Revised: March 2022

TS-ONE® Capsule 20
TS-ONE® Capsule 25
< Tegafur, Gimeracil and Oteracil potassium Capsule >

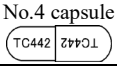
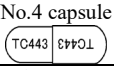
WARNINGS

1. **Cancer chemotherapy with TS-ONE® should be administered only to patients for whom treatment with TS-ONE® has been judged appropriate, under the supervision of experienced physicians who are familiar with cancer chemotherapy and who are based in medical institutions with adequate emergency facilities. A patient who will receive chemotherapy that includes TS-ONE® should be carefully selected with reference to the package insert of each concomitant drug. TS-ONE® should only be administered after the effectiveness and risks have been explained, and informed consent has been given by the patient or by the patient's guardian before chemotherapy is started.**
2. **Since the dose-limiting toxicity (DLT) of TS-ONE® is bone marrow depression (See Adverse Events), in which it is different from conventional oral fluorouracil-group drugs, it is necessary to be alert for changes in the laboratory data. Laboratory tests should be performed frequently.**
3. **Inasmuch as there may occur severe hepatic disorders, such as fulminant hepatitis, the patient's hepatic functions should be monitored closely by periodic hepatic function tests to detect hepatic disorder early. Close monitoring is necessary to detect possible malaise accompanied by anorexia, which is thought to be a sign or subjective symptom of hepatic disorder. If jaundice (yellow ocular coloring) appears, TS-ONE® should be discontinued immediately, and appropriate measures should be taken.**
4. **TS-ONE® should not be combined with other fluoropyrimidine-group anti-cancer drugs, combination therapies with them, or the antifungal agent flucytosine because there is a possibility that combination with these drugs may cause adverse reactions such as serious blood dyscrasia (See Drug Interactions).**
5. **Read this package insert carefully before using TS-ONE®. In addition, TS-ONE® should be administered in strict conformity with the Dosage and Administration.**

CONTRAINDICATIONS
(TS-ONE® is contraindicated in the following patients.)

1. Patients with a history of severe hypersensitivity to the ingredients of TS-ONE®
2. Patients with severe bone marrow depression [Bone marrow depression may be aggravated.]
3. Patients with severe renal disorder [The urinary excretion of gimeracil, a catabolic enzyme inhibitor of fluorouracil (5-FU), is markedly decreased, thereby the blood concentration of 5-FU is increased. These suggest that adverse reactions such as bone marrow depression may be enhanced (See Pharmacokinetics).]
4. Patients with severe hepatic disorder [Hepatic disorder may be aggravated.]
5. Patients receiving treatment with other fluoropyrimidine-group anti-cancer drugs including combination therapies with them (See Drug Interactions)
6. Patients receiving treatment with flucytosine (See Drug Interactions)
7. Pregnant women or women suspected of being pregnant (See Use during Pregnancy, Delivery or Lactation)

DESCRIPTION

Brand name	TS-ONE® Capsule 20	TS-ONE® Capsule 25
Ingredient/ contents	Tegafur 20 mg, Gimeracil 5.8 mg and Oteracil potassium 19.6 mg per capsule	Tegafur 25 mg, Gimeracil 7.25 mg and Oteracil potassium 24.5 mg per capsule
Inactive ingredients	Lactose hydrate, Magnesium stearate, Gelatin, Sodium lauryl sulfate, Titanium oxide	Lactose hydrate, Magnesium stearate, Gelatin, Sodium lauryl sulfate, Titanium oxide, FD&C Yellow No.6
Description	TS-ONE® is an opaque, hard-shell capsule with a white cap and white body containing white powder and granules.	TS-ONE® is an opaque, hard-shell capsule with an orange cap and white body containing white powder and granules.
Appearance	No.4 capsule 	No.4 capsule 
Size and weight	Total length: 14.5 mm Long diameter (cap): 5.2 mm Short diameter (body): 5.0 mm Weight: approx. 179 mg	Total length: 14.5 mm Long diameter (cap): 5.2 mm Short diameter (body): 5.0 mm Weight: approx. 214 mg
Identification code	TC442	TC443

INDICATIONS

- Post-operative adjuvant chemotherapy for locally advanced (stage II (excluding T1), IIIA or IIIB) gastric cancer
- For the treatment of locally advanced or metastatic adenocarcinoma of the pancreas
- For the treatment of locally advanced or metastatic non-small cell lung cancer in patients who have been previously treated with platinum-based chemotherapy

DOSAGE AND ADMINISTRATION

The standard doses in Table 1 below are the recommended initial dose for adults according to body surface area. TS-ONE® should be administered twice daily, after breakfast and after the evening meal, for 28 consecutive days, followed by a 14-day rest. This is regarded as one course of the regimen.

Table 1: Standard dose calculations by body surface area (BSA) (m^2)

Body surface area (m^2)	Initial dose (tegafur equivalent)
< 1.25	40 mg twice daily
1.25 - < 1.5	50 mg twice daily
≥ 1.5	60 mg twice daily

The initial dose can be decreased according to the patient's tolerance to the medication. The reduction of dose may be done in 10 mg intervals, with a lower limit of 40 mg.

Precautions on Dosage and Administration

1. When the dose is decreased according to the patient's condition, the following standard doses should be referenced.

Initial dose	Decrease
40 mg twice daily	drug rest
50 mg twice daily	40 mg twice daily → drug rest
60 mg twice daily	50 mg twice daily → 40 mg twice daily → drug rest

2. If a drug rest period therapeutically needs to be shortened, it should be implemented after confirming that no drug-induced abnormalities in laboratory findings (hematological tests, liver and renal function tests) and no gastrointestinal symptoms occur, i.e., the drug is not problematic in terms of safety. A minimum drug rest period of 7 days must be provided.

3. To avoid serious adverse reactions such as bone marrow depression and fulminant hepatitis, the patient's condition should be monitored thoroughly by performing laboratory tests (hematological tests, liver and renal function tests) before the start of each course and at least once every 2 weeks during dosing. If any abnormal findings are observed, appropriate measures should be taken, such as prolongation of the drug rest period, dosage reduction according to the above-mentioned standard doses, or discontinuing administration of TS-ONE®.

4. Since basic investigations (rats) have revealed that the bioavailability of oteracil potassium changes when the drug is administered in the fasting state, it is speculated that phosphorylation of fluorouracil is inhibited and that its antitumor effect is reduced. TS-ONE® should be administered after meals.

5. The recommended treatment course for post-operative adjuvant chemotherapy for gastric cancer is one year after surgery. Treatment with TS-ONE® beyond one year after surgery has not been studied.

PRECAUTIONS

1. Careful Administration (TS-ONE® should be administered with care in the following patients.)

(1) Patients with bone marrow depression [Bone marrow depression may be aggravated.]

(2) Patients with renal disorder [The urinary excretion of gimeracil, a catabolic enzyme inhibitor of fluorouracil (5-FU), is markedly decreased, thereby the blood concentration of 5-FU is increased. These suggest that adverse reactions such as bone marrow depression may be enhanced (See Pharmacokinetics).]

(3) Patients with hepatic disorder [Hepatic disorder may be aggravated.]

(4) Patients having infectious disease [Infectious disease may be aggravated as a result of bone marrow depression.]

(5) Patients with abnormal glucose tolerance [Abnormal glucose tolerance may be aggravated.]

(6) Patients with a current or previous history of interstitial pneumonia [Interstitial pneumonia may be aggravated or may develop.]

(7) Patients with a current or previous history of heart disease [Symptoms may be aggravated.]

(8) Patients with gastrointestinal ulcer or hemorrhage [Symptoms may be aggravated.]

(9) Elderly patients (See Use in the Elderly)

(10) Patients with varicella [Fatal systemic damage may occur.]

2. Important Precautions

(1) A minimum washout period of 7 days must be provided when other fluoropyrimidine-group anti-cancer drugs or the antifungal agent flucytosine are used after withdrawal of TS-ONE® (See Drug Interactions).

(2) An appropriate washout period must be provided when TS-ONE® is used after withdrawal of other fluoropyrimidine-group anti-cancer drugs or the antifungal agent flucytosine in consideration of the influence of these prior agents (See Drug Interactions).

(3) Since patients who have died of septic shock or disseminated intravascular coagulation due to serious infectious disease (septicemia) caused by bone marrow depression have been reported, care should be taken to avoid the appearance or aggravation of infection or bleeding tendency.

(4) Administration to patients with reproductive potential should be performed with consideration of potential gonadic effects.

(5) TS-ONE® may cause or aggravate interstitial pneumonia with a possible fatal outcome. Therefore, patients must be examined for the presence of interstitial pneumonia before receiving TS-ONE®, and be properly monitored for respiratory status and the onset of symptoms such as cough and fever while receiving TS-ONE®. Monitoring should include chest X-ray examination. If the onset or progression of interstitial pneumonia is observed, TS-ONE® should be discontinued, and appropriate measures should be taken. Pulmonary disorders including interstitial pneumonia are more likely to occur in patients with non-small cell lung cancer than in patients with other cancers (See Adverse Events).

(6) Since administration of TS-ONE® in hepatitis B virus carriers, HBs antigen negative and HBc antibody positive patients, or HBs antigen negative and HBs antibody positive patients may result in reactivation of hepatitis B, the status of previous exposure to hepatitis infection should be confirmed, and appropriate measures should be taken before administration. Following administration of TS-ONE®, it is necessary to pay attention to signs or symptoms of the reactivation of hepatitis B, and follow-up monitoring for hepatic function tests or viral markers are recommended.

(7) If dehydration secondary to severe enteritis occurs, take proper measures such as fluid replacement. (See Clinically significant adverse reactions.)

3. Drug Interactions

(1) Contraindications for coadministration (TS-ONE® should not be coadministered with the following drugs.)

Drugs	Signs, Symptoms and Treatment	Mechanism and Risk Factors
Fluoropyrimidine-group anti-cancer drugs fluorouracil tegafur/uracil tegafur doxifluridine capecitabine carmofur	Serious blood dyscrasia and gastrointestinal disorder such as diarrhea and stomatitis may occur early when coadministered with these agents (therapies). These agents should not be administered within at least 7 days after withdrawal of TS-ONE®. Additionally, when TS-ONE® is used after withdrawal of these agents, an appropriate washout period must be provided in consideration of the influence of these agents.	The gimeracil contained in TS-ONE® inhibits the catabolism of the combined fluorouracil or the combined fluoropyrimidine produced fluorouracil, thereby blood concentration of fluorouracil is markedly increased (See Pharmacokinetics).
Folinate plus Tegafur-Uracil combination therapy Levofolinate and fluorouracil combination therapy		
Fluoropyrimidine-group antifungal agent flucytosine		

(2) Precautions for coadministration (TS-ONE® should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms and Treatment	Mechanism and Risk Factors
Phenytoin	Since phenytoin intoxication (nausea, vomiting, nystagmus and movement disorder) may develop, the patient's condition should be monitored closely. If any abnormal findings are observed, appropriate measures should be taken, such as discontinuation of treatment.	Phenytoin metabolism is inhibited by tegafur, and blood concentration of phenytoin is increased.
Warfarin potassium	Since the effect of warfarin potassium may be enhanced, caution should be exercised with respect to fluctuation of coagulating ability.	The mechanism is unknown.
Other anti-cancer drugs or radiation therapy	Since adverse reactions such as blood dyscrasias and gastrointestinal disorder may be aggravated, the patient's condition should be monitored closely. If any abnormal findings are observed, appropriate measures should be taken, such as dose reduction or discontinuation of treatment.	Adverse reactions may be aggravated mutually.

4. Adverse Events

Table 2 shows the frequency of adverse events occurring in ≥5% of patients reported in the randomized study of post-operative adjuvant chemotherapy with TS-ONE® for gastric cancer. The data are shown for 517 evaluable patients in the TS-ONE® group and 526 evaluable patients in surgery alone group for adverse events. Frequency of all adverse events was 100% in the TS-ONE® group and 93.3% in the surgery alone group respectively.

Table 2: Frequency of adverse events occurring in ≥5% of patients in the randomized study of post-operative adjuvant chemotherapy with TS-ONE® for gastric cancer

	TS-ONE® group (517 patients)		Surgery alone group (526 patients)	
Adverse events	Frequency of all grades	Frequency of CTC Grade 3 or 4 #1	Frequency of all grades	Frequency of CTC Grade 3 or 4 #1
Leukopenia	59.4%	1.2%	24.1%	0.4%
Decreased hemoglobin	90.1%	1.2%	72.1%	0.8%
Thrombocytopenia	25.9%	0.2%	6.8%	0.4%
Neutrophil count decreased	12.0%	6.0%	0.4%	0.0%
Increased AST (GOT)	44.9%	1.7%	42.8%	3.4%
Increased ALT (GPT)	43.3%	1.2%	43.0%	3.2%
Increased bilirubin	46.0%	1.5%	11.2%	1.1%
Increased creatinine	5.2%	0.0%	5.3%	0.4%
Glycosuria	7.0%	1.2%	4.2%	1.1%
Stomatitis	32.1%	0.2%	3.4%	0.0%
Anorexia	61.1%	6.0%	15.8%	2.1%
Nausea	39.1%	3.7%	10.1%	1.1%
Vomiting	22.6%	1.2%	11.0%	1.9%
Diarrhea	59.8%	3.1%	18.4%	0.2%
Abdominal pain	9.3%	1.2%	5.7%	0.2%
Constipation	9.3%	0.6%	6.3%	0.4%
Rash	32.5%	1.0%	2.3%	0.4%
Pigmentation	46.6%	0.0%	0.4%	0.0%
Lacrimation	8.3%	0.0%	0.0%	0.0%
Taste abnormality	13.2%	0.0%	1.0%	0.0%
Dizziness	9.1%	0.4%	2.3%	0.2%
Weight decreased	9.5%	1.5%	8.2%	1.1%
Pyrexia	7.4%	0.4%	1.9%	0.0%
Nasopharyngitis	9.5%	0.0%	2.1%	0.0%
Fatigue	59.0%	0.6%	18.1%	0.6%

#1: Grades of the adverse events were defined according to NCI-CTC version 2.0.

Table 3 shows the frequency of adverse events occurring in >10% of patients reported in the randomized phase III study of gemcitabine versus TS-ONE® versus TS-ONE® plus gemcitabine in locally advanced or metastatic adenocarcinoma of the pancreas. The data is shown for 272 evaluable patients in the TS-ONE® group. The 3 most frequently seen adverse events in the TS-ONE® group were decreased hemoglobin, anorexia and nausea.

Table 3: Frequency of adverse events occurring in >10% of patients in the randomized phase III study of gemcitabine versus TS-ONE® versus TS-ONE® plus gemcitabine in locally advanced or metastatic adenocarcinoma of the pancreas

	Gemcitabine group (273 patients)		TS-ONE® group (272 patients)		TS-ONE® plus gemcitabine group (267 patients)	
Adverse events	Frequency of all grades	Frequency of CTC Grade 3 or higher #1	Frequency of all grades	Frequency of CTC Grade 3 or higher #1	Frequency of all grades	Frequency of CTC Grade 3 or higher #1
Leukopenia	75.8%	18.7%	42.6%	3.7%	87.6%	37.8%
Decreased hemoglobin	80.2%	14.3%	68.0%	9.6%	85.4%	17.2%
Thrombocytopenia	78.4%	11.0%	46.3%	1.5%	81.3%	17.2%
Neutrophil count decreased	68.1%	41.0%	33.5%	8.8%	82.8%	62.2%
Increased ALT (GPT)	58.2%	15.0%	42.3%	5.9%	59.6%	10.9%
Increased AST (GOT)	59.7%	15.0%	48.5%	7.7%	61.0%	12.0%
Increased bilirubin	26.0%	9.5%	53.3%	14.3%	39.0%	8.6%
Increased creatinine	17.9%	0.7%	19.1%	1.1%	16.1%	0.4%
Stomatitis	13.9%	0.0%	25.0%	0.7%	33.7%	2.2%
Anorexia	57.9%	7.3%	66.2%	11.4%	65.2%	9.4%
Nausea	42.5%	1.8%	54.0%	1.8%	55.1%	4.5%
Vomiting	27.1%	0.7%	31.6%	1.5%	33.7%	4.5%
Diarrhea	20.9%	1.1%	38.6%	5.5%	37.5%	4.5%
Alopecia	10.6%	0.0%	2.9%	0.0%	18.0%	0.0%
Rash	27.8%	0.7%	18.8%	0.7%	41.2%	4.1%
Pigmentation	2.9%	0.0%	34.2%	0.0%	28.1%	0.0%
Fatigue	45.1%	3.7%	52.9%	6.6%	65.5%	4.9%

#1: Grades of the adverse events were defined according to CTCAE version 3.0.

Table 4 shows the frequency of adverse events occurring in ≥10% of patients reported in the randomized phase III study of docetaxel versus TS-ONE® in locally advanced or metastatic non-small cell lung cancer patients who have been previously treated with platinum-based chemotherapy. The data is shown for 560 evaluable

patients in the docetaxel group and 569 evaluable patients in the TS-ONE® group. The most common adverse events observed at a higher incidence in the TS-ONE® group than in the docetaxel group (≥10% difference) were anorexia, diarrhea, skin hyperpigmentation and weight decreased.

Table 4: Frequency of adverse events occurring in ≥10% of patients in the randomized phase III study of docetaxel versus TS-ONE® in locally advanced or metastatic non-small cell lung cancer patients previously treated with platinum-based chemotherapy

	Docetaxel group (560 patients)		TS-ONE® group (569 patients)	
Adverse events	Frequency of all grades	Frequency of CTC Grade 3 or higher #1	Frequency of all grades	Frequency of CTC Grade 3 or higher #1
Leukopenia	44.1%	29.3%	9.8%	1.2%
Anemia	10.5%	1.8%	14.9%	3.7%
Thrombocytopenia	2.3%	0.2%	11.2%	1.4%
Neutrophil count decreased	54.8%	47.7%	15.1%	5.4%
Febrile neutropenia	13.6%	13.6%	0.9%	0.9%
Stomatitis	14.5%	0.9%	23.9%	2.5%
Anorexia	37.9%	2.7%	52.7%	6.9%
Nausea	27.9%	1.4%	37.3%	0.9%
Vomiting	12.5%	0.7%	19.9%	1.6%
Diarrhea	18.2%	1.1%	37.4%	6.3%
Constipation	21.1%	0.2%	17.6%	0.5%
Alopecia	46.8%	0.0%	1.9%	0.0%
Rash maculo-papular	8.6%	0.2%	10.9%	0.9%
Pigmentation	2.1%	0.0%	31.5%	0.0%
Peripheral sensory neuropathy	16.6%	0.7%	4.7%	0.2%
Weight decreased	5.5%	0.0%	16.2%	0.5%
Pyrexia	13.4%	0.0%	13.2%	0.2%
Cough	11.3%	0.4%	10.2%	0.2%
Dyspnea	10.0%	1.8%	10.0%	1.2%
Fatigue	20.2%	0.9%	18.3%	1.4%
Malaise	24.1%	0.9%	19.5%	0.2%
Edema peripheral	17.0%	0.9%	3.0%	0.0%

#1: Grades of the adverse events were defined according to CTCAE version 4.0.

A post-marketing drug use investigation in patients with non-small cell lung cancer in Japan reported incidence rates of 0.7% (11/1669) for interstitial pneumonia and 0.7% (12/1669) for other pulmonary disorders including radiation pneumonitis, dyspnea, and respiratory failure.

(1) Clinically significant adverse reactions

The overall safety profile of TS-ONE® is based on data from 751 patients treated with TS-ONE® monotherapy in clinical studies for advanced or recurrent cancer and from post-marketing experiences in multiple indications in Japan. The following adverse reaction frequencies were calculated from data for these clinical studies.

1) Bone marrow depression and hemolytic anemia: Since severe bone marrow depression such as pancytopenia, agranulocytosis (symptoms: fever, sore throat and malaise), leukopenia (46.7%), anemia (40.6%) and thrombocytopenia (15.7%) and hemolytic anemia (incidence unknown) may occur, the patient's condition should be monitored closely. If any abnormal findings are observed, appropriate measures should be taken, such as discontinuing administration of TS-ONE®.

2) Disseminated intravascular coagulation (DIC): Since disseminated intravascular coagulation (DIC) (0.4%) may occur, the patient's condition should be monitored closely. If any abnormal findings are observed on blood tests including those for platelet count, serum FDP level and plasma fibrinogen level, TS-ONE® administration should be discontinued, and appropriate measures should be taken.

3) Severe hepatic disorder such as fulminant hepatitis: Since severe hepatic disorders such as fulminant hepatitis (including reactivation of hepatitis B virus) (incidence unknown) may occur, the patient's condition should be monitored closely by periodic hepatic function tests. If any abnormal findings are observed, appropriate measures should be taken, such as discontinuing administration of TS-ONE® (See WARNINGS).

4) Dehydration: Since severe diarrhea may occur, and may lead to dehydration (incidence unknown), the patient's condition should be monitored closely. If any such symptoms are observed, TS-ONE® administration should be discontinued, and appropriate measures should be taken, such as fluid replacement.

5) Severe enteritis (0.5%): Since hemorrhagic enterocolitis, ischaemic enterocolitis and necrotizing enterocolitis may occur, the patient's condition should be monitored closely. If severe symptoms such as abdominal pain and diarrhea occur, TS-ONE® administration should be discontinued, and appropriate measures should be taken.

6) Interstitial pneumonia: Since interstitial pneumonia (0.3%) (early symptoms: cough, shortness of breath, dyspnea and fever) may occur, the patient's condition should be monitored closely. If any abnormal findings are observed, TS-ONE® administration should be discontinued, and appropriate measures should be taken, such as chest X-ray examination and treatment with corticosteroids.

7) Myocardial infarction, angina pectoris, arrhythmia and cardiac failure: Since myocardial infarction, angina pectoris, arrhythmia (including ventricular tachycardia) and cardiac failure (the incidences of these adverse reactions are unknown) may occur, the patient's condition should be monitored closely. If chest pain, syncope, palpitation, abnormal ECG or breathlessness are observed, TS-ONE® administration should be discontinued, and appropriate measures should be taken.

8) Severe stomatitis, gastrointestinal ulcer, gastrointestinal hemorrhage and gastrointestinal perforation: Since severe stomatitis (incidence unknown), gastrointestinal ulcer (0.5%), gastrointestinal hemorrhage (0.3%) and gastrointestinal perforation (incidence unknown) may occur, the patient's condition should be monitored closely. If any abnormal findings are observed, TS-ONE® administration should be discontinued and appropriate measures should be taken, such as examination by abdominal X-ray.

9) Acute kidney injury and nephrotic syndrome: Since severe renal disorder such as acute kidney injury and nephrotic syndrome (incidence unknown) may occur, the patient's condition should be monitored closely. If any abnormal findings are observed, TS-ONE® administration should be discontinued, and appropriate measures should be taken.

10) Toxic epidermal necrolysis (TEN) and muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome): Since toxic epidermal necrolysis and muco-cutaneo-ocular syndrome (incidence unknown) may occur, the patient's condition should be monitored closely. If any abnormal findings are observed, TS-ONE® administration should be discontinued, and appropriate measures should be taken.

11) Psychoneurologic disorders including leukoencephalopathy or other symptoms: Since leukoencephalopathy (major symptoms include consciousness disturbance, cerebellar ataxia, and

dementia-like symptoms), consciousness disturbance, disorientation, somnolence, hypomnesia, extrapyramidal symptoms, speech disorder, quadriplegia, gait disturbance, urinary incontinence, or sensory disturbance (the incidences of these adverse reactions are unknown) may occur, the patient's condition should be monitored closely, and if any such symptoms are observed, TS-ONE® administration should be discontinued.

12) Acute pancreatitis: Since acute pancreatitis (incidence unknown) may occur, the patient's condition should be monitored closely. If abdominal pain or increased serum amylase were observed, TS-ONE® administration should be discontinued, and appropriate measures should be taken.

13) Rhabdomyolysis: Since rhabdomyolysis (incidence unknown) marked by muscle pain, feeling of weakness, increased CK (CPK) and increased myoglobin in the blood or urine may occur, TS-ONE® administration should be discontinued, and appropriate measures should be taken. Also, care should be taken to avoid appearance of acute kidney injury due to rhabdomyolysis.

14) Anosmia: Since dysosmia (0.1%) may occur, and anosmia (incidence unknown) may develop, the patient's condition should be monitored closely. If any abnormal findings are observed, appropriate measures should be taken, such as discontinuing administration of TS-ONE®.

15) Lacrimal duct obstruction: Lacrimal duct obstruction (incidence unknown) may occur, and some patients have been reported to undergo surgical procedures. If any symptoms such as lacrimation are observed, appropriate measures should be taken, such as ophthalmic examination.

(2) Clinically significant adverse reactions (similar drugs)

Since the following adverse reactions have been reported to be caused by tegafur, if any abnormal findings are observed, appropriate measures should be taken, such as discontinuing administration of TS-ONE®.

Hepatic cirrhosis: prolonged prothrombin time, decreased albumin and decreased cholinesterase

(3) Other adverse reactions

Since the following adverse reactions may occur, if any abnormal findings are observed, appropriate measures should be taken, such as dose reduction or discontinuing administration of TS-ONE®. If hypersensitivity is observed, TS-ONE® administration should be discontinued, and appropriate measures should be taken.

Classification \ Frequency	≥ 5%	0.1% to < 5%	Incidence unknown[1)]
Hematologic	Leukopenia, neutropenia, thrombocytopenia, erythrocytopenia, decreased hemoglobin, decreased hematocrit value, lymphopenia	Bleeding tendency (subcutaneous bleeding spot, epistaxis, abnormal coagulation factor), eosinophilia, leukocytosis	
Hepatic	Increased AST (GOT), increased ALT (GPT), increased bilirubin, increased Al-P	Jaundice, urobilinogen urine positive	
Renal		Increased BUN, increased creatinine, proteinuria, hematuria	
Gastrointestinal	Anorexia, nausea/ vomiting, diarrhea, stomatitis, taste abnormality	Intestinal obstruction, ileus, abdominal pain, enlarged feeling of abdomen, epigastric pain, gastritis, borborygmus, white stool, constipation, angular stomatitis, cheilitis, glossitis, oral dryness	
Dermatologic	Pigmentation	Erythema, desquamation, flushing, blisters, hand & foot syndrome, skin ulcer, dermatitis, alopecia, nail abnormality, paronychia, herpes simplex, skin dry/roughness	Photo-sensitivity, DLE-like eruption
Hypersensitivity	Rash	Itching	
Psycho-neurologic	General malaise	Numbness, headache, feeling of dull headache, dizziness	Lightheaded feeling, neuropathy peripheral
Cardiovascular		Hypotension, hypertension, abnormal ECG, Raynaud's syndrome	Palpitation
Ophthalmic		Lacrimation, conjunctivitis, keratitis, corneal erosion, eye pain, visual acuity reduced, dry eye	Corneal ulcer, corneal opacity, limbal stem cell deficiency
Others	Increased LDH, decreased total protein, decreased albumin	Fever, general hot feeling, rhinitis, pharyngitis, sputum, glycosuria, increased blood sugar level, edema, myalgia, increased CK (CPK), arthralgia, electrolyte abnormality (increased serum sodium, decreased serum sodium, increased serum potassium, decreased serum potassium, increased serum calcium, decreased serum calcium, increased serum chloride, decreased serum chloride), weight loss	Increased serum amylase level

The incidence was calculated from the clinical study results of TS-ONE® monotherapy conducted before approval.

1) Frequency of side effects reported only by spontaneous reports was indicated as incidence unknown.

In patients who were administered TS-ONE® in the randomized study of post-operative adjuvant chemotherapy for gastric cancer, frequency of lacrimation (7.2%) was higher than in the studies for treatment of advanced or recurrent cancer.

(4) Other adverse reactions (similar drugs)

Since the following adverse reactions have been reported to be caused by tegafur, if any abnormal findings are observed, appropriate measures should be taken, such as dose reduction or discontinuing administration of TS-ONE®.

Fatty liver, difficulty in swallowing, tinnitus, excitement, increased serum uric acid, gynecomastia

5. Use in the Elderly

Since elderly patients often have decreased physiological functions, TS-ONE® should be administered with care.

6. Use during Pregnancy, Delivery or Lactation

(1) TS-ONE® is contraindicated in patients who are or may be pregnant. [It has been reported that pregnant women treated with tegafur/uracil have been delivered of neonates with malformation.] Teratogenicity is also reported in animal experiments. [Consecutive oral administration of TS-ONE® (corresponding to 7 mg/kg and 1.5 mg/kg as tegafur) to pregnant rats and rabbits has been observed to have fetal visceral anomalies, skeletal anomalies and retarded ossification.]

(2) When TS-ONE® is administered to nursing mothers, breastfeeding should be discontinued. [There is no clinical data. Excretion to milk has been reported in animal (rats) experiments.]

7. Pediatric Use

The efficacy and safety of TS-ONE® in children and adolescents have not been established. Therefore, use in this patient population is not recommended.

8. Precautions concerning Use

Precaution in giving the drug to patients:
For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.]

9. Other Precautions

(1) It has been reported that acute leukemia (in some cases accompanied with preleukemic phase) or myelodysplastic syndrome (MDS) have occurred in patients treated with TS-ONE®.

(2) It has been reported that deficiency of dihydropyrimidine dehydrogenase (DPD), a catabolic enzyme of fluorouracil, exists in extremely rare patients, and if fluorouracil-group drugs are administered to such patients, serious adverse reactions (such as stomatitis, diarrhea, blood dyscrasia and neuropathy) may occur in the early stages of administration.

(3) Although the causality of TS-ONE® was unknown, it has been reported that cerebral infarction has occurred.

(4) It has been reported that a remarkable decrease in gastric pH may induce diarrhea, because oteracil potassium is labile to decompose in the gastric fluid under a hyperacid condition (in dogs) and its relief effect on the gastrointestinal toxicity is reduced when its composition ratio is decreased (in rats).

(5) Repeated administration of TS-ONE® to dogs has been reported to cause bulbar conjunctival and scleral pigmentation and nebula.

PHARMACOKINETICS

1. Pharmacokinetics

(1) Pharmacokinetic parameters obtained from the plasma concentrations of TS-ONE® administered to 12 cancer patients in a single oral dose of 32-40 mg/m^2 after a meal are shown in the table. The amount excreted in the urine within 72 hours after administration accounted for 52.8% of the gimeracil (CDHP), 7.8% of the tegafur (FT), 2.2% of the oteracil potassium (Oxo), 11.4% of the metabolite cyanuric acid (CA) and 7.4% of the fluorouracil (5-FU).

	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{(0\text{-}48h)}$ (ng·hr/mL)	$T_{1/2}$ (hr)
FT	1971.0±269.0	2.4±1.2	28216.9±7771.4	13.1±3.1
5-FU	128.5±41.5	3.5±1.7	723.9±272.7	1.9±0.4
CDHP	284.6±116.6	2.1±1.2	1372.2±573.7	3.0±0.5
Oxo	78.0±58.2	2.3±1.1	365.7±248.6	3.0±1.4
CA	117.9±184.4	3.4±1.0	892.0±1711.7	3.8±1.6

(n=12, mean ± S.D.)

When TS-ONE® was orally administered at a dose of 25-200 mg/body, the AUC and C_{max} of FT, CDHP, Oxo and 5-FU increased in a dose-dependent manner. When the plasma concentration of TS-ONE® was measured 1, 7, 14 and 28 days after administration of 32-40 mg/m^2 of TS-ONE® twice a day for 28 consecutive days, it rapidly reached a constant level. Endogenous uracil (Ura) rapidly decreased even after consecutive administration of TS-ONE®, and the CDHP-induced DPD inhibition was reversible, and no enhancing effect was observed.

(2) (Reference): TS-ONE®, alone or in combination with other fluoropyrimidine-group drugs, was orally administered to rats for 7 consecutive days, and the plasma concentration of 5-FU was measured 2 hours after the final dose. It was found to be 4.1, 8.1, 2.8, 5.7, 6.9 and 2.3 times higher when combined with 5-FU, FT, FT・Ura, carmofur, doxifluridine and flucytosine, respectively, than when administered alone. This suggests that the combined use of TS-ONE® and other fluoropyrimidine-group drugs may enhance adverse reactions.

(3) (Reference): When TS-ONE® was administered to a renal dysfunction rabbit, CDHP renal clearance was found to be decreased, and the blood concentration of 5-FU was markedly increased compared to control animal. These suggest that adverse reactions may be enhanced.

(4) Creatinine clearance value (Ccr estimate) was calculated from serum creatinine value, gender, age, and weight using the Cockcroft-Gault equation*) for the clinical study patients for whom pharmacokinetics were examined in detail. The AUCs of two patient groups with normal and slightly impaired renal function were tabulated by range of creatinine clearance value (Ccr estimate).

	$AUC_{(0\text{-}8hr)}$	
(Ccr estimate)	>80 mL/min	50-80 mL/min
FT	10060 ± 1842	11320 ± 2717
5-FU	541.2 ± 174.8	812.4 ± 244.9
CDHP	977.8 ± 327.9	1278.0 ± 306.6
Oxo	155.7 ± 97.5	458.2 ± 239.7

(n=17 (Ccr: >80 mL/min), n=11 (Ccr: 50-80 mL/min), mean ± S.D.)

In a Phase I TS-ONE® monotherapy study that investigated the

*) Cockcroft-Gault equation:

In men:

$$Ccr = \frac{(140 - Age) \times Weight\ (kg)}{72 \times Serum\ creatinine\ (mg/dL)}$$

In women:

$$Ccr = \frac{(140 - Age) \times Weight\ (kg)}{72 \times Serum\ creatinine\ (mg/dL)} \times 0.85$$

pharmacokinetics of its components and metabolites in patients with normal and impaired renal function, patients with mild renal impairment (CrCl 51 to 80 ml/min) receiving the same monotherapy dose of 30 mg/m^2 twice daily as patients with normal renal function (CrCl >80 ml/min) had a 70% increase in mean 5-FU $AUC_{0\text{-}inf}$ relative to that of the normal patients. Patients with moderate renal impairment (CrCl 30 to 50 ml/min) who received a reduced dose of 20 mg/m^2 twice daily showed no significant increase in mean 5-FU $AUC_{0\text{-}inf}$ relative to that of the normal group.

Following a reduced dose of TS-ONE® 20 mg/m^2 administered once daily to the severe renal impairment group (CrCl <30 ml/min), the single dose $AUC_{0\text{-}inf}$ and multiple dose $AUC_{0\text{-}\tau}$ values for 5-FU were approximately 2-fold higher in the severe renal impairment group compared to those observed in the normal renal function group receiving 30 mg/m^2 twice daily [Note: for normal renal function group, $AUC_{0\text{-}\tau} = AUC_{0\text{-}12}$; for severe renal impairment group, $AUC_{0\text{-}\tau} = AUC_{0\text{-}24}$]. Therefore, the daily exposure to 5-FU would be expected to be comparable in these groups, since the daily exposure in patients in the severe renal impairment group is based on the administration of TS-ONE® once a day, while the daily exposure to 5-FU in the patients with normal renal function is based on the administration of TS-ONE® twice daily.

Insufficient data are currently available to recommend dose modifications in patients with renal impairment. TS-ONE® should be administered with caution in such patients. There is insufficient data to recommend the use of TS-ONE® in patients with severe renal impairment. Unless the benefits clearly outweigh the risks, treatment with TS-ONE® is not recommended in patients with severe renal impairment due to possibly higher incidence of adverse events of the blood and lymphatic system and the possibility of unexpectedly higher exposure to 5-FU as a result of fluctuations in renal function in these patients. No data is available regarding TS-ONE® administration in patients with end stage renal disease requiring dialysis. Hence, TS-ONE® is contraindicated in such patients with severe renal disorder (See Contraindications).

(5) There were no significant differences in AUCs of 5-FU, tegafur, gimeracil, or oteracil after either single or multiple dose administration of TS-ONE® 30 mg/m^2 twice daily in patients with mild, moderate, or severe hepatic impairment compared to those with normal hepatic function. After single dose administration, there was a statistically significant decrease in 5-FU and gimeracil C_{max} for the severe hepatic impairment group relative to that of the normal group, but this difference was not observed after multiple dose administration.

2. Protein binding

The rates of protein binding of each component and 5-FU in human serum were 49-56% for FT, 32-33% for CDHP, 7-10% for Oxo and 17-20% for 5-FU (*in vitro*).

3. Metabolic enzyme

It has been reported that CYP2A6 is the major cytochrome P450 isoenzymes in human liver microsomes involved in the metabolic transformation of FT to 5-FU (*in vitro*).

CLINICAL STUDIES

1. Randomized phase III study of post-operative adjuvant chemotherapy in locally advanced gastric cancer

The survival benefit of TS-ONE® monotherapy (one year after surgery, 529 patients) was compared with surgery alone (530 patients) in patients with stage II or III gastric cancer after curative gastrectomy (median post-operative follow-up period: 3 years). TS-ONE® reduced the risk of death by 32% compared with surgery alone, with a hazard ratio for death of 0.675 (95% confidence interval: 0.523 – 0.871, p=0.0024 by the log-rank test). The three-year survival rate after surgery was 80.5% in the TS-ONE® group and 70.1% in the surgery alone group. TS-ONE® reduced the risk of relapse by 38% compared with surgery alone, with a hazard ratio for relapse or death of 0.622 (95% confidence interval: 0.501 – 0.772, p<0.0001 by the log-rank test). The three-year relapse-free survival rate was 72.2% in the TS-ONE® group and 60.1% in the surgery alone group.

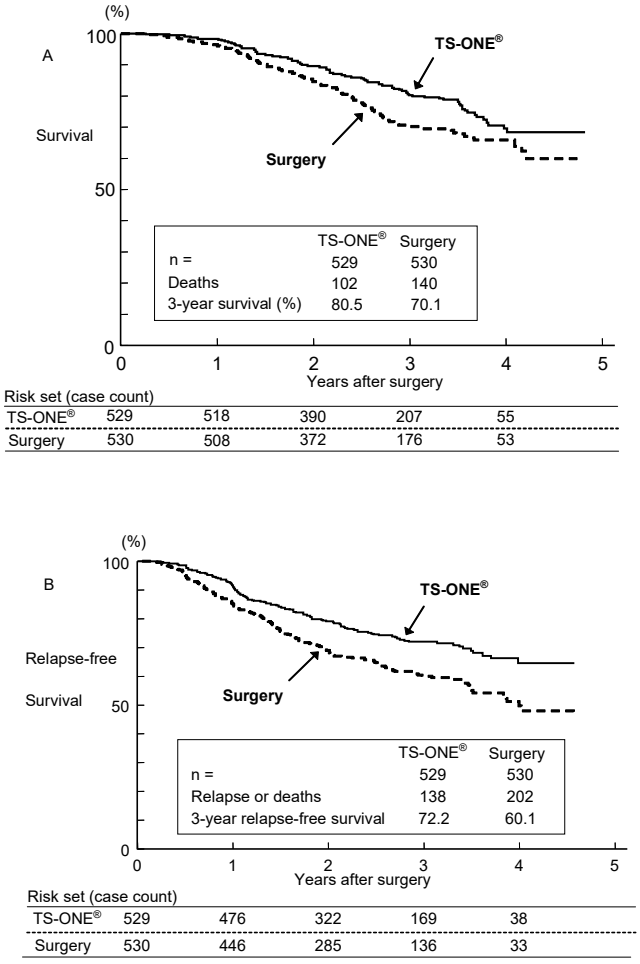
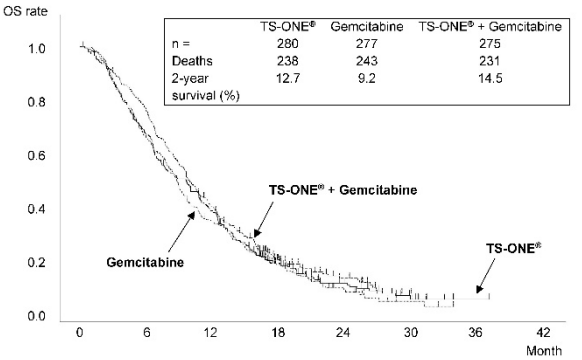


Figure 1: Kaplan-Meier curves of (A) survival and (B) relapse-free survival according to treatment group in the randomized phase III study of post-operative adjuvant chemotherapy in locally advanced gastric cancer

2. Randomized phase III study of TS-ONE® monotherapy in locally advanced or metastatic adenocarcinoma of the pancreas

The survival benefit of TS-ONE® monotherapy (280 patients) and TS-ONE® plus gemcitabine combination therapy (275 patients) was compared with gemcitabine monotherapy (277 patients) in chemotherapy-naïve patients with locally advanced or metastatic adenocarcinoma of the pancreas. Median overall survival was 8.80

months (95% confidence interval, 8.02 to 9.66) in the gemcitabine group, 9.66 months (95% confidence interval, 7.62 to 10.78) in the TS-ONE® group, and 10.05 months (95% confidence interval, 9.03 to 11.20) in the TS-ONE® plus gemcitabine group. TS-ONE® monotherapy could be stated as non-inferior to gemcitabine therapy (hazard ratio, 0.957; p = 0.0003 for non-inferiority). Although the TS-ONE® plus gemcitabine group has demonstrated a higher median survival duration as compared with the gemcitabine group, superiority of TS-ONE® plus gemcitabine was not demonstrated (hazard ratio, 0.875; p = 0.1496 > 0.0125).

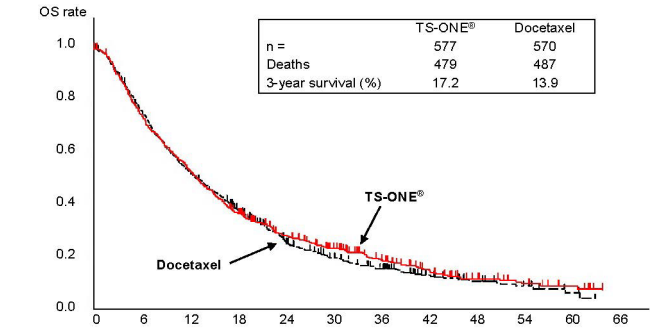


Risk set (case count)								
Gemcitabine	277	184	97	41	12	3	0	0
TS-ONE®	280	186	104	45	18	5	1	0
TS-ONE® + Gemcitabine	275	209	108	42	19	3	0	0

Figure 2: Kaplan-Meier curve of overall survival according to treatment group in the randomized phase III study of TS-ONE® monotherapy in locally advanced or metastatic adenocarcinoma of the pancreas

3. Randomized phase III study of TS-ONE® monotherapy in patients with locally advanced or metastatic non-small cell lung cancer previously treated with platinum-based chemotherapy

The survival benefit of TS-ONE® monotherapy (577 patients) was compared with docetaxel monotherapy (570 patients) in patients with locally advanced or metastatic non-small cell lung cancer who have been previously treated with platinum-based chemotherapy. The demographics and baseline characteristics were well-balanced between the TS-ONE® and docetaxel groups, except a significantly higher proportion of subjects in the docetaxel group had a target lesion, compared to the subjects in the TS-ONE® group (p=0.0153). The median survival time was 12.75 months (95% confidence interval: 11.53 – 14.00) in the TS-ONE® group and 12.52 months (95% confidence interval: 11.14 – 14.36) in the docetaxel group. The estimated overall survival hazard ratio (TS-ONE®/docetaxel) was 0.945 (95% confidence interval: 0.833 – 1.073, p=0.3818), which confirmed the non-inferiority of TS-ONE® monotherapy to docetaxel therapy. The estimated progression-free survival hazard ratio (TS-ONE®/docetaxel) was 1.033 (95% confidence interval: 0.913 – 1.168, p=0.6080). The median time to progression was 2.89 months (95% confidence interval: 2.79 – 3.09) in docetaxel group and 2.86 months (95% confidence interval: 2.73 – 3.12) in the TS-ONE® group. The estimated time to treatment failure hazard ratio (TS-ONE®/docetaxel) was 0.886 (95% confidence interval: 0.788 – 0.997, p=0.0436). The median time to treatment failure as 2.56 months (95% confidence interval: 2.04 – 2.76) in the docetaxel group and 2.66 months (95% confidence interval: 2.17 – 2.79) in the TS-ONE® group. The response rate was 9.9% in the docetaxel group and 8.3% in the TS-ONE® group. The difference in the response rate between both groups was not significant (p=0.3761, based on chi-square test). The overall survival and progression-free survival results of subgroup analyses are shown in Figures 4 and 6 respectively.



Risk set (case count)												
TS-ONE®	577	422	300	197	131	96	60	35	18	12	6	
Docetaxel	570	429	292	200	119	81	55	31	17	10	3	

Figure 3: Kaplan-Meier curve of overall survival according to treatment group in the randomized phase III study of TS-ONE® monotherapy in patients with locally advanced or metastatic non-small cell lung cancer previously treated with platinum-based chemotherapy

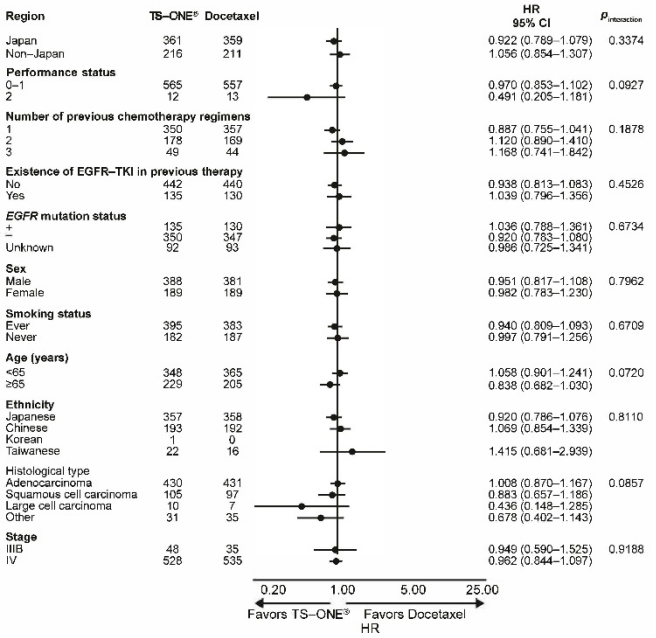
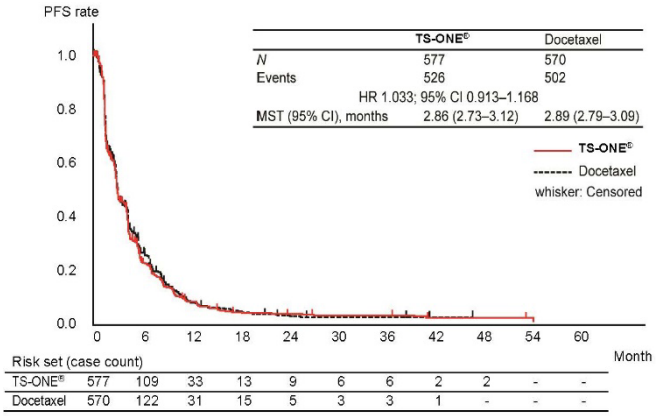


Figure 4: Forest plot for overall survival of subgroup analysis in the randomized phase III study of TS-ONE® monotherapy in patients with locally advanced or metastatic non-small cell lung cancer previously treated with platinum-based chemotherapy



Risk set (case count)												
TS-ONE®	577	109	33	13	9	6	6	2	2	-	-	
Docetaxel	570	122	31	15	5	3	3	1	-	-	-	

Figure 5: Kaplan-Meier curve of progression-free survival according to treatment group in the randomized phase III study of TS-ONE® monotherapy in patients with locally advanced or metastatic non-small cell lung cancer previously treated with platinum-based chemotherapy

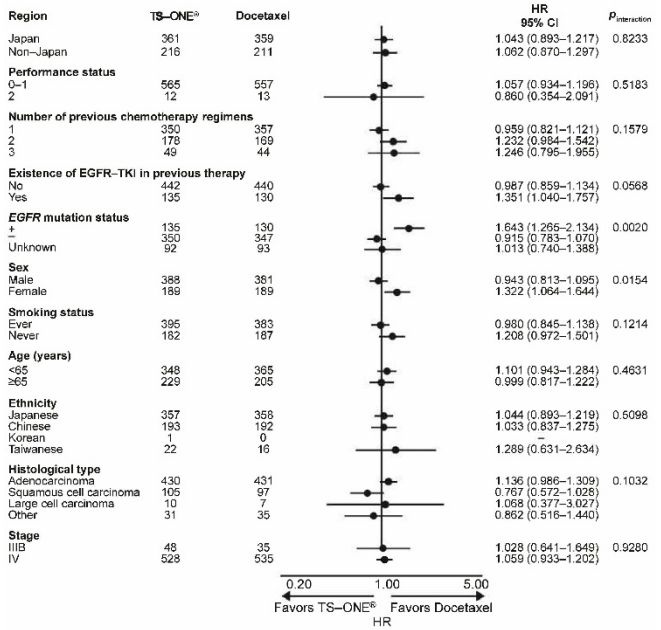


Figure 6: Forest plot for progression-free survival of subgroup analysis in the randomized phase III study of TS-ONE® monotherapy in patients with locally advanced or metastatic non-small cell lung cancer previously treated with platinum-based chemotherapy

4. Time of occurrence of adverse reactions and period of recovery

The time of occurrence of noteworthy adverse reactions following administration of TS-ONE® was analyzed in 453 patients enrolled in late clinical phase II studies of TS-ONE® for advanced or recurrent cancer in Japan. The results were as follows.

Among abnormal laboratory test results below any of the criteria including a WBC count of 3000/mm^3, a hemoglobin level of 8 g/dL, and a platelet count of 7.5 × 10^4/mm^3, the median time to nadir in the cycle where the lowest level in a case was reached was 27 days for WBC count, 25 days for hemoglobin level, and 24 days for platelet count.

On the other hand, in patients who were confirmed to have recovered from the above criteria, the median between the nadir of these values and recovery from them in the course were 7 days, 5.5 days and 6 days, respectively.

Abnormal clinical laboratory findings	Number of incidence	Period of up to nadir value: median (range)	Number of recovery	Period of up to recovery: median (range)
Leukopenia	92	27 days (4 - 43 days)	85	7 days (1 - 93 days)
Decreased hemoglobin	29	25 days (5 - 43 days)	24	5.5 days (1 - 21 days)
Thrombocytopenia	28	24 days (9 - 51 days)	25	6 days (1 - 46 days)

When the time of occurrence of adverse reactions after the start of the first dose of TS-ONE® was examined to assess the causality between them, the median until the occurrence of diarrhea, rash and stomatitis, which were judged adverse reactions, were 24.5 days, 21 days, and 28 days, respectively.

On the other hand, the median between the highest grade of these adverse reactions and the improvement from them were 9 days for diarrhea, 14 days for rash, and 13.5 days for stomatitis.

Abnormal clinical findings	Number of incidence	Period of up to occurrence: median (range)	Number of recovery	Period of up to improvement occurrence: median (range)
Diarrhea	100	24.5 days (2 - 189 days)	95	9 days (1 - 62 days)
Rash	67	21 days (2 - 248 days)	63	14 days (2 - 254 days)
Stomatitis	100	28 days (3 - 262 days)	94	13.5 days (2 - 99 days)

5. Adverse reactions in the presence of renal disorder

In the post-marketing surveys of TS-ONE® in patients with gastric cancer, the incidence of adverse reactions was tabulated by the range of creatinine clearance value (Ccr estimate), calculated from serum creatinine value, gender, age and weight using Cockcroft-Gault equation. The results were as follows.

In the patients, as creatinine clearance value decreased, the incidence of adverse reactions increased and the severity of the adverse reactions also increased. Additionally, in the patients who were treated initially at the lower dose (mostly, one stage lower than the standard), the incidence of adverse reactions was low, compared with the patients who were treated initially at the standard dose.

Ccr estimate (mL/min)	The patients who were administrated initially at the standard dose		The patients who were administrated initially at the lower dose	
	Frequency of adverse reactions	Frequency of severe adverse reactions (Grade 3 or 4)	Frequency of adverse reactions	Frequency of severe adverse reactions (Grade 3 or 4)
< 30	90.0% (18/20)	75.0% (15/20)	82.4% (14/17)	47.1% (8/17)
30 ≤ < 50	87.4% (319/365)	42.5% (155/365)	79.9% (123/154)	33.8% (52/154)
50 ≤ < 80	80.8% (1087/1345)	32.3% (434/1345)	71.7% (309/431)	26.0% (112/431)
80 ≤	79.2% (835/1054)	26.8% (282/1054)	70.7% (224/317)	24.3% (77/317)

PHARMACOLOGY

1. Antitumor activity

TS-ONE® has effects to inhibit the growth of tumors such as Yoshida sarcoma, AH-130 hepatoma, Sato lung carcinoma (in rats), Sarcoma-180, Lewis lung carcinoma and Colon-26 (in mice) transplanted subcutaneously. TS-ONE® also has effects to inhibit the growth of human cancers such as gastric, colorectal, breast, lung, pancreatic and renal when transplanted subcutaneously to nude rats or nude mice. TS-ONE® also has survival effects in the mouse Lewis lung carcinoma and L5178Y metastasis models, and has effects to inhibit the growth of tumors in nude rat models in which human gastric cancer and colorectal cancer cell lines were orthotopically implanted.

2. Mechanism of action

TS-ONE® contains FT, CDHP and Oxo, and the antitumor activity of TS-ONE® after oral administration is based on 5-FU that appears gradually in the body via the transformation of FT. CDHP increased the concentration of 5-FU, which is converted from FT, by selectively and reversibly inhibiting DPD, a catabolic enzyme of 5-FU, which is particularly distributed in the liver. 5-fluoronucleotides, phosphorylated metabolites of 5-FU, are highly maintained in tumor tissues, thereby enhancing the antitumor activity in proportion to the increase in the concentration of 5-FU in the body. Oxo selectively inhibits the production of 5-fluoronucleotides from 5-FU by distributing in the gastrointestinal tissue as a result of oral administration and selectively and reversibly inhibiting orotate phosphoribosyltransferase.

The main mechanisms of action of 5-FU is the inhibition of DNA synthesis resulting from the antagonistic effect of the active metabolite FdUMP acting upon dUMP to form ternary complex with thymidylate synthase and the reduced folic acid. RNA function is also thought to be damaged by conversion of 5-FU to FUTP, and its incorporation into RNA molecule.

PACKAGING

TS-ONE® Capsule 20:
56 capsules in press-through packages
(14 capsules × 4 sheets)

TS-ONE® Capsule 25:
56 capsules in press-through packages
(14 capsules × 4 sheets)

STORAGE CONDITION

Store below 30°C

Manufactured by:

Taiho Pharmaceutical Co., Ltd.
224-15 Aza-ebisuno, Hiraishi, Kawauchi-cho,
Tokushima-shi, Tokushima, 771-0194, Japan