Revised: February 2018 (8th version)

Standard Commodity Classification No. of Japan
875200

■135■

- Kampo-preparation-

TSUMURA Inchinkoto 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)1150
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 Inchinkoto extract granules (hereafter TJ-135) contains 1.5 g of a dried extract of the following mixed crude drugs. JP Artemisia Capillaris Flower ..... 4.0 g JP Gardenia Fruit ……...…… 3.0 g JP Rhubarb ……..... 1.0 g (JP: The Japanese Pharmacopoeia)	
	Inactive ingredients	JP Magnesium Stearate JP Lactose Hydrate
Description	Dosage form	Granules
	Color	Light brown
	Smell	Characteristic smell
	Taste	Slightly astringent
	ID code	TSUMURA/135

INDICATIONS

TJ-135 is indicated for the relief of the following symptoms of those patients with a comparatively strong constitution and decreased urine volume who are somewhat likely to have constipation:

Jaundice, hepatic cirrhosis, nephrosis, urticaria, and stomatitis

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-135 should be administered with care in the following patients.)

(1) Patients with diarrhea or soft feces [These symptoms may be aggravated.]

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

(3) Patients with greatly declined constitution [Adverse reactions are likely to occur, and the symptoms may be aggravated.]

2. Important Precautions

(1) When TJ-135 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) Long-term administration of a gardenia fruit-containing preparation (usually 5 years or longer) may cause mesenteric phlebosclerosis accompanied by discoloration, edema, erosion, ulceration, and stenosis of the colon. Periodical examinations such as CT scanning and colonoscopy would be desirable in cases of its long-term administration.

(3) When TJ-135 is coadministered with other Kampo-preparations (Japanese traditional herbal medicines), etc., attention should be paid to the duplication of the contained crude drugs. Special caution should be exercised when TJ-135 is coadministered with preparations containing Rhubarb.

(4) Since there is an individual difference in the cathartic action of Rhubarb, caution should be exercised concerning the dosage and administration.

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-135 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) 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 care-

fully monitored for abnormal findings. Administration should be discontinued and appropriate therapeutic measures should be taken, if abnormalities are observed.

2) **Mesenteric phlebosclerosis**: Mesenteric phlebosclerosis may occur with long-term administration. If symptoms such as abdominal pain, diarrhea, constipation, and abdominal distension repeatedly occur, or if the patient tests positive for fecal occult blood, administration should be discontinued. At the same time, tests such as CT and colonoscopy should be performed, and appropriate measures should be taken. Intestinal resection has been reported in some cases.

(2) Other adverse reactions

	Incidence unknown
Gastrointestinal	Anorexia, Epigastric distress, Abdominal pain, Diarrhea, etc.

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

(1) Use of TJ-135 in pregnant women, women who may possibly be pregnant is not recommended. [The uterotonic action and congestive action on the intrapelvic organs of Rhubarb contained in TJ-135 may cause premature birth or abortion.]

(2) TJ-135 should be administered with care in nursing mothers. [Anthraquinone derivatives in Rhubarb contained in TJ-135 may be excreted in breast milk and induce diarrhea in nursing infants.]

6. Pediatric Use

The safety of TJ-135 in children has not been established. [Insufficient clinical data.]

PHARMACOLOGY

1. Actions on hepatopathy

(1) Oral pretreatment with Inchinkoto in mice with Fas-induced fatal hepatic apoptosis prolonged survival, and inhibited increases in the serum levels of AST (GOT) and ALT (GPT). Histologically, it inhibited an increase in the number of apoptotic hepatocytes and the deterioration of hepatocellular disorder[1].

(2) Oral pretreatment with Inchinkoto in mouse D-galactosamine- or LPS-induced hepatopathy models inhibited an increase in the serum ALT (GPT) level. Histologically, it reduced hepatocellular necrosis and inflammatory cell infiltration[2].

(3) Seven-week co-oral administration of Inchinkoto with LCA-added diet inhibited the elevations of serum AST(GOT), ALT(GPT), total cholesterol, total bile acid in rats.[3].

(4) A diet containing Inchinkoto was given to a rat carbon tetrachloride-induced hepatopathy model. It inhibited an increase in the serum Al-P level[4].

(5) Oral pretreatment with Inchinkoto in a mouse concanavalin A-induced hepatopathy model inhibited increases in the serum levels of AST (GOT), ALT (GPT), and LDH. Histologically, it reduced inflammatory cell infiltration and hepatocellular necrosis[5].

2. Inhibition of liver fibrosis

A diet containing Inchinkoto was given to a rat choline-deficient L-amino acid-defined (CDAA) diet-related liver fibrosis model. It inhibited increases in the liver hydroxyproline and serum hyaluronic acid levels, liver tissue extracellular matrix (type III procollagen mRNA) expression, and the proliferation of activated hepatic stallate cells. Histologically, it reduced fibrosis[6].

3. Cholagogic actions

Oral treatment with Inchinkoto to rats inhibited an ethynyl estradiol-induced decrease in baseline bile secretion[3].

4. Action mechanism

Inchinkoto exhibits pharmacological effects via the following actions:

(1) Actions on hepatopathy

In cultured rat hepatocytes, Inchinkoto inhibited TGF-β1 addition-related apoptosis (*in vitro*) [7].

(2) Inhibition of liver fibrosis

In LI90 human hepatic stellate cells, Inchinkoto inhibited MAP kinase (ERK, JNK) activity, type III procollagen mRNA expression, and the concentration of PIIINP (*in vitro*) [6].

(3) Actions on cytokines

Oral pretreatment with Inchinkoto in a mouse concanavalin A-induced hepatopathy model inhibited the serum levels of interleukin (IL)-2, IL-12, and interferon (IFN)- γ after 2 or 8 hours, and increased the serum level of IL-10 (*in vivo*). In splenocytes isolated from this model, Inchinkoto reduced IL-12 and IFN- γ production, and increased IL-10 production (*in vitro*) [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) Yamamoto, M. et al. Gastroenterology. 2000, 118(2), p.380.
2) Mase, A. et al. J. Traditional Med. 1998, 15(5), p.392.
3) Hasegawa, M. et al. J. Traditional Med. 1996, 13(4), p.314.
4) Kameyama, S. et al. Prog. Med. 1998, 18(4), p.889.
5) Yamashiki, M. et al. Clin. Sci. 2000, 99, p.421.
6) Sakaida, I. et al. J. Hepatol. 2003, 37, p.762.
7) Yamamoto, M. et al. Hepatology. 1996, 23(3), p.552.

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