Revised: July 2009 (7th version)

Standard Commodity Classification No. of Japan
875200

■12■

- Kampo-preparation-

TSUMURA Saikokaryukotsuboreito Extract Granules for Ethical Use

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)3265
Date of listing in the NHI reimbursement price	October 1986
Date of initial marketing in Japan	October 1986

DESCRIPTION

Composition	7.5 g of TSUMURA Saikokaryukotsuboreito extract granules(hereafter TJ-12) contains 4.5 g of a dried extract of the following mixed crude drugs. JP Bupleurum Root ..... 5.0 g JP Pinellia Tuber ..... 4.0 g JP Cinnamon Bark ..... 3.0 g JP Poria Sclerotium ..... 3.0 g JP Scutellaria Root ..... 2.5 g JP Jujube ..... 2.5 g JP Ginseng ..... 2.5 g JP Oyster Shell ..... 2.5 g JP Longgu ..... 2.5 g JP Ginger ..... 1.0 g (JP : The Japanese Pharmacopoeia)	
	Inactive ingredients	JP Magnesium Stearate JP Lactose Hydrate Sucrose Esters of Fatty Acids
Description	Dosage form	Granules
	Color	Yellow-brown
	Smell	Characteristic smell
	Taste	Slightly bitter
	ID code	TSUMURA/12

INDICATIONS

TJ-12 is indicated for the relief of the following symptoms of those patients with comparatively strong constitution, palpitation, insomnia, and neurological symptoms such as irritability:
Hypertension, arteriosclerosis, chronic renal disease, neurasthenia, neurotic palpitation, epilepsy, hysteria, night cry in childhood, and impotence

DOSAGE AND ADMINISTRATION

The usual adult dose is 7.5 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 TJ-12 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) When TJ-12 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. Adverse Reactions

TJ-12 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 TJ-12 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 TJ-12 immediately and to make contact with the physician in the event of fever, cough, dyspnea, etc.

2) **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, Redness, Pururitus, Urticaria, etc.
Gastrointestinal	Epigastric distress, etc.

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

3. Use in the Elderly

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

4. Use during Pregnancy, Delivery or Lactation

The safety of TJ-12 in pregnant women has not been established. Therefore, TJ-12 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.

5. Pediatric Use

The safety of TJ-12 in children has not been established. [Insufficient clinical data]

6. Other Precautions

According to the results of a review of overseas placebo-controlled clinical studies (199 cases) of multiple anti-epileptics for the treatment of epilepsy and mental disease, etc., the risk of occurrence of suicidal thoughts or behaviors was approximately two times higher in the anti-epileptic group as compared with the placebo group (anti-epileptic group: 0.43%, placebo group: 0.24%). The prevalence in the anti-epileptic group was calculated to be 1.9/1000 more than that in the placebo group (95% confidence interval: 0.6-3.9). In addition, the prevalence in the subgroup of epileptics was calculated to be 2.4/1000 more than that in the placebo group.

PHARMACOLOGY

1. Hypotensive actions

Pretreatment with a diet containing Saikokaryukotsuboreito in rabbits inhibited noradrenalin-induced vasoconstriction and elevation of blood pressure[1].

2. Antiarteriosclerotic actions

(1) Oral administration of Saikokaryukotsuboreito to spontaneously hypertensive rats improved aortic intimal thickening[2].

(2) Pretreatment with a high cholesterol diet containing Saikokaryukotsuboreito in rats in which the carotid artery was scraped inhibited vascular intimal thickening and proliferation of vascular smooth muscle cells[3].

3. Antipsychotic actions

(1) Treatment with a diet containing Saikokaryukotsuboreito in E1 mice improved spontaneous locomotor hyperactivity and a decrease in time of sodium pentobarbital-induced sleep during the light periods[4].

(2) Oral administration of Saikokaryukotsuboreito to rats that were chronically stressed with waterimmersion and restraint improved a depressive state in rotarod behavior[5].

4. Mechanisms of action Anticonvulsive actions

Oral administration of Saikokaryukotsuboreito to mice shortened the duration of clonic cramps induced by electric stimulation and prolonged the interval until death induced by pentetrazol or picrotoxin treatment[6].

5. Mechanisms of action

Saikokaryukotsuboreito exhibits pharmacological effects via the following actions:

(1) Antiarteriosclerotic actions

- Administration of a high cholesterol food containing Saikokaryukotsuboreito to rabbits with hereditary hypercholesterolemia decreased the plasma levels of total cholesterol and LDL and increased the mRNA levels of apoE and LDL-receptor in the liver. In addition, Saikokaryukotsuboreito inhibited atherosclerotic lesions at the thoracic aortic arch[7].
- In a human hepatocellular carcinoma cell line, Hep G2 cells, Saikokaryukotsuboreito inhibited the intracellular synthesis of cholesterol ester and triglyceride, decreasing secretion of apoB (*in vitro*) [8].

(2) Antipsychotic actions

- Oral administration of Saikokaryukotsuboreito to rats that were chronically stressed with water-immersion and restraint inhibited adrenal gland weight gain and improved attenuation of the glucocorticoid negative feedback[9].
- Oral administration of Saikokaryukotsuboreito to rats that were chronically stressed with water-immersion and restraint improved a decrease in the release of serotonin and dopamine in the prefrontal cortex[5].

PACKAGING

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

REFERENCES

1) Okano, H. et al. in vivo. 1999, 13(4), p.333.
2) Yamada, T. et al. The Journal of Japan Atherosclerosis Society. 1988, 16(7), p.999.
3) Chung, H. -J. et al. Biol. Pharm. Bull. 2003, 26(1), p.56.
4) Iizuka, S. et al. Meth. Find. Exp. Clin. Pharmacol. 1998, 20(1), p.19.
5) Mizoguchi, K. et al. Pharmacol. Biochem. Behav. 2003, 75, p.419.
6) Itoh, T. et al. Kampo to saishin chiryo. 1992, 1(3), p.274.
7) Yoshie, F. et al. Pharmacol. Res. 2001, 43(5), p.481.

8) Furukawa, S. et al. J. Traditional Med. 1994, 11(3), p.236.
9) Mizoguchi, K. et al. Life Sci. 2002, 72(1), p.67.

■ **REQUEST FOR LITERATURE SHOULD BE MADE TO:**

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