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Standard Commodity Classification No. of Japan
875200

■14■

- Kampo-preparation-

TSUMURA Hangeshashinto 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)3257
Date of listing in the NHI reimbursement price	October 1986
Date of initial marketing in Japan	October 1986

CONTRAINDICATIONS (TSUMURA Hangeshashinto extract granules (hereafter TJ-14) is contraindicated in the following patients.)

1. Patients with aldosteronism
2. Patients with myopathy
3. Patients with hypokalemia

[1-3: These diseases or symptoms may be aggravated.]

DESCRIPTION

Composition	7.5 g of TJ-14 contains 4.5 g of a dried extract of the following mixed crude drugs. JP Pinellia Tuber ..... 5.0 g JP Scutellaria Root ..... 2.5 g JP Processed Ginger ..... 2.5 g JP Glycyrrhiza …..... 2.5 g JP Jujube ..... 2.5 g JP Ginseng ..... 2.5 g JP Coptis Rhizome ……..... 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
	Odor	Characteristic smell
	Taste	Slightly sweet and pungent
	ID code	TSUMURA/14

INDICATIONS

TJ-14 is indicated for the relief of the following symptoms of those patients with blocked feeling in the stomach pit and occasional nausea, vomiting, anorexia, borborygmus, and a tendency to loose stools or diarrhea:

Acute or chronic gastrointestinal catarrh, fermentative diarrhea, dyspepsia, gastroptosis, nervous gastritis, gastrasthenia, hang-over, belching, heartburn, stomatitis, and neurosis

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-14 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-14 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-14 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. Drug Interactions

Precautions for coadministration (TJ-14 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.

3. Adverse Reactions

TJ-14 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-14 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-14 immediately and to make contact with the physician in the event of fever, cough, dyspnea, etc.

2) **Pseudoaldosteronism**: 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**: Myopathy may occur as a result of hypokalemia. The patient should be carefully monitored, and if any abnormality such as weakness, convulsion/paralysis of limbs, etc. are observed, administration should be discontinued and appropriate measures such as administration of potassium preparations should be taken.

4) **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, Urticaria, 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-14 in pregnant women has not been established. Therefore, TJ-14 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-14 in children has not been established. [Insufficient clinical data.]

7. Precaution Concerning Use

When taking TJ-14 for stomatitis, TJ-14 can be slowly swallowed after keeping it within the mouth.

PHARMACOLOGY

1. Promotion of gastric emptying

(1)Administration of TJ-14 for 2 weeks to chronic gastritis patients(n=8) with upper abdominal symptoms and delayed gastric emptying promoted gastric emptying (acetaminophen method) [1].

(2)Oral administration of Hangeshashinto to rats promoted gastric emptying. In addition, oral pre-administration inhibited the reduction of gastric emptying induced by barium chloride [2].

2. Actions on gastric mucosal disorder

Oral pre-administration of Hangeshashinto to rats inhibited ethanol-induced hemorrhagic lesions in the stomach[3].

3. Antiemetic actions

Oral pre-administration of Hangeshashinto to ferrets inhibited apomorphine-induced vomiting[2].

4. Antidiarrheal actions

(1) Oral pre-administration of Hangeshashinto to mice relieved castor oil-induced diarrhea[4].

(2) Oral pre-administration of Hangeshashinto to rats relieved irinotecan hydrochloride-induced diarrhea, inhibited weight loss, inhibited degeneration/necrosis of villi and crypt cells in the ileum and descending colon, and increased the number of goblet cells[5].

5. Action mechanism

Hangeshashinto exhibits pharmacological effects via the following actions:

(1) Protection of the gastric mucosa

Oral administration of Hangeshashinto to rats inhibited taurocholic acid-induced decreases in the gastric mucosa levels of phospholipids, a reduction of gastric mucosal potential differences, and gastric mucosa back diffusion of H^+ [6], and inhibited an ethanol-induced decrease in the volume of mucus in the superficial gastric mucosa and the deep mucosa of the gastric body[3].

(2) Anti-inflammatory actions

- Oral pre-administration of Hangeshashinto to rats inhibited an irinotecan hydrochloride-induced[5] or cholera toxin- induced[7] increase in the large intestinal mucosa level of prostaglandin E_2.
- Oral administration of Hangeshashinto to rats increased the plasma level of corticosterone (*in vivo*), and inhibited cyclooxygenase-2 activity (*in vitro*) [8].
- Hangeshashinto inhibited the productions of prostaglandin (PG) E2, PGD2 and PGF2a in human oral keratinocytes induced by IL-1b stimulation (in vitro)9). Hangeshashinto also inhibited PEG2 metabolic activity in HOK expressing highly activated COX-2 (in vitro)[9].
- In a human mast cell strain (HMC-1), Hangeshashinto inhibited the PMA/A23187 stimulation-related production of interleukin (IL)-6 (*in vitro*). In addition, Oral pre-administration of Hangeshashinto to a mouse carrageenin-induced pleuritis model inhibited the production of IL-6[10].

(3) Enhancement of large intestinal water absorption

Oral administration of Hangeshashinto to rats enhanced water absorption in the large intestine[11].

Oral pre-administration of Hangeshashinto inhibited the irinotecan hydrochloride-induced reduction of water absorption in the large intestine[5].

(4) The gastrointestinal motility inhibitory effect

Hangeshashinto inhibited the spontaneous contraction of circular smooth muscle from the rat distal colon. This inhibitory effect was partially cancelled by treatment with a non-selective NO synthase inhibitor (L-NNA) or guanylate cyclase inhibitor (ODQ). In addition, Hangeshashinto inhibited the cholinergic nerve-mediated contractile response caused by transmural nerve stimulation (*in vitro*)[12].

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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12) Kito,Y. et al. J. Physiol. Gastrointest. Liver Physiol. 2012, 303(9), p.G1059.

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