Revised: October 2014 (6th version)

Standard Commodity Classification No. of Japan
875200

■23■

- Kampo-preparation-

TSUMURA Tokishakuyakusan 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)1166
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 Tokishakuyakusan extract granules(hereafter TJ-23) contains 4.0 g of a dried extract of the following mixed crude drugs. JP Peony Root ..... 4.0 g JP Atractylodes Lancea Rhizome..... 4.0 g JP Alisma Rhizome ..... 4.0 g JP Poria Sclerotium ..... 4.0 g JP Cnidium Rhizome ..... 3.0 g JP Japanese Angelica Root ..... 3.0 g (JP : The Japanese Pharmacopoeia)	
	Inactive ingredients	JP Magnesium Stearate JP Lactose Hydrate
Description	Dosage form	Granules
	Color	Light grayish brown
	Smell	Characteristic smell
	Taste	Slightly astringent
	ID code	TSUMURA/23

INDICATIONS

TJ-23 is indicated for the relief of the following symptoms of those patients who have generally weak muscles and are easily fatigued and whose waist and lower limbs are susceptible to cold:

Anemia, malaise, climacteric disturbance (dull headache, headache, dizziness, shoulder stiffness, etc.), menstrual irregularity, dysmenorrhea, infertility, palpitation pounding, chronic nephritis, diseases during pregnancy (edema, habitual abortion, hemorrhoids, abdominal pain), beriberi, hemiplegia and valvular diseases of the heart

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. Careful Administration (TJ-23 **should be administered with care in the following patients.)**

(1) Patients with an extremely weak gastrointestinal tract [Anorexia, epigastric distress, nausea, vomiting, abdominal pain, diarrhea, etc. may occur.]

(2) Patients with anorexia, nausea or vomiting [These symptoms may be aggravated.]

2. Important Precautions

(1) When TJ-23 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-23 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.

3. Adverse Reactions

TJ-23 has not been investigated (drug use investigations, etc.) to determine the incidence of adverse reactions. Therefore, the incidence of adverse reactions is not known.

	Incidence unknown
Hypersensitivity Note 1)	Rash, Pruritus, etc.
Hepatic	Abnormality of hepatic function [increased AST (GOT), ALT (GPT) levels, etc.]
Gastrointestinal	Anorexia, epigastric distress, nausea, vomiting, abdominal pain, diarrhea, 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 TJ-23 in pregnant women has not been established. Therefore, TJ-23 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 TJ-23 in children has not been established. [Insufficient clinical data.]

PHARMACOLOGY

1. Actions on hormones

Tap water containing Tokishakuyakusan was given to juvenile female rats. The uterus weight and uterine estrogen receptor count increased. This finding was not observed in an ovariectomy model[1].

2. Ovulation-inducing actions

Tap water containing Tokishakuyakusan was given to juvenile female rats, and human menopausal gonadotropin (hMG) was administered. This treatment increased the rate of ovulation compared to single administration of hMG[1].

3. Actions on pregnant rats

Administration of Tokishakuyakusan in drinking water inhibited the placental blood circulation and the decrease of the weight of fetus in spontaneously hypertensive pregnant rats[2].

4. Actions on climacteric disturbance

Oral administration of Tokishakuyakusan to overectomized mice inhibited a stress loading-related reduction of the duration of pentobarbital sodium-induced sleep[3].

5. Actions on uterus

Tokishakuyakusan decreased the strength of prostaglandin F2a-induced contraction in myometrium isolated from rats (in vitro)[4].

6. Action mechanism

Tokishakuyakusan shows pharmacological effects via the following actions:

(1) Actions on hormones

-Tokishakuyakusan promoted the secretion of estradiol and progesterone in human granulosa cells (*in vitro*)[5].

-In cultured rat pituitary gland cells, Tokishakuyakusan promoted the secretion of LH and FSH (*in vitro*)[6].

(2) Removal of free radicals

- Tokishakuyakusan removed fat-soluble radicals, superoxide radicals, and hydroxyradicals, and inhibited ascorbate-ferric chloride-induced carbon center radicals and hyperoxidation of lipids (*in vitro*)[7].
- Tap water containing Tokishakuyakusan was given to pregnant mice. It improved the pregnancy rate that had decreased in the presence of a superoxide-deleting enzyme inhibitor, diethyldithiocarbamate[8].

(3) Actions on cytokines

In human peripheral blood monocytes, Tokishakuyakusan increased the levels of TNF-α and IFN-γ (Th1 cytokine), but did not influence the level of IL-4 (Th2 cytokine)[9]. In human decidua monocytes, it increased the TNF-α level, but did not influence the IFN-γ or IL-4 levels (*in vitro*)[10].

(4) Actions on climacteric disturbance

Oral administration of Tokishakuyakusan to overectomized mice inhibited the stress loading-induced enhancement of hypothalamic noradrenalin metabolic turnover[3].

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) Koyama, T. et al. Recent progress of KAMPO MEDI-CINE in obstetrics and gynecology No.6. Sindan to Chiryosha, 1989, p.76.
2) Watanabe, K. et al. Acta Med. Biol. 1989, 37(2), p.91.
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4) Kushihiki, M. et al. J. Med. Pharm. Soc. WAKAN-YAKU. 2000, 17(4), p.170.
5) Tanaka, T. et al. Clin. Endocrinol. 1990, 38(9), p.935.
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7) Ueda, Y. et al. Neurochem. Res. 1996, 21(8), p.909.
8) Ota, H. et al. Reprod. Fertil. Dev. 1999, 11, p.451.
9) Fujii, T. et al. Am. J. Reprod. Immunol. 2000, 44, p.342.
10) Fujii, T. et al. Am. J. Reprod. Immunol. 2000, 46, p.369.

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