Revised: April 2014 (10th version)

Standard Commodity Classification No. of Japan
875200

■9■

- Kampo-preparation –

TSUMURA Shosaikoto 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)3280
Date of listing in the NHI reimbursement price	October 1986
Date of initial marketing in Japan	October 1986
Date of latest reevaluation	March 1995
Date of latest reevaluation	April 2014

WARNINGS

1. **Treatment with TSUMURA Shosaikoto Extract Granules (hereafter TJ-9) may cause interstitial pneumonia which may result in serious outcomes such as death unless appropriate measures are taken in the early phase. The patient should be carefully monitored, and if fever, cough, dyspnea, abnormal pulmonary sound (fine crackle), X-ray abnormalities, etc. are observed, administration of TJ-9 should be discontinued immediately.**
2. **The patient should be advised to discontinue TJ-9 and to contact the physician in the event of fever, cough, dyspnea, etc.**
   (Refer to the section "Clinically significant adverse reactions".)

CONTRAINDICATIONS (TJ-9 is contraindicated in the following patients.)

1. Patients receiving treatment with interferon preparations (Refer to the section "Drug Interactions".)
2. Patients with liver cirrhosis or hepatoma [Interstitial pneumonia may occur and cause serious outcomes such as death.]
3. Patients with liver dysfunction in chronic hepatitis with a platelet count of 100,000/mm^3 or below [Liver cirrhosis is suspected.]

DESCRIPTION

Composition	7.5 g of TJ-9 contains 4.5 g of a dried extract of the following mixed crude drugs. JP Bupleurum Root ..... 7.0 g JP Pinellia Tuber ..... 5.0 g JP Scutellaria Root ..... 3.0 g JP Jujube ..... 3.0 g JP Ginseng ..... 3.0 g JP Glycyrrhiza ..... 2.0 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	Light yellow-brown
	Smell	Characteristic smell
	Taste	Slightly sweet
	ID code	TSUMURA/9

INDICATIONS

1. TJ-9 is indicated for the relief of the following symptoms of those patients with moderately strong constitution, right upper abdominal tenderness accompanied by fullness and discomfort, coated tongue, oral cavity discomfort, anorexia, and/or those with slight fever and nausea:
   Various acute febrile diseases, pneumonia, bronchitis, common cold, lymphadenitis, chronic gastrointestinal disorder, and insufficient postpartum recovery
2. TJ-9 is indicated for the improvement of liver dysfunction due to chronic hepatitis.

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-9 should be administered with care in the following patients.)

(1) Patients with severe apophylaxis [Adverse reactions are likely to occur, and the symptoms may be aggravated.]

(2) Patients with liver dysfunction in chronic hepatitis with a platelet count of 150,000/mm^3 or below [The disease may have progressed to cirrhosis.]

2. Important Precautions

(1) During treatment with TJ-9 for liver dysfunction in chronic hepatitis, attention should be paid to possible change in the platelet count, and if a decreased platelet count is observed, administration should be discontinued.

(2) When TJ-9 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.

(3) Since TJ-9 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.

(4) When TJ-9 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

(1) Contraindications for coadministration (TJ-9 should not be coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Interferon preparations Interferon-α Interferon-β	Interstitial pneumonia may occur. (Refer to the section "Clinically significant adverse reactions".)	The mechanism is not known.

(2) Precautions for coadministration (TJ-9 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 (3) Loop diuretics Furosemide Etacrynic acid (4) Thiazide diuretics Trichlormethiazide	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 and diuretics have 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

Summary of the incidence of adverse reactions

In the drug experience investigation (October 1995 to March 1997), including abnormal laboratory tests, 88 adverse reactions were reported in 69 of 2,495 patients (2.8%). The data shown here include adverse reactions (reported from the time of approval to July 1998) whose incidence could not be calculated.

(1) Clinically significant adverse reactions

1) Interstitial pneumonia (≤0.1%): If fever, cough, dyspnea, abnormal pulmonary sound (fine crackle), etc. are observed, administration of TJ-9 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-9 immediately and to make contact with the physician in the event of fever, cough, dyspnea, etc.

2) Pseudoaldosteronism (≤0.1%): 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 (incidence unknown): As a result of hypokalemia, myopathy/rhabdomyolysis may occur. If weakness, muscle weakness, myalgia, convulsion/paralysis of limbs, increased CK (CPK), increased blood/urinary myoglobin are observed, administration should be discontinued and appropriate measures such as an administration of a potassium preparation taken.

4) Hepatic dysfunction and jaundice (incidence unknown): Hepatic dysfunction and/or jaundice with remarkable 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 dis-

continued and appropriate therapeutic measures should be taken, if abnormalities are observed.

(2) Other adverse reactions

	Incidence unknown	5%> ≧0.1%	<0.1%
Hypersensitivity[1)]			Rash, Pruritus, Urticaria
Gastrointestinal	Constipation	Anorexia, Epigastric distress, Vomiting, Diarrhea	Nausea, Abdominal pain
Urinary[2)]	Hematuria, Feeling of residual urine, Cystitis		Pollakiuria, Micturition pain

Note

1) In the event of such symptoms, administration should be discontinued.
2) Since these symptoms may occur. The patient should be carefully monitored, and if abnormalities are observed, administration of the drug should be discontinued and appropriate therapeutic measures taken.

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-9 in pregnant women has not been established. Therefore, TJ-9 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-9 in children has not been established. [Insufficient clinical data]

PHARMACOKINETICS

The pharmacokinetic parameters that were determined from the changes in the plasma drug concentrations in healthy persons after single-dose administration of TJ-9 are shown below[1)].

average ± S.D.

pharmacokinetic parameter		Glycyrrhizic acid (n=5)	Baicalin (n=6)
tmax (hr)	2.5 g group	14.8 ± 0.5	7.3 ± 1.4
	7.5 g group	13.2 ± 1.4	7.3 ± 0.8
Cmax (ng/mL)	2.5 g group	34.0 ± 7.3	16.7 ± 3.9
	7.5 g group	119.4 ± 13.3	54.2 ± 9.4

PHARMACOLOGY

1. Prevention of hepatopathy

(1) Oral administration of Shosaikoto to rats inhibited D-galactosamine-induced disorders in the hepatocellular membrane and endoplasmic reticulum enzymes[2)], increases in the serum levels of AST (GOT) and ALT (GPT), and decreases in the serum levels of total protein and albumin[3)].

(2) Oral administration of Shosaikoto to a rat alcoholic fatty liver model inhibited lipid droplet accumulation in the liver[4)].

(3) A diet containing Shosaikoto was given to rats. It inhibited a diethylnitrosamine (DEN)-induced elevation of the 8-hydroxy-2'-deoxyguanosine (8-OHdG) level in the liver[5)].

2. Inhibition of decrease in hepatic blood flow

Oral administration of Shosaikoto to a rat chronic hepatopathy model induced by choline-deficient/ethionine -supplemented diet inhibited a decrease in hepatic blood flow[6)].

3. Promotion of liver regeneration

(1) Oral administration of Shosaikoto to rats promoted liver regeneration after partial hepatectomy under ischemia/reperfusion (Pringle maneuver) [7)].

(2) Oral administration of Shosaikoto to a rat dimethylnitrosamine (DMN)-induced hepatopathy model after partial hepatectomy increased the rate of liver regeneration and the number of regenerative cells in the liver[8)].

4. Inhibition of liver fibrosis

(1) A diet containing Shosaikoto was given to a rat DMN- or pig serum (PS)-induced liver fibrosis model. It inhibited type I collagen deposition in the liver. Furthermore, it decreased the number of α-SMA positive stellate cells in the liver, and inhibited a decrease in the liver retinoid level[9)].

(2) Oral administration of Shosaikoto to a rat choline-deficient L-amino acid-defined (CDAA) diet- liver fibrosis model inhibited increases in liver hydroxyproline and serum hyaluronic acid, the liver tissue expression of type III procollagen α1 mRNA, and proliferation of activated stellate cells[10)].

5. Immunomodulatory effect

Oral administration of TJ-9 to mice enhanced phagocytic activity against Candida parapsilosis[11)].

6. Clearance of immune complex

Oral administration of Shosaikoto to B/W F_1 mice improved the impaired immune complex clearance from the blood induced by LPS[12)].

7. Protective effect against gastric mucosal lesions

Oral administration of Shosaikoto to rats inhibited gastric mucosal lesions induced by ethanol or water-immersion stress[13)].

8. Action mechanism

Shosaikoto shows pharmacological effects via the following actions:

(1) Promotion of liver regeneration

A diet containing Shosaikoto was given to rat model of dimethylnitrosamine (DMN)-induced hepatopathy after partial hepatectomy. It increased the HGF level, and decreased the TGF-β level in liver[14)].

(2) Inhibition of liver fibrosis

1) In rat liver stellate cells, Shosaikoto inhibited proliferation and transformation to myofibroblast-like cells, and suppressed type I/III procollagen mRNA expression (*in vitro*) [15)].

2) A diet containing Shosaikoto was given to a rat fibrosis model induced by DMN- or PS. It inhibited an increase in the malondialdehyde level (*in vivo*). Furthermore, it inhibited oxidative stress in rat liver stellate cells and hepatocytes (*in vitro*) [9].

(3) Immunomodulatory effect

1) Activation of macrophages (Mϕ)
Oral administration of Shosaikoto to rats activated liver Mϕ[16].

2) Regulatory effect on cytokine production
- Shosaikoto increased the production of interleukin (IL)-1 in mouse liver sinusoid endothelial cells (*in vitro*) [17].
- In peripheral blood mononuclear cells derived from healthy individuals and chronic hepatitis patients, Shosaikoto increased the production of IL-1β, IL-6, GM-CSF, G-CSF, and TNF-α (*in vitro*) [18].
- In peripheral blood mononuclear cells derived from patients with chronic hepatitis C, Shosaikoto increased the production of IL-1, IL-10, TNF-α, and G-CSF, and inhibited the excessive production of IL-4 and IL-5 (*in vitro*) [19].
- In peripheral blood mononuclear cells derived from healthy individuals and HBe antigen-positive chronic active hepatitis patients, Shosaikoto increased the production of IFN-γ (*in vitro*) [18)20].

3) Activation of natural killer (NK) cells
In human peripheral blood mononuclear cells, Shosaikoto enhanced NK cell activity (*in vitro*) [21].

(4) Anti-allergic actions

1) In mouse peritoneal mast cells, Shosaikoto inhibited Compound 48/80-induced histamine release and degranulation (*in vitro*) [22].

2) Shosaikoto inhibited histamine release from basophils in the presence of house dust or anti-human IgE antibody (*in vitro*) [23].

(5) Inhibition of active oxygen accumulation
Oral administration of Shosaikoto to mice inhibited an endotoxin-induced reduction of superoxide dismutase and glutathione peroxidase activities[24].

PACKAGING

Bottles of 500 g
2.5 g × 42 packets
2.5 g × 189 packets

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