Revised: May 2007 (6th version)

Standard Commodity Classification No. of Japan
875200

- Kampo-preparation-

TSUMURA Bakumondoto Extract Granules for Ethical Use

<bakumondoto>

Storage
Store in light-resistant, air-tight containers.

Expiration date
Use before the expiration date indicated on the container and the outer package.

Approval No.	(61AM)3269
Date of listing in the NHI reimbursement price	October 1986
Date of initial marketing in Japan	October 1986

DESCRIPTION

Composition	9.0 g of TSUMURA Bakumondoto extract granules contains 6.0 g of a dried extract of the following mixed crude drugs. JP Ophiopogon Tuber ..... 10.0 g JP Brown Rice ..... 5.0 g JP Pinellia Tuber ..... 5.0 g JP Jujube ..... 3.0 g JP Glycyrrhiza ..... 2.0 g JP Ginseng ..... 2.0 g (JP: The Japanese Pharmacopoeia)	
	Inactive ingredients	JP Magnesium Stearate JP Lactose Hydrate Sucrose Esters of Fatty Acids
Description	Dosage form	Granules
	Color	Light grayish brown
	Smell	Characteristic smell
	Taste	Sweet
	ID code	TSUMURA/29

INDICATIONS

Bakumondoto is indicated for the relief of the following symptoms:

Coughing with a hard, obstructive sputum, bronchitis, and bronchial asthma

DOSAGE AND ADMINISTRATION

The usual adult dose is 9.0 g/day orally in 2 or 3 divided doses before or between meals. The dosage may be adjusted according to the patient's age and body weight, and symptoms.

PRECAUTIONS

1. Important Precautions

(1) When this product is used, the patient's "SHO" (constitution/symptoms) should be taken into account. The patient's progress should be carefully monitored, and if no improvement in symptoms/findings is observed, continuous treatment should be avoided.

(2) Since this product contains Glycyrrhiza, careful attention should be paid to the serum potassium level, blood pressure, etc., and if any abnormality is observed, administration should be discontinued.

(3) When this product is coadministered with other Kampo-preparations (Japanese traditional herbal medicines), etc., attention should be paid to the duplication of the contained crude drugs.

SHO: The term "SHO" refers to a particular pathological status of a patient evaluated by the Kampo diagnosis, and is patterned according to the patient's constitution, symptoms, etc. Kampo-preparations (Japanese traditional herbal medicines) should be used after confirmation that it is suitable for the identified "SHO" of the patient.

2. Drug Interactions

Precautions for coadministration (Bakumondoto should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
(1) Preparations containing Glycyrrhiza (2) Preparations containing glycyrrhizinic acid or glycyrrhizinates	Pseudoaldosteronism is likely to occur. Besides, myopathy is likely to occur as a result of hypokalemia. (Refer to the section "Clinically significant adverse reactions".)	Since glycyrrhizinic acid has an accelerating action on the potassium excretion at the renal tubules, an acceleration of decrease in the serum potassium level has been suggested.

3. Adverse Reactions

This product has not been investigated (drug use investigations, etc.) to determine the incidence of adverse reactions. Therefore, the incidence of adverse reactions is not known.

(1) Clinically significant adverse reactions

1) **Interstitial pneumonia**: If fever, cough, dyspnea, abnormal pulmonary sound (fine crackle), etc. are observed, administration of this product should be discontinued, and examinations such as X-ray should be performed immediately and appropriate measures such as administration of adrenocortical hormones taken. Besides, the patient should be advised to discontinue this product immediately and to make contact with the physician in the event of fever, cough, dyspnea, etc.

2) **Pseudoaldosteronism**: Pseudoaldosteronism such as hypokalemia, increased blood pressure, retention of sodium/body fluid, edema, increased body weight, etc. may occur. The patient should be carefully monitored (measurement of serum potassium level, etc.), and if any abnormality is observed, administration should be discontinued and appropriate measures such as administration of potassium preparations should be taken.

3) **Myopathy**: Myopathy may occur as a result of hypokalemia. The patient should be carefully monitored, and if any abnormality such as weakness, convulsion/paralysis of limbs, etc. are observed, administration should be discontinued and appropriate measures such as administration of potassium preparations should be taken.

4) **Hepatic dysfunction and jaundice**: Hepatic dysfunction and/or jaundice with elevation of AST (GOT), ALT (GPT), Al-P and γ-GTP or other symptoms may occur. The patient should be carefully monitored for abnormal findings. Administration should be discontinued and appropriate therapeutic measures should be taken, if abnormalities are observed.

(2) Other adverse reactions

	Incidence unknown
Hypersensitivity Note 1)	Rash, Urticaria, etc.

Note 1) If such symptoms are observed, administration should be discontinued.

4. Use in the Elderly

Because elderly patients often have reduced physiological function, careful supervision and measures such as reducing the dose are recommended.

5. Use during Pregnancy, Delivery or Lactation

The safety of this product in pregnant women has not been established. Therefore, the product should be used in pregnant women, women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

6. Pediatric Use

The safety of this product in children has not been established. [Insufficient clinical data.]

PHARMACOLOGY

1. Anti-tussive actions

(1) Oral administration of Bakumondoto inhibited the cough reflex induced by mechanical or chemical (spray of citrate solution) stimulation of the tracheal mucosa in SO_2 gas inhalation model of bronchitis in guinea pigs but not in normal animals[1].

(2) Oral administration of Bakumondoto inhibited the substance P-related cough reflex in SO_2 gas inhalation model of bronchitis in guinea pigs[2].

(3) Oral administration of Bakumondoto inhibited an increase in spontaneous discharge by the superior laryngeal nerve in SO_2 gas inhalation model of bronchitis in guinea pigs[1].

2. Expectorant actions

(1) Local administration of Bakumondoto into quail airway with DNA, a substance that enhances adhesiveness, restored mucociliary transport velocity (MCTV) reduction induced by DNA[3].

(2) Oral administration of Bakumondoto inhibited the reduction of MCTV in a quail model which decreased airway clearance by human neutrophil elastase or DNA [4].

3. Bronchodilative actions

(1) Oral administration of Bakumondoto inhibited acetylcholine-induced bronchoconstriction in SO_2 gas inhalation model of bronchitis in guinea pigs[5].

(2) Oral administration of Bakumondoto inhibited a decrease in the threshold of histamine, which induces airway hypersensitivity in ozone inhalation airway hypersensitivity model in guinea pigs[6].

(3) Oral administration of Bakumondoto inhibited an increase in immediate/delayed type respiratory resistance in ovalbumin-sensitized guinea pigs with asthma[7].

4. Mechanisms of action

Bakumondoto exhibits pharmacological effects via the following actions:

(1) Anti-tussive actions

Oral administration of Bakumondoto inhibited the cough reflex induced by phospholamidon a neutral end peptidase (NEP) inhibitor, in guinea pigs. It also inhibited the reduction of NEP activity in the trachea[2].

(2) Expectorant actions

- Bakumondoto promoted the pulmonary secretion of a surfactant (phosphatidyl choline) in alveolar type II cells isolated from rats. It inhibited an increase in the pulmonary secretion of a surfactant (phosphatidyl choline) induced by polymorphonuclear leukocytes (PMN) activated by substance P (*in vitro*) [8].
- Bakumondoto specifically increased the β1-adrenergic receptor mRNA level in alveolar type II cells isolated from rats. This action disappeared in the presence of a cyclic AMP-dependent protein kinase inhibitor, H-89[9]. Furthermore, Bakumon-

doto increased the intracellular level of cyclic AMP (*in vitro*) [9)10)].

- Bakumondoto inhibited the enhancement of mucus secretion induced by PMN activated by substance P (*in vitro*) in hamster tracheal epithelial cells[8)].
- Oral administration of Bakumondoto inhibited increases in the airway surface fluid (ASF) levels of DNA, fucose, and protein in a quail model in which human neutrophil elastase decreased airway clearance[4)].
- Administration of Bakumondoto on the mucosal side of cultured canine tracheal mucosa reduced the short-circuit current (SCC) reflecting active ion transport and was increased by submucosal administration. The reaction to submucosal treatment was not influenced by a Na-channel blocker, amiloride, but reduced under Cl-free conditions (*in vitro*) [11)].

(3) Bronchodilative actions

Bakumondoto enhanced muscle relaxation and an increase in cyclic AMP by β-adrenergic receptor stimulation in canine bronchial smooth muscle (*in vitro*) [12)].

(4) Anti-allergic actions

- Bakumondoto reduced survival rate and inhibited degranulation induced by ovalbumin in human eosinophils (*in vitro*) [13)].
- Oral administration of Bakumondoto inhibited the production of IL-6 induced by bacterial LPS in mice pretreated with P. Acnes (*in vivo*). Bakumondoto inhibited the production of IL-6 induced by IL-1β stimulation in MG63 cells, macrophage-like cells (*in vitro*) [14)].

PACKAGING

Bottles of 500 g and boxes of 5 kg (500 g × 10 bottles)
3.0 g × 42 packets
3.0 g × 189 packets

REFERENCES

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