean ± S.D., n=30)

Serum concentration and parameters such as AUC and C<sub>max</sub> may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

2. Dissolution profile

SHIGMABITAN COMBINATION CAPSULES B25 have been confirmed to conform to the corresponding dissolution standards of Befotiamine, Pyridoxine Hydrochloride, Cyanocobalamin defined in the third section of the Japanese Pharmaceutical Codex<sup>2)</sup>.

PHARMACOLOGY

1. Pyridoxine hydrochloride

Pyridoxine hydrochloride, vitamin B<sub>6</sub>, is converted primarily into pyridoxal phosphate (a cofactor in enzymatic activities of vitamin B<sub>6</sub>) in the body. It acts an essential role for the degradations and syntheses of various amino acids and proteins as a coenzyme of the amino acid-protein metabolizing enzyme group. It is also involved in fat metabolism and is required particularly when unsaturated fatty acids are utilized in the body.<sup>3)</sup>

2. Cyanocobalamin

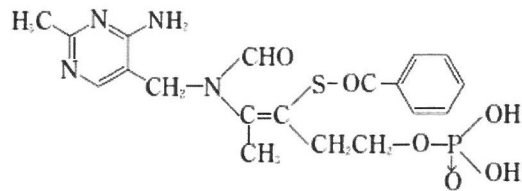
Cyanocobalamin, vitamin B<sub>12</sub>, is involved in various metabolic processes, playing a key role in normal developmental growth, hematopoiesis, and myelination in nerve tissues. Cyanocobalamin is indirectly involved in DNA synthesis by activating folate that is essential in the process of DNA synthesis, and in addition, it facilitates hematopoietic function by being involved in the conversion of methylmalonyl coenzyme A (CoA) to succinyl CoA. Cyanocobalamin also protects reduced sulfhydryl (SH) groups and affects the synthesis of proteins via its role in the process of methionine synthesis, thereby increasing myelination and improving nucleic acid/protein metabolism in glial cells. Regarding the effects of cyanocobalamin on eyes, it increases oxygen consumption and adenosine triphosphate

(ATP) production, and also alleviates accommodative asthenopia.<sup>4)</sup>

## PHYSICO-CHEMISTRY

### 1. Benfotiamine

Structural formula:



Nonproprietary name:

Benfotiamine

Chemical name:

S-benzoylthiamine monophosphate

Molecular formula:

C<sub>19</sub>H<sub>23</sub>N<sub>4</sub>O<sub>6</sub>PS

Molecular weight:

466.45

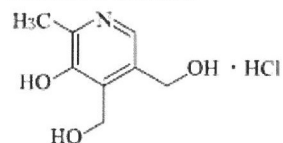
Description:

Benfotiamine occurs as a white crystals or crystalline powder. It is odorless, and has a bitter taste. It is slightly soluble in water and in methanol, very slightly soluble in ethanol (95), and practically insoluble in diethyl ether and in chloroform. It dissolves in sodium hydroxide TS, in sodium carbonate TS and in dilute hydrochloric acid. A saturated solution of Benfotiamine is acidic.

Melting point: about 200°C (with decomposition)

### 2. Pyridoxine Hydrochloride

Structural formula



Nonproprietary name:

Pyridoxine Hydrochloride

Commonly used name:

Pyridoxine Hydrochloride vitamin B<sub>6</sub>

Chemical name:

4,5-Bis (hydroxymethyl)-2-methylpyridin-3-ol monohydrochloride

Molecular formula:

C<sub>8</sub>H<sub>11</sub>NO<sub>3</sub> · HCl

Molecular weight:

205.64

Description:

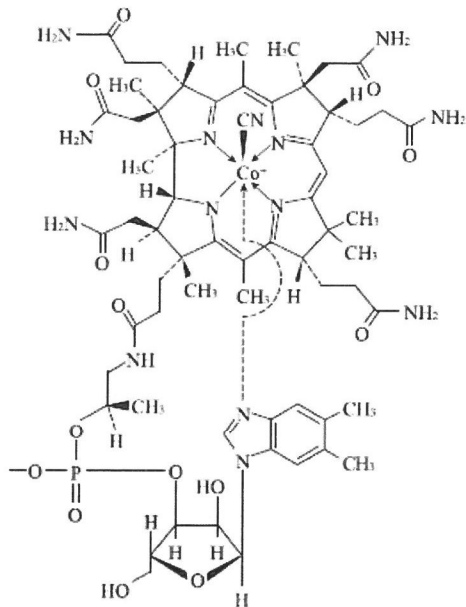
Pyridoxine Hydrochloride occurs as a white to pale yellow, crystalline powder. It is freely soluble in water, slightly soluble in ethanol (99.5), and practically insoluble in acetic anhydride and in acetic acid (100). It is gradually affected by light.

Melting point:

About 206°C (with decomposition).

### 3. Cyanocobalamin

Structural formula



Nonproprietary name:

Cyanocobalamin

Commonly used name:

Vitamin B<sub>12</sub>

Chemical name:

Co α-[α-(5,6-Dimethyl-1-H-benzoimidazol-1-yl)]-Co β-cyanocobamide

Molecular formula:

C<sub>63</sub>H<sub>88</sub>CoN<sub>14</sub>O<sub>14</sub>P

Molecular weight:

1355.37

Description:

Cyanocobalamin occurs as dark red, crystals or powder. It is sparingly soluble in water, and slightly soluble in ethanol (99.5). It is hygroscopic.

## PRECAUTIONS FOR HANDLING

Stability test

In an accelerated test using final packaged products (at 40°C and 75% relative humidity for 6 months), SHIGMABITAN COMBINATION CAPSULES B25 was estimated to be stable for 3 years under normal distribution conditions<sup>5)</sup>.

## PACKAGING

SHIGMABITAN COMBINATION CAPSULES B25

Boxes of 100 capsules, 1000 capsules (PTP)

Polyethylene containers of 1000 tablets

## REFERENCES

- 1) Internal data of Towa Pharmaceutical Co., Ltd.: Bioequivalence test
- 2) Internal data of Towa Pharmaceutical Co., Ltd.: Dissolution test
- 3) The 16th revision Japanese Pharmacopoeia explanatory, C-3779, 2011
- 4) The 16th revision Japanese Pharmacopoeia explanatory, C-1801, 2011
- 5) Internal data of Towa Pharmaceutical Co., Ltd.: Stability test

Manufacturer and Distributor  
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