Revised: June 2016 (10th version)

Standard Commodity Classification No. of Japan
875200

■54■

- Kampo-preparation-

TSUMURA Yokukansan 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)1133
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 Yokukansan extract granules (hereafter TJ-54) contains 3.25 g of a dried extract of the following mixed crude drugs. JP Atractylodes Lancea Rhizome ..... 4.0 g JP Poria Sclerotium ..... 4.0 g JP Cnidium Rhizome ..... 3.0 g JP Uncaria Hook …..... 3.0 g JP Japanese Angelica Root ..... 3.0 g JP Bupleurum Root ..... 2.0 g JP Glycyrrhiza ..... 1.5 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 sweet and astringent
	ID code	TSUMURA/54

INDICATIONS

TJ-54 is indicated for the relief of the following symptoms of those patients with delicate constitution and nervousness:
Neurosis, insomnia, night cry in children, and peevishness in children

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-54 should be administered with care in the following patients.)

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

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

2. Important Precautions

(1) When TJ-54 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 TJ-54 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 TJ-54 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. Drug Interactions

Precautions for coadministration (TJ-54 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.

4. Adverse Reactions[1)]

In a clinical survey of adverse reactions of 3,141 patients treated with TJ-54 (October 2012 - March 2014), 162 adverse reactions including abnormal laboratory values were reported for 136 patients (4.3%).

(1) Clinically significant adverse reactions

1) Interstitial pneumonia (incidence unknown) **:** If fever, cough, dyspnea, abnormal pulmonary sound, etc. are observed, administration of TJ-54 should be discontinued, and examinations such as X-ray or chest CT should be performed immediately and appropriate measures such as administration of adrenocortical hormones taken.

2) Pseudoaldosteronism (incidence unknown) : 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) Heart failure (<0.1%): Heart failure may occur. Adequately monitor the patient, and discontinue administration and take appropriate measures if fluid buildup, rapid weight gain, and signs and symptoms of heart failure (e.g., shortness of breath, increased cardiothoracic ratio, pleural effusion) are observed.

4) Myopathy, rhabdomyolysis (incidence unknown)**:** Myopathy and rhabdomyolysis may occur as a result of hypokalemia. Adequately monitor the patient, and discontinue administration and take appropriate measures such as administration of a potassium preparation if sluggishness, muscular weakness, myalgia, limb cramping/paralysis, elevated CK (CPK) levels, and elevated blood and urine myoglobin levels are observed.

5) Hepatic dysfunction and jaundice (incidence unknown): Hepatic dysfunction and/or jaundice with remarkable elevation of AST (GOT), ALT (GPT), Al-P and γ-GTP etc. 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

	5% > ≥0.1%	<0.1%
Hypersensitivity Note 1)		Rash, Redness, Pruritus, etc.
Hepatic	Abnormality of hepatic function	
Gastrointestinal	Anorexia, Epigastric distress, Nausea, Diarrhea, etc.	
Psychoneurologic	Sleepiness	
Others	Hypokalemia, Increase in blood pressure, Edema, Malaise	

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

5. Use in the Elderly

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

6. Use during Pregnancy, Delivery or Lactation

The safety of TJ-54 in pregnant women has not been established. Therefore, TJ-54 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.

7. Pediatric Use

The safety of TJ-54 in children has not been established. [Insufficient clinical data]

PHARMACOLOGY

1. Anxiolytic effect

Oral administration of TJ-54 showed an anxiolytic-like effect in performance of an improved elevated-plus maze in mice[2)]. A similar effect was observed in cerebrovascular ischemia rats[3)] and aged rats[4)].

2. Ameliorative effects on aggressiveness

Oral administration of TJ-54 ameliorated aggressiveness observed in amyloid precursor protein transgenic mice[5)], intraventricularly amyloid β protein-injected mice[6)], and zinc-deficient rats[7)].

3. Ameliorative effects on sleep disturbance

Oral administration of TJ-54 ameliorated the shortening of pentobarbital-induced sleeping time in socially isolated mice[8)].

4. Action mechanism

TJ-54 shows pharmacological effects via the following actions:

Ameliorative effects on aggressiveness

(1) Inhibition of glutamate release

TJ-54 inhibited the increase of the hippocampal extracellular glutamate concentration in zinc-deficient rats[9)]; it also inhibited exocytosis in hippocampal brain slices of zinc-deficient rats orally administered TJ-54[10)].

(2) Modulation of glutamate transport

TJ-54 ameliorated thiamine deficiency-induced decreases in glutamate transport, protein, and mRNA expression of glutamate transporters in cultured rat cortical astrocytes[10)].

(3) Down-regulation of serotonin $(5HT)_{2A}$ receptors

Oral administration of TJ-54 induced down-regulation of $5\text{-}HT_{2A}$ receptors in the prefrontal cortex and inhibited the 2,5-dimethoxy-4-iodoamphetamine (DOI; $5\text{-}HT_{2A}$ receptor agonist)-induced head-twitch response in mice[11)].

(4) 5-HT_{1A} receptor partial agonistic effect

・Oral administration of TJ-54 ameliorated the increase in aggressive behavior and decrease in social behavior of ρ-chloroamphetamine-treated rats[12] and socially isolated mice[13]. These ameliorative effects were counteracted by co-administration of WAY-100635 (5-HT_{1A} receptor antagonist). In an *in vitro* receptor binding assay, TJ-54 showed a partial agonistic effect on 5-HT_{1A} receptors[14].

・Anxiolytic effect of TJ-54 in elevated plus-mase test was inhibited by WAY-100635 (5-HT_{1A} receptor antagonist)[15].

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

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