TS-ONE® OD Tablet 20 and
TS-ONE® OD Tablet 25
Tegafur + Gimeracil + Oteracil potassium
20 mg and 25 mg Orally Disintegrating Tablet

WARNINGS

1. Cancer chemotherapy with TS-ONE®, as a single drug or in combination, 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 Reactions), in which it is different from conventional oral fluorouracil-group drugs, it is necessary to pay attention to changes in the laboratory data. Laboratory tests should be performed frequently.
3. In as much 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 should be given to detect possible malaise accompanied by anorexia, in 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 (such as folinate plus Tegafur-Uracil combination therapy), 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.

FORMULATION

Each TS-ONE® OD Tablet 20 contains 20 mg of Tegafur, 5.8 mg Gimeracil and 19.6 mg Oteracil potassium.

Each TS-ONE® OD Tablet 25 contains 25 mg of Tegafur, 7.25 mg Gimeracil and 24.5 mg Oteracil potassium.

DESCRIPTION

Brand name	TS-ONE® OD Tablet 20			TS-ONE® OD Tablet 25		
Ingredient/ contents	Tegafur 20 mg, Gimeracil 5.8 mg and Oteracil potassium 19.6 mg per tablet			Tegafur 25 mg, Gimeracil 7.25 mg and Oteracil potassium 24.5 mg per tablet		
Inactive ingredients	Lactose hydrate, Microcrystalline cellulose, Crospovidone, Partly pregelatinized starch, Aspartame, Magnesium stearate, Hydroxypropylcellulose, Flavor (Peach Micron ZE-2798), Yellow ferric oxide, Blue No. 2 aluminium lake			Lactose hydrate, Microcrystalline cellulose, Crospovidone, Partly pregelatinized starch, Aspartame, Magnesium stearate, Hydroxypropylcellulose, Flavor (Peach Micron ZE-2798), Yellow ferric oxide, Yellow No. 5 aluminium lake		
Description	TS-ONE® OD Tablet 20 is an orally disintegrating, pale blue-green tablet with a white disc inset centrally in one face, having a characteristic odor.			TS-ONE® OD Tablet 25 is an orally disintegrating, pale orange tablet with a white disc inset centrally in one face, having a characteristic odor.		
Appearance	Front	Back	Side	Front	Back	Side
						

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Size and weight	Diameter: 7.5 mm Thickness: 3.5 mm Weight: approx. 146 mg	Diameter: 8.0 mm Thickness: 3.9 mm Weight: approx. 182 mg
Identification code	TC41	TC43

INDICATIONS

- For post-operative adjuvant chemotherapy for locally advanced [stage II (excluding T1), IIIA or IIIB] gastric cancer
- For the treatment of advanced gastric cancer when given in combination with cisplatin
- For the treatment of metastatic colorectal cancer when given in combination with oxaliplatin as first-line treatment, or in combination with irinotecan as second-line treatment
- For post-operative adjuvant chemotherapy for pancreatic cancer
- For the treatment of locally advanced or metastatic pancreatic cancer

DOSAGE AND ADMINISTRATION

The recommended standard dose is based on studies performed in an Asian population and differs from the dosing recommended in Caucasian patients.

The standard TS-ONE® doses when given as post-operative adjuvant therapy or in combination with cisplatin are provided in Table 1.

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

Body surface area (m^2)	Each dose* (Two doses per day)	Number of tablets for each dose (2 doses per day)	
		20 mg tablet* (pale blue-green/white)	25 mg tablet* (pale orange/white)
< 1.25	40 mg	2	0
1.25 - < 1.5	50 mg	0	2
≥ 1.5	60 mg	3	0

*Expressed as tegafur content

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.

The patient's body surface area (BSA) must be recalculated and the TS-ONE® dose adjusted accordingly to the BSA listed in Table 1 if a patient's weight increases or decreases by ≥10% from the one used for the previous calculation of BSA and the change is clearly not related to fluid retention.

Patients treated with TS-ONE® should be closely monitored and laboratory tests, including haematology, liver function, renal function and serum electrolytes, should be performed frequently. Treatment should be discontinued if progressive disease or intolerable toxicity is observed.

Patients should be provided with anti-emetic and anti-diarrhoeal medicinal product, if required.

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For post-operative adjuvant chemotherapy for locally advanced [stage II (excluding T1), IIIA or IIIB] gastric cancer

The standard initial recommended dose for TS-ONE® is based on the patient's BSA as per Table 1 and should be taken twice daily, after meals in the morning and evening, for 28 consecutive days followed by a 14-day rest (1 treatment cycle). This treatment cycle is repeated every 6 weeks.

Based on the patient's condition, the dose may be reduced according to Table 2.

For the treatment of advanced gastric cancer when given in combination with cisplatin

The standard initial recommended dose of TS-ONE® is based on the patient's BSA as per Table 1. TS-ONE® should be given twice daily, after meals in the morning and evening, for 21 consecutive days followed by a 14-day rest period (1 treatment cycle). This treatment cycle is repeated every 5 weeks.

The recommended dose of cisplatin with this regimen is 60 mg/m^2 by intravenous infusion administered on Day 8 of each treatment cycle. Cisplatin should be discontinued after 6 cycles without withdrawal of TS-ONE®. If cisplatin is discontinued before 6 cycles, TS-ONE® treatment alone can be resumed when the criteria for restarting it are met.

For the treatment of metastatic colorectal cancer when given in combination with oxaliplatin as first-line treatment, or in combination with irinotecan as second-line treatment

The standard initial recommended dose of TS-ONE® is based on the patient's BSA as per Table 1.

For first-line treatment, TS-ONE® is recommended to be administered twice daily, after meals in the morning and evening, for 14 consecutive days, in combination with oxaliplatin 130 mg/m^2 on Day 1 as a 2-hour intravenous infusion. This treatment is repeated every 3 weeks.

For second-line treatment, TS-ONE® is recommended to be administered twice daily, after meals in the morning and evening, from Day 1 to 14, in combination with irinotecan 125 mg/m^2 on Days 1 and 15. This treatment is repeated every 4 weeks.

For post-operative adjuvant chemotherapy for pancreatic cancer
For the treatment of locally advanced or metastatic pancreatic cancer

The standard initial recommended dose for TS-ONE® is based on the patient's BSA as per Table 1 and should be taken twice daily, after meals in the morning and evening, for 28 consecutive days followed by a 14-day rest (1 treatment cycle).

Adjustments during treatment

General

Toxicity due to TS-ONE® in combination with cisplatin administration should be managed with symptomatic treatment and/or treatment interruption or dose reduction. Patients taking TS-ONE® in combination with cisplatin should be informed of the risks and instructed to contact their physician immediately if moderate or severe toxicity occurs.

Doses omitted for toxicity are not replaced; and, if a patient vomits after taking a dose, this dose should not be replaced.

Once the TS-ONE® dose has been reduced, it should not be increased again.

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TS-ONE® dose modification criteria

Dose modification for toxicity should be made according to Tables 2, 3, 4, 5 and 6. The initial dose can be decreased according to the patient's tolerability to the medication. The reduction of dose should be in 10 mg intervals, with a lowest dose of 40 mg. A maximum of two consecutive dose reductions can be applied in case of toxicity.

Table 2: Dose reductions (expressed as tegafur content)

Standard dose		Dose reduction 1		Dose reduction 2		Dose reduction 3
40 mg	→	Drug rest	→	-	→	-
50 mg		40 mg		Drug rest		-
60 mg		50 mg		40 mg		Drug rest

TS-ONE® dose modifications for toxicity when used in combination with cisplatin can be made in two ways:

- *During a 5-week cycle of treatment*
  During a treatment cycle, dose adjustment should be performed for each individual medicinal product that is considered to be causally related to toxicity, if such a distinction can be made. If both medicinal products are considered to be causing the toxicity or it is not possible to distinguish them, then dose reduction should be performed for both according to the recommended dose reduction schedule. Dose modification for toxicity of TS-ONE® and cisplatin should be made according to Table 2 and Table 3, respectively.

Table 3: Dose reductions for cisplatin

Standard dose		Dose reduction 1		Dose reduction 2
60 mg/m^2	→	50 mg/m^2	→	40 mg/m^2

- *At the initiation of subsequent cycles of treatment*
  If a treatment delay is indicated for either TS-ONE® or cisplatin, then administration of both medicinal products should be delayed until the requirements for restarting both are met unless one of the medicinal products has been permanently discontinued.

Dose modifications for TS-ONE® for adverse reactions in general except for haematologic and renal toxicities

Table 4: TS-ONE® dose reduction schedule for treatment-related toxicities in general, except for haematologic and renal toxicities

Toxicity grades[a]	**TS-ONE® dose changes within a treatment cycle**	**TS-ONE® dose adjustment for next dose/next cycle**
Grade 1		
Any occurrence	Maintain treatment at same dose level	None
Grade 2[b,c]		
Any occurrence	Suspend treatment until Grade 0 or 1	None
Grade 3 or Higher[c]		
First occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from previous level
Second occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from previous level
Third occurrence	Discontinue treatment	Discontinue treatment

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[a] According to the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 3.0.
[b] For Grade 2 nausea and/or vomiting, the anti-emetic therapy should be optimized prior to suspension of TS-ONE®.
[c] At the discretion of the treating physician, patients may continue with treatment without reduction or interruption for adverse events (irrespective of grade) considered unlikely to become serious or life-threatening (e.g. alopecia, changes in sexual function and dry skin).

Dose modifications for renal toxicities

Creatinine clearance (CrCl) must be determined for every cycle before the start of treatment on Day 1.

Table 5: TS-ONE® and cisplatin dose modification according to creatinine clearance values at the start of a cycle of treatment

Creatinine clearance	TS-ONE® dose modification at the start of the cycle of treatment	Cisplatin dose modification at the start of the cycle of treatment
≥ 50 ml/min	No dose adjustment	Dose reduction should be in accordance to Table 3 as per patient's condition.
30 to 49 ml/min	Dose reduction 1 in Table 2	
< 30 ml/min	Not recommended	

Dose modifications for haematologic toxicities

Table 6: Haematologic toxicities for which TS-ONE® treatment shouldbe suspended

Units	Neutrophils	Platelets	Haemoglobin	TS-ONE® dose modification
IU	$< 0.5\times10^9$/l	$< 25\times10^9$/l	4.0 mmol/l	Suspend treatment until resumption criteria is met (see Table 7) and then resume dosing at one reduced dose level

Resumption criteria for TS-ONE® treatment

Table 7: Minimum criteria to resume TS-ONE® treatment following its suspension due to toxicity

Non-haematologic	**Haematologic**
Baseline or Grade 1	Platelet count $\geq 100\times10^9$/l
Calculated creatinine clearance ≥ 30 ml/min	Neutrophils $\geq 1.5\times10^9$/l
	Haemoglobin ≥ 6.2mmol/l
CrCl must be calculated at the beginning of every cycle before the start of treatment with TS-ONE® on Day 1.	

Dose modifications for special populations

Renal impairment

- Mild renal impairment (CrCl 51 to 80 ml/min)
  No adjustment of the standard dose is recommended in patients with mild renal impairment.

- Moderate renal impairment (CrCl 30 to 50 ml/min)
  The recommended standard dose in patients with moderate renal impairment is corresponding to Dose reduction 1 in Table 2 (See TS-ONE® dose modification criteria).

- Severe renal impairment (CrCl below 30 ml/min)
  Use is not recommended in severe renal impairment.

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Elderly
No adjustment of the standard dose is recommended in patients >70 years old (see Use in the Elderly).

Pediatric population
The safety and efficacy of TS-ONE® in pediatric patients under 18 years old have not been established. No data are available. Therefore, TS-ONE® should not be administered to pediatric patients under 18 years of age.

Method of administration

This drug is disintegrated in the oral cavity, but because it is not absorbed from the oral mucosa, it should be swallowed with water or saliva (See Precautions concerning Use).

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 (haematological 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 (haematological 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®. Laboratory tests should be performed frequently, particularly when one course of the regimen is conducted and the dose is increased.
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. Efficacy and safety of combination therapy with TS-ONE® and chest or abdominal radiation have not yet been established.
6. 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.
7. 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).]
8. Patients with hepatic disorder [Hepatic disorder may be aggravated.]
9. Patients having infectious disease [Infectious disease may be aggravated as a result of bone marrow depression.]
10. Patients with abnormal glucose tolerance [Abnormal glucose tolerance may be aggravated.]
11. Patients with a current or previous history of interstitial pneumonia [Interstitial pneumonia may be aggravated or may develop.]
12. Patients with a current or previous history of heart disease [Symptoms may be aggravated.]
13. Patient with gastrointestinal ulcer or hemorrhage [Symptoms may be aggravated.]
14. Elderly patients (See Use in the Elderly)
15. Patients with varicella [Fatal systemic damage may occur.]

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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. Treatment within 4 weeks with dihydropyrimidine dehydrogenase (DPD) inhibitors, including sorivudine or its chemically related analogues such as brivudine.
8. Pregnant women or women suspected of being pregnant or breastfeeding mothers (See Use during Pregnancy, Delivery or Lactation)
9. Patients with known DPD deficiency
10. For TS-ONE® in combination with cisplatin, refer to cisplatin SmPC for contraindications of cisplatin.

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 (See Adverse Reactions).
(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

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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 and symptoms of the reactivation of Hepatitis B and follow up monitoring for hepatic function tests or viral markers are recommended.

(7) This drug is disintegrated in the oral cavity, but because it is not absorbed from the oral mucosa, it should be swallowed with water or the saliva (See Precautions concerning Use).

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	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 during 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,	Adverse reaction may be aggravated mutually.

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	appropriate measures should be taken, such as dose reduction or discontinuation of treatment.	

4. Adverse Events/Reactions

Summary of safety profile

a) TS-ONE® monotherapy

The overall safety profile of TS-ONE® monotherapy when used as post-operative adjuvant chemotherapy for locally advanced [stage II (excluding T1), IIIA or IIIB] gastric cancer is based on data from ACTS-GC study, a randomized study of post-operative adjuvant chemotherapy with TS-ONE® for gastric cancer.

Table 8 shows the frequency of adverse events that occurred in ≥ 5% of patients in the TS-ONE® group by CTC grade combined and the corresponding event rates in the surgery-only group. The data are shown for 517 evaluable patients in the TS-ONE® group and 526 evaluable patients in the surgery-alone group. Frequency of all adverse events was 100% in the TS-ONE® group and 93.3% in the surgery-alone group respectively.

Table 8: Frequency of adverse events occurring in ≥ 5% of patients in the TS-ONE® group by CTC grade combined and corresponding event rates in the surgery-only group

	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

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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.

The following table summarizes the adverse reactions of patients treated with TS-ONE® for pancreatic cancer in the randomized phase III study (GEST) of Gemcitabine versus TS-ONE® versus Gemcitabine plus TS-ONE® in locally advanced or metastatic pancreatic cancer. In 272 evaluable patients who are treated with TS-ONE® monotherapy, the most common drug related adverse event was decrease in haemoglobin. Anorexia and nausea were also noted as common drug related adverse events.

Table 9: Frequency of adverse reactions of patients treated with TS-ONE® for pancreatic cancer in the randomized phase III study (GEST) of Gemcitabine versus TS-ONE® versus Gemcitabine plus TS-ONE® in locally advanced or metastatic pancreatic cancer

AE term	GEM, N (%)	TS-1, N (%)	GEM+TS-1, N (%)
Patients analysis (N)	273	272	267
Hemoglobin	199 (72.9)	158 (58.1)	215 (80.5)
Leukocytes	205 (75.1)	111 (40.8)	231 (86.5)
Neutrophils	182 (66.7)	87 (32.0)	219 (82.0)
Platelets	200 (73.3)	121 (44.5)	210 (78.7)
ALT	94 (34.4)	57 (21.0)	101 (37.8)
AST	90 (33.0)	65 (23.9)	108 (40.4)
Bilirubin	19 (7.0)	64 (23.5)	42 (15.7)
Creatinine	27 (9.9)	22 (8.1)	23 (8.6)
Fatigue	94 (34.4)	117 (43.0)	156 (58.4)
Alopecia	28 (10.3)	8 (2.9)	48 (18.0)
Hyperpigmentation	7 (2.6)	92 (33.8)	73 (27.3)
Rash	69 (25.3)	44 (16.2)	103 (38.6)
Anorexia	123 (45.1)	152 (55.9)	155 (58.1)
Diarrhea	39 (14.3)	90 (33.1)	88 (33.0)
Mucositis (clinical exam) – Oral cavity	34 (12.5)	67 (24.6)	90 (33.7)
Nausea	95 (34.8)	126 (46.3)	134 (50.2)
Vomiting	53 (19.4)	63 (23.2)	76 (28.5)

*GEM – Gemcitabine
*TS-1 – TS-ONE®

b) <u>TS-ONE® in combination with cisplatin</u>

The overall safety profile of TS-ONE® in combination with cisplatin is based on clinical study data from 148 Asian patients with advanced gastric cancer treated with this regimen (SPIRITS study).

Table 10 shows the frequency of adverse reactions that occurred in ≥ 5% of patients in the TS-ONE® plus cisplatin group.

Table 10: Frequency of adverse reactions occurring in ≥ 5% of patients in the TS-ONE® plus cisplatin group

	TS-ONE® + CDDP group (148 patients)	
Adverse Reactions	Frequency of all grades (%)	Frequency of CTC Grade 3 or 4 [#2] (%)
White blood cell count decreased	70.3	11.5
Neutrophil count decreased	73.6	39.9

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Platelet count decreased	47.3	5.4
Red blood cell count decreased	7.4	1.4
Haemoglobin decreased	66.9	23.6
Haematocrit decreased	7.4	1.4
AST (GOT) increased	10.1	-
ALT (GPT) increased	11.5	-
Blood bilirubin increased	24.3	0.7
Blood ALP increased	5.4	0.7
Blood creatinine increased	20.3	-
Protein urine present	14.2	-
Anorexia	72.3	29.7
Nausea	66.2	11.5
Vomiting	35.8	4.1
Diarrhoea	34.5	4.1
Stomatitis	28.4	0.7
Dysgeusia	31.8	-
Parosmia	9.5	-
Pigmentation disorder	35.1	-
Exfoliative rash	21.6	2.0
Alopecia	8.1	-
Skin reaction	8.8	-
Lacrimation increased	17.6	-
Fatigue	56.1	3.4
Pyrexia	6.1	-
Glucose urine present	8.1	-
Blood albumin decreased	14.2	-
Blood sodium decreased	8.8	2.7
Weight decreased	20.3	1.4

#2: Graded by NCI-CTC version 2.0

(1) Clinically significant adverse reactions

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

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5) Severe enteritis: Since hemorrhagic enterocolitis, ischaemic enterocolitis and necrotising 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 (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, cardiac failure: Since myocardial infarction, angina pectoris, arrhythmia (including ventricular tachycardia) and cardiac failure 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, gastrointestinal ulcer, gastrointestinal hemorrhage and gastrointestinal perforation 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 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 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 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 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 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 may occur, and anosmia 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 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

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(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. In patients who were administered TS-ONE® in the post-marketing clinical study for unresectable or recurrent gastric cancer (SPIRITS study), the incidence of lacrimation was high (16.0% and 17.6%) in TS-ONE® alone group and TS-ONE® + CDDP group, respectively.

Incidence / Classification	≥ 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, proteinurea, 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 and foot syndrome, skin ulcer, dermatitis, alopecia, nail abnormality, paronychia, herpes simplex, skin dry/roughness	Photosensitivity, DLE-like eruption
Hyper-sensitivity	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 amylase level

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		increased serum potassium, decreased serum potassium, increased serum calcium, decreased serum calcium, increased serum chloride, decreased serum chloride), weight loss	

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.

(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. No studies have been performed with TS-ONE® in pediatric patients. 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].

Precaution in taking the drug:
TS-ONE® OD Tablet can be taken with or without water. When the drug is placed on the tongue, saliva can infiltrate into the drug to disintegrate it, therefore the drug can be taken without water. Otherwise, the drug can also be taken with water. When the patient is unable to sit up from a lying position, the drug should not be taken without water.

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 an extremely rare group of 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. Although the causality of TS-ONE® was unknown, it has been reported that cerebral infarction has occurred.

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(3) 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).

(4) 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/m² after a meal are shown in the table below. 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/m² 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) 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, 6.9 and 2.3 times higher when combined with 5-FU, FT, FT-Ura, 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) 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 (clinical pharmacology, pancreatic cancer, biliary tract cancer). The AUCs of two patient groups with normal and slightly impaired renal function were tabulated by range of creatinine clearance value (Ccr estimate).

	AUC (0-8hr)	
(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.)

*) Cockcroft-Gault equation:

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In men:

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

In women:

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

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*).

4. Bioequivalence study

When TS-ONE® OD tablets or TS-ONE® capsules were orally administered at a single dose of 40 mg/body (20 mg × 2 tablets or capsules) under the fasting condition with or without water (for OD tablets) or with water (for capsules), these pharmaceutical forms could be considered bioequivalent.

Drug and administration method	5-FU	
	C_{max} (ng /mL)	$AUC_{(0\text{-}48hr)}$ (ng·hr /mL)
OD tablet, with water (1st group)	101.8	573.4
OD tablet, without water (2nd group)	116.3	684.8
Capsule, (1st / 2nd group) *	106.4 / 112.1	594.2 / 642.4

*: administration with water in both 1st and 2nd groups

CLINICAL STUDIES

1. Randomized phase III study of postoperative adjuvant chemotherapy

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 postoperative 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.

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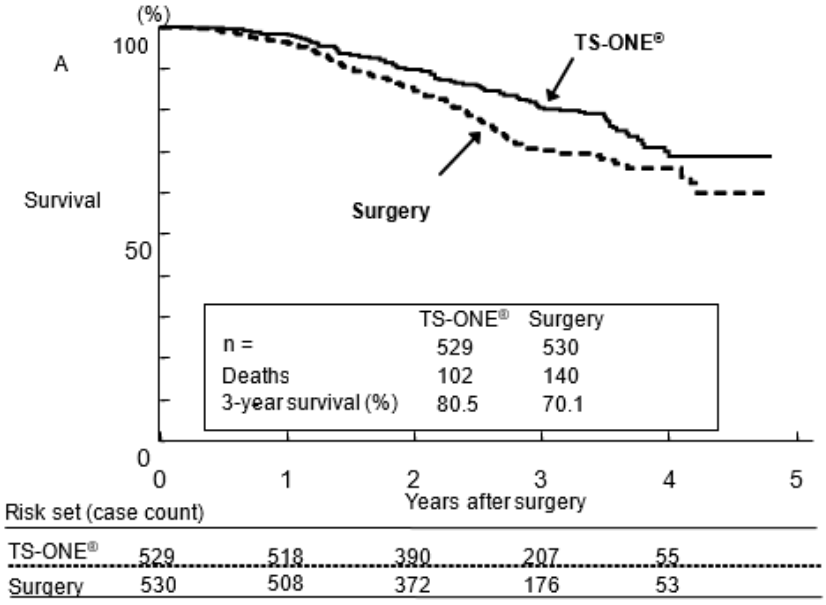

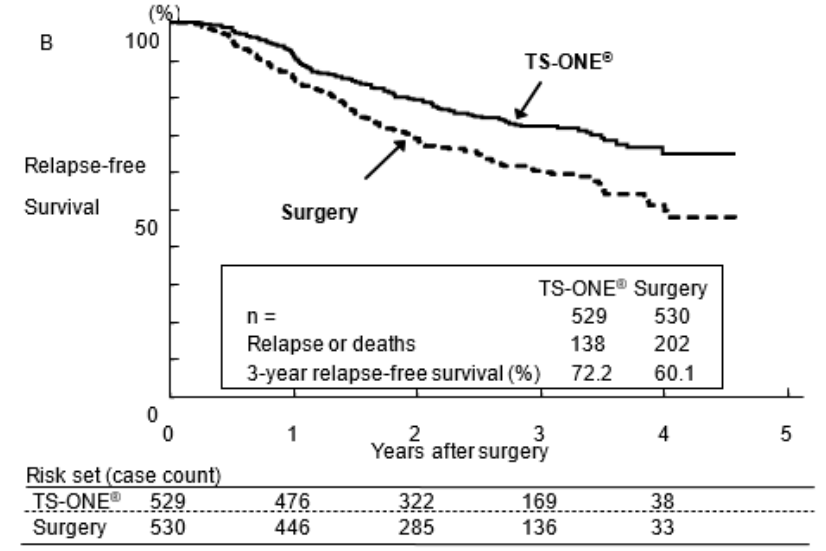

Figure 1: Kaplan-Meier curves for (A) overall survival and (B) relapse-free survival in TS-ONE® group and surgery-alone group in the randomized phase III study of post-operative adjuvant chemotherapy

2. Randomized phase III study of TS-ONE® plus cisplatin combination therapy in advanced gastric cancer

The survival benefit of TS-ONE® in combination with cisplatin (148 patients) was compared with TS-ONE® alone (150 patients) in chemotherapy-naïve patients with advanced gastric cancer. Median overall survival was significantly longer in patients assigned to TS-ONE® plus cisplatin (13.0 months [IQR 7.6 – 21.9]) than in those assigned to TS-ONE® alone (11.0 months [5.6 – 19.8]; hazard ratio for death, 0.77; 95% CI 0.61 – 0.98; p=0.04). Progression-free survival was significantly longer in patients assigned to TS-ONE® plus cisplatin than in those assigned to TS-ONE® alone (median progression-free survival 6.0 months [3.3 – 12.9] vs 4.0 months [2.1 – 6.8]; p<0.0001).

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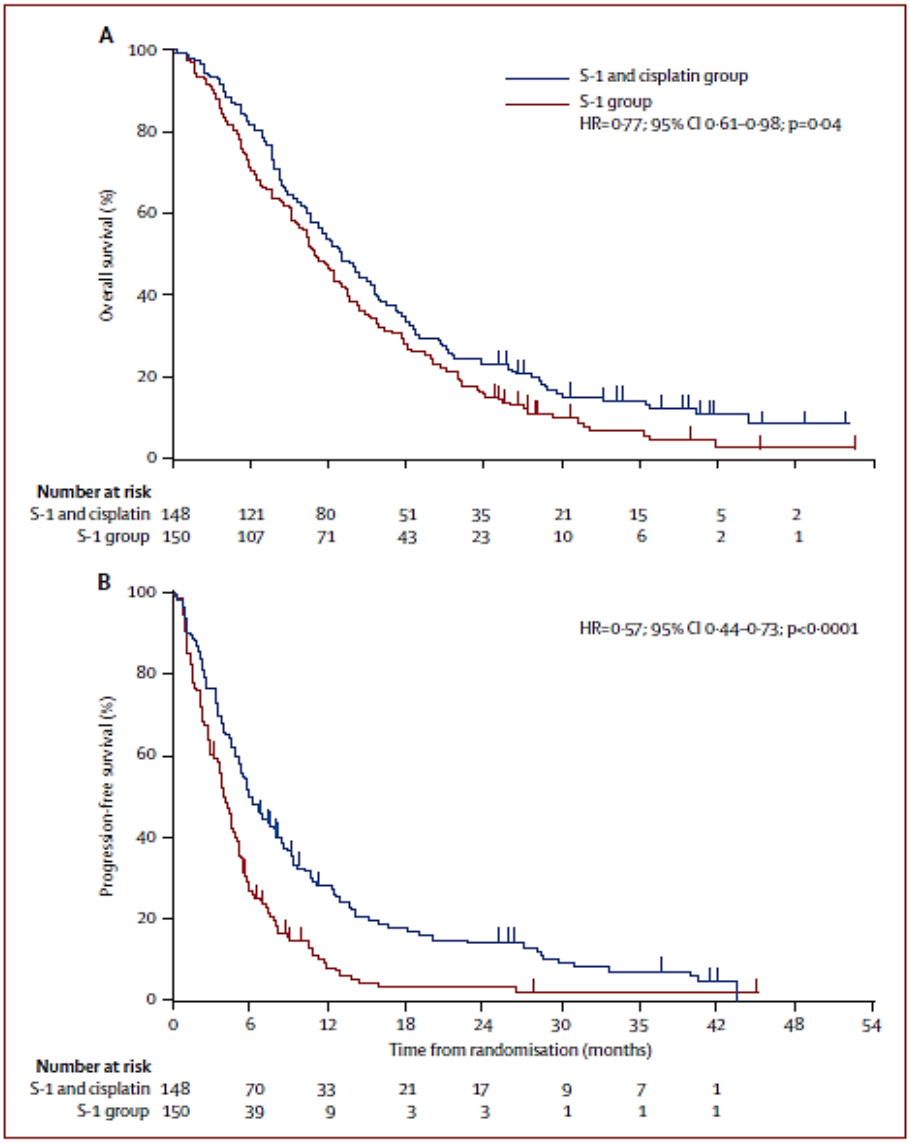

Figure 2: Kaplan-Meier curves for (A) overall survival and (B) progression-free survival in TS-ONE® + Cisplatin group and TS-ONE® group

3. Randomized phase III study of TS-ONE® monotherapy in locally advanced or metastatic pancreatic cancer

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 pancreatic cancer. 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).

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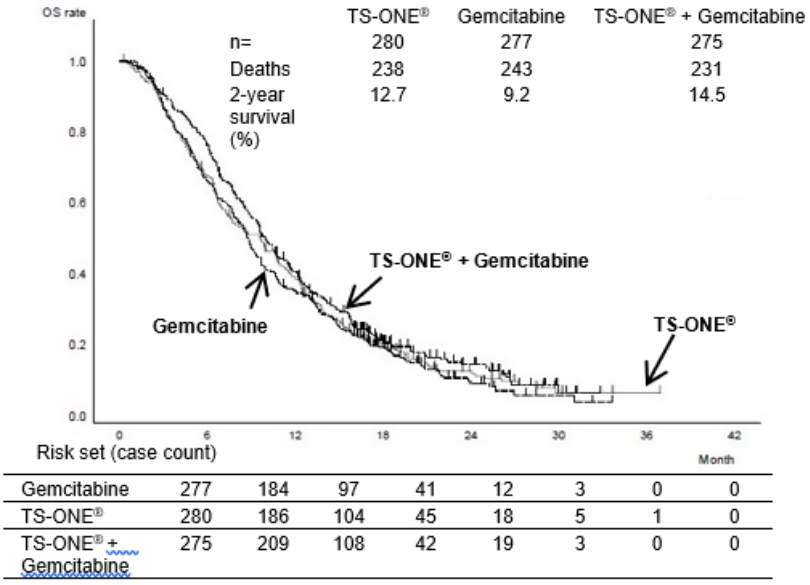

Figure 3: Kaplan-Meier curve of overall survival according to treatment group in the randomized phase III study of TS-ONE® monotherapy in locally advanced or metastatic pancreatic cancer patients

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

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

Among abnormal laboratory test results below any of the criteria including a WBC count of 3000/mm³, a hemoglobin level of 8 g/dL, and a platelet count of 7.5×10^4/mm³, 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 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.

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Abnormal clinical findings	Number of incidence	Period of up to occurrence: median (range)	Number of recovery	Period of up to improved 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 administrated 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 administered initially at the standard dose.

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

PHARMACOLOGY

Pharmacotherapeutic Group: antineoplastic agents, antimetabolites, ATC code: L01BC53

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.

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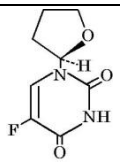
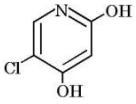
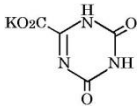
2. Mechanism of action

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 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. Gastrointestinal toxicity appears to be relieved as a result, without interfering with the antitumor activity of 5-FU.

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.

PHYSICOCHEMISTRY

Names of active ingredients / Item	Tegafur	Gimeracil	Oteracil potassium
Structural formula	 and enantiomer		
Nonproprietary name	Tegafur	Gimeracil	Oteracil potassium
Chemical name	5-Fluoro-1-[(2*RS*)-tetrahydrofuran-2-yl]uracil	5-Chloro-2,4-dihydroxypyridine	Monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate
Molecular formula	$C_8H_9FN_2O_3$	$C_5H_4ClNO_2$	$C_4H_2KN_3O_4$
Molecular weight	200.17	145.54	195.17
Melting point	166 – 171°C	Approximately 262°C (decomposition)	More than 300°C
Description	Tegafur occurs as a white crystalline powder. It is slightly soluble in methanol or acetone, sparingly soluble in water and ethanol (95%). It dissolves in dilute sodium hydroxide test solution. Methanol solution (1→50) shows no optical solution.	Gimeracil occurs as a white crystalline powder. It is soluble in sodium hydroxide test solution and *N*,*N*-dimethylformamide, sparingly soluble in methanol, slight soluble in ethanol (99.5%), and very slightly soluble in water.	Oteracil potassium occurs as a white crystalline powder. It is slightly soluble in pH8.0 phosphate buffer and water, and practically insoluble in ethanol (99.5%) and methanol.

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PRESENTATION

TS-ONE® OD Tablet 20:
56 tablets in press-through CPP/AL blister sheets
(14 tablets × 2 sheets × 2 pouches),
TS-ONE® OD Tablet 25:
56 tablets in press-through CPP/AL blister sheets
(14 tablets × 2 sheets × 2 pouches)

Store below 30°C. Store in a place avoiding moisture after opening the package.

Use under prescription of a physician
HARUS DENGAN RESEP DOKTER

Registration Number:
TS-ONE® OD Tablet 20: DKI1938400381A1

TS-ONE® OD Tablet 25: DKI1938400381B1

Manufactured by:
Taiho Pharmaceutical Co., Ltd, Tokushima, Japan

Imported by:
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Leaflet Informasi Pasien

TS-ONE®OD Tablet 20
TS-ONE®OD Tablet 25

Lembaran ini merupakan ringkasan dan tidak memberikan informasi menyeluruh kepada anda tentang TS-ONE®OD Tablet 20 dan TS-ONE®OD Tablet 25.

Hubungi dokter atau apoteker anda bila anda mengkhawatirkan sesuatu tentang obat ini.

Tentang obat ini

Apakah kegunaan obat ini:

Pada orang dewasa TS-ONE® digunakan untuk:
- Kemoterapi adjuvant pasca operasi pada penderita kanker lambung lokal stadium lanjut [stadium II (tidak termasuk T1)], IIIA atau IIIB
- Pengobatan pada penderita kanker lambung stadium lanjut, bila dikombinasikan dengan cisplatin.
- Pengobatan kanker kolorektal metastase bila diberikan dalam kombinasi dengan oxaliplatin sebagai pengobatan lini pertama, atau dalam kombinasi dengan irinotecan sebagai pengobatan lini kedua
- Kemoterapi adjuvant pasca operasi untuk kanker pankreas
- Pengobatan kanker pankreas lokal stadium lanjut atau metastatik

Tanyakan pada dokter anda bila anda ingin bertanya sebab obat ini diresepkan untuk anda.

Dokter anda mungkin saja meresepkan obat ini untuk alasan lainnya.

Cara kerja obat:

TS-ONE® dimasukkan ke dalam golongan obat fluoropyrimidine, yaitu golongan obat “agen anti neoplasma”, yang berfungsi untuk menghentikan pertumbuhan sel kanker.

Kapan obat ini tidak boleh dipergunakan:

TS-ONE® tidak boleh dipergunakan bila anda:

- Alergi (hipersensitif) terhadap tegafur, gimeracil, oteracil atau kandungan lainnya yang terdapat dalam TS-ONE®
- Memiliki kelainan darah berat
- Memiliki kelainan ginjal yang membutuhkan dialisis
- Mengalami gangguan berat pada hati
- Diketahui secara genetik kekurangan enzim *dihydropyrimidine dehydrogenase* (DPD)
- Pada saat kini sedang mempergunakan obat anti kanker fluoropyrimidine seperti fluorouracil maupun capecitabine atau bisa mengalami reaksi tak terduga atau efek samping berat bila memakai fluoropyrimidine
- Sedang menjalani perawatan atau baru saja menjalani perawatan tersebut pada 4 minggu yang lalu mempergunakan obat sorivudine, brivudine atau obat-obatan dari golongan obat antivirus yang serupa
- Sedang hamil ataupun menyusui
- Sedang memakai flucytosine

Seperti apakah obat ini:

TS-ONE®OD Tablet 20:

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Setiap tablet berwarna biru-kehijauan pucat dengan piringan putih di tengah pada satu sisi, memiliki bau khas.

TS-ONE®OD Tablet 25:
Setiap tablet berwarna orange pucat dengan piringan putih di tengah pada satu sisi, memiliki bau khas.

Apakah isi obat:

TS-ONE®OD Tablet 20:
Setiap tablet mengandung 20 mg tegafur, 5.8 mg gimeracil dan 19.6 mg potassium oteracil (setara dengan 15.8 mg oteracil bebas asam) sebagai bahan aktif.

TS-ONE®OD Tablet 25:
Setiap tablet mengandung 25 mg tegafur, 7.25 mg gimeracil dan 24.5 mg potassium oteracil (setara dengan 19.7 mg oteracil bebas asam) sebagai bahan aktif.

Apakah bahan tambahan obat ini:

Lactose hydrate
Microcrystalline cellulose
Crospovidone
Partly pregelatinized starch
Aspartame
Magnesium stearate
Hydroxypropylcellulose
Flavor(Peach Micron ZE-2798)
Yellow ferric oxide
Blue No.2 aluminium lake (untuk TS-ONE®OD Tablet 20)
Yellow No.5 aluminium lake (untuk TS-ONE®OD Tablet 25)

Tanyakan kepada dokter atau apoteker anda bila anda menduga alergi terhadap salah satu atau lebih dari daftar kandungan bahan yang tertera di atas.

Berapakah besaran dosis sediaan yang tersedia:

TS-ONE® tersedia dalam *orally disintegrating* tablet 20 mg dan 25 mg.

Peringatan dan hal-hal yang perlu diwaspadai

Sebelum maupun **sewaktu** mempergunakan TS-ONE®

Sebelum memulai perawatan dengan TS-ONE®, berkonsultasilah dengan dokter maupun apoteker bila anda:

- Memiliki kelainan pada sistem pendarahan
- Memiliki penyakit ginjal
- Menderita penyakit hepar / hati
- Menderita penyakit menular
- Menderita diabetes
- Sedang menderita atau memiliki riwayat pernah menderita penyakit *pneumonia interstitial*.
- Mempunyai penyakit jantung atau riwayat penyakit jantung
- Menderita tukak atau pendarahan lambung
- Sedang menggunakan obat-obatan anti kanker dari golongan fluoropyrimidine

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- Mempergunakan TS-ONE® setelah *withdrawal* / menghentikan pemakaian obat anti kanker golongan fluoropyrimidine.
- Pasien usia lanjut
- Pasien dengan varicella

Kehamilan dan menyusui

Sebelum memulai pengobatan, anda harus memberitahukan kepada dokter maupun apoteker anda jika anda menduga diri anda hamil atau sedang berusaha hamil. TS-ONE® tidak boleh dipergunakan bila anda hamil, atau adanya dugaan kehamilan.

Namun bila ternyata benar terdapat kehamilan sewaktu proses pengobatan maka berkonsultasilah dengan dokter anda.

Menyusui tidak diperbolehkan bila anda sedang menjalani perawatan TS-ONE®.

Mintalah saran dari dokter maupun apoteker anda sebelum mempergunakan obat apapun.

Pada periode pemakaian TS-ONE®

Hal yang harus anda lakukan

Beritahukanlah pada dokter maupun apoteker anda secepat mungkin, bila anda merasa tidak sehat setelah pemakaian TS-ONE®.

Selama perawatan, uji laboratorium (uji darah,fungsi hati dan ginjal) tetap dilakukan secara teratur setidaknya 2 minggu sekali untuk mendeteksi adanya efek samping tanpa gejala sedini mungkin. Pastikan untuk selalu berkonsultasi dengan dokter anda.

Bila anda akan memulai jenis obat-obatan baru, informasikan pada dokter maupun apoteker anda bahwa anda sedang memakai TS-ONE®.

Beritahukan pada dokter lain, dokter gigi dan apoteker yang merawat anda bahwa anda sedang memakai obat ini.

Bila anda akan menjalani pembedahan, beritahukan pada dokter bedah atau dokter anestesi anda bahwa anda sedang memakai obat ini. Obat ini mungkin mempengaruhi obat-obatan lain yang dipergunakan sewaktu pembedahan.

Bila anda mengalami kehamilan sewaktu menjalani perawatan dengan obat ini, informasikan kepada dokter anda secepat mungkin.

Hal-hal yang tidak boleh dilakukan

Jangan menggunakan obat ini bila sudah melewati tanggal kadaluwarsa yang tercetak pada kemasan obat. Jangan memakai obat ini bila kemasannya rusak atau menunjukkan tanda-tanda adanya kerusakan.

Hal-hal yang perlu diwaspadai

Obat ini dipergunakan untuk pengobatan kanker lambung stadium lanjut, atau sebagai adjuvant setelah operasi kanker lambung, namun bisa menyebabkan efek merugikan pada sebagian orang. Semua jenis obat-obatan bisa menyebabkan efek samping.

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Kadang-kadang efek samping yang terjadi adalah efek serius, namun kebanyakan efek yang terjadi merupakan gangguan ringan. Anda mungkin membutuhkan bantuan medis bila mengalami sebagian efek samping tersebut.

Interaksi dengan obat ini

Sebelum memulai pengobatan, anda diharapkan untuk menginformasikan pada dokter maupun apoteker anda bila sedang menggunakan obat-obatan lainnya, termasuk obat-obatan yang diperoleh tanpa resep. Hal ini merupakan sesuatu yang sangat penting, karena pemakaian lebih dari satu obat pada saat yang bersamaan dapat memperkuat atau memperlemah efek obat.

TS-ONE® tidak boleh digunakan bersamaan dengan obat-obat berikut:

- Obat-obatan anti kanker dari golongan Fluoropyrimidine:
  * Fluorouracil
  * Tegafur/uracil
  * Tegafur
  * Doxifluridine
  * Capecitabine
- Terapi kombinasi Folinate dengan Tegafur-Uracil
- Terapi kombinasi Levofolinat dengan Fluorouracil
- Fluoropyrimidine dengan kelompok obat antijamur golongan flucytosine

TS-ONE® dengan obat-obatan ini bisa berinteraksi dengan kuat satu sama lainnya dan kemudian menyebabkan efek samping secara serius.

Obat-obatan ini tidak boleh dipakai setidaknya 7 hari setelah menghentikan pemakaian TS-ONE®.

Sebagai tambahan, bila TS-ONE® dipakai setelah menghentikan salah-satu dari obat-obatan ini, maka perlu diberikan waktu untuk terjadi "washout" guna menghindari pengaruh dari obat-obatan ini. TS-ONE® tidak boleh dipakai bersamaan dengan obat-obat ini.

Mohon diinformasikan pada dokter anda bila anda sedang memakai obat-obat yang memiliki kandungan bahan yang telah disebutkan di atas, sebelum memakai TS-ONE®.

TS-ONE® harus dipakai dengan penuh kewaspadaan ketika dipakai bersama-sama dengan obat-obat berikut:

- Phenytoin
  Mual,muntah, *nystagmus* dan gangguan pergerakan mungkin bisa terjadi.
- Warfarin potasium
  Efek warfarin potasium mungkin bertambah kuat.
- Obat-obatan anti kanker lainnya atau terapi radiasi
  Gangguan kelainan pendarahan dan gangguan saluran cerna mungkin bertambah berat.

Mohon beritahukan pada dokter anda bila anda sedang memakai phenytoin, warfarin potassium atau obat-obatan anti kanker lainnya atau terapi radiasi.

Pemakaian obat secara benar

Administrasi:

TS-ONE®OD Tablet dapat diberikan dengan atau tanpa air sesudah makan. Bila obat tersebut diletakkan di lidah, air liur bisa menyusup ke dalam obat untuk menghancurkannya, oleh karenanya obat dapat digunakan tanpa air.

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Jika tidak, obat itu juga bisa dikonsumsi dengan air. Bila pasien tidak dapat duduk tegak dari posisi berbaring, obat tersebut tidak boleh dikonsumsi tanpa air. TS-ONE® harus diminum dua kali sehari (sesudah makan pagi dan sesudah makan malam).

Dosis umum:

Selalu memakai dosis TS-ONE® persis seperti yang diinstruksikan oleh dokter anda. Anda perlu berkonsultasi kembali dengan dokter anda bila tidak yakin dengan dosisnya.

Dokter anda akan memberitahukan besarnya dosis obat yang dipakai, jadwal pemakaian obat dan durasi (lamanya pemakaian obat). Dosis TS-ONE® yang anda pakai biasanya ditentukan oleh dokter anda berdasarkan tinggi dan berat badan anda. Bila terjadi efek samping yang terlalu berat, maka dokter anda mungkin mengurangi dosis obat.

Biasanya dosis standar didefinisikan sebagai dosis awal (dosis tunggal) untuk dewasa berdasarkan luas permukaan tubuh.

Sebagai kemoterapi adjuvant paska operasi kanker lambung:

Dosis TS-ONE® yang dianjurkan sebagai monoterapi adalah 40–60 mg (sebagai tegafur) tergantung dari luas permukaan tubuh penderita. Diberikan 2 kali sehari, sesudah makan pagi dan sesudah makan malam selama 28 hari berturut turut, diikuti 14 hari rehat obat (satu siklus pengobatan), pengobatan ini diulangi setiap 6 minggu.

Sebagai pengobatan pada penderita kanker lambung stadium lanjut pemberian, dikombinasikan dengan cisplatin:

Dosis TS-ONE® yang dianjurkan 40–60 mg (sebagai tegafur), tergantung dari luas permukaan tubuh penderita. Diberikan 2 kali sehari, sesudah makan pagi dan sesudah makan malam selama 21 hari berturut turut, diikuti 14 hari rehat obat, pengobatan ini diulangi setiap 5 minggu.

Dosis cisplatin yang dianjurkan adalah 60mg/m^2 pemberian secara infus melalui IV, diberikan pada hari ke 8 pada setiap siklus terapi. Hentikan pemberian cisplatin setelah 6 siklus tanpa menghentikan TS-ONE®. Bila pemberian cisplatin dihentikan sebelum 6 siklus, pengobatan dengan TS-ONE® saja dapat dimulai bila kriteria untuk memulai pengobatannya sudah memenuhi persyaratan.

Untuk pengobatan kanker kolorektal metastase bila diberikan dalam kombinasi dengan oxaliplatin sebagai pengobatan lini pertama, atau dalam kombinasi dengan irinotecan sebagai pengobatan lini kedua:

Dosis standar TS-ONE® yang direkomendasikan bila diberikan sebagai monoterapi adalah 40 - 60 mg (dinyatakan sebagai isi tegafur) tergantung pada luas permukaan tubuh pasien.

Untuk pengobatan lini pertama, TS-ONE® diminum dua kali sehari, sesudah makan pagi dan sesudah makan malam selama 14 hari berturut-turut, dikombinasikan dengan oxaliplatin 130 mg / m^2 pada Hari 1 sebagai infus intravena 2 jam. Pengobatan ini diulangi setiap 3 minggu.

Untuk pengobatan lini kedua, TS-ONE® diminum dua kali sehari, sesudah makan pagi dan sesudah makan malam hari selama 14 hari berturut-turut, dikombinasikan dengan irinotecan 125 mg / m^2 pada Hari 1 dan 15. Pengobatan ini diulangi setiap 4 minggu.

Untuk kemoterapi adjuvant pasca operasi untuk kanker pankreas
Untuk pengobatan kanker pankreas lokal stadium lanjut atau metastase

Dosis standar TS-ONE® yang direkomendasikan bila diberikan sebagai monoterapi adalah 40 - 60 mg (dinyatakan sebagai isi tegafur) tergantung pada luas permukaan tubuh pasien. Ini diminum dua kali sehari, sesudah makan

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pagi dan sesudah makan malam selama 28 hari berturut-turut, diikuti dengan masa istirahat 14 hari (1 siklus pengobatan).

TS-ONE® tidak direkomendasikan untuk anak-anak di bawah 18 tahun.

TS-ONE® tidak bisa digantikan dengan pengobatan fluoropyrimidine oral lainnya.

Overdosis:

Bila anda meminum tablet lebih banyak dari dosis yang seharusnya, segera hubungi dokter anda.

Dosis yang terlewatkan:

Bila anda melewati satu kali dosis TS-ONE®, JANGAN menggandakan dosis anda pada jadwal pemakaian obat selanjutnya. Lanjutkan dosis anda sebagaimana harusnya, dan konsultasikan dengan dokter anda.

Efek samping dan penanggulangannya

Sebagaimana halnya dengan semua jenis obat, TS-ONE® dapat menyebabkan efek samping, walaupun tidak semua orang mengalami hal ini. Beberapa jenis efek samping dapat dengan mudah dikenali bahkan oleh pasien sendiri, beberapa jenis efek samping lainnya membutuhkan test darah untuk memastikannya. Dokter anda akan membahas hal ini dengan anda dan kemudian menjelaskan efek samping yang dapat terjadi dan keuntungan dari perawatan yang akan dilakukan.

Bila anda khawatir efek samping tersebut di bawah ini, konsultasikan dengan dokter anda.

Beberapa efek samping umum yang terjadi antara lain:

- **Darah**: jumlah sel darah putih menurun, anemia, jumlah trombosit menurun
- **Hati**: perubahan-perubahan pada test darah, dimana hal ini menunjukkan keadaan kerja hati
- **Saluran cerna**: hilangnya nafsu makan, mual, muntah, diare, stomatitis, pengecapan tidak normal
- **Kulit**: pigmentasi
- **Hipersensitivitas (alergi)**: ruam
- **Psikoneurologis**: lemas

Efek samping yang tidak umum meliputi:

- **Darah**:Kecenderungan terjadinya pendarahan(titik-titik pendarahan pada subkutan, mimisan, kelainan faktor pembekuan darah), gangguan pembekuan darah dan pendarahan
- **Pernapasan**: *pneumonia interstitial* (gejala awal: batuk, nafas memendek, *dypsnea* dan demam), rhinitis, pharyngitis (radang tenggorokan), sputum (munculnya dahak)
- **Hati**: kuning pada mata dan kulit (*Jaundice*)
- **Ginjal**: Perubahan pada tes darah, yang memperlihatkan kerja ginjal, proteinuria, darah pada urin.
- **Saluran cerna**: penyumbatan usus, sakit perut, perasaan kembung pada perut/perut membesar, peradangan usus, ulkus saluran cerna, pendarahan saluran cerna, *cheilitis*, *glossitis*, konstipasi, mulut kering
- **Kulit**: timbulnya bercak merah (eritema), pengelupasan kulit (desquamasi), *flushing* (rona merah), bintil, *hand and foot syndrome* (sakit, bengkak dan kemerahan pada tangan dan/atau kaki), ulkus pada kulit, dermatitis, rambut rontok (alopesia), kelainan kuku, paronikia, herpes simplex, kulit kering/kasar.
- **Hipersensitivitas**: gatal
- **Psikoneurologis**: perasaan baal, sakit kepala, pusing, *dysosmia*
- **Jantungdanpembuluhdarah**: tekanan darah tinggi atau rendah, ECG tidak normal, Sindroma *Raynauds*

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- **Mata**: peningkatan produksi air mata (lakrimasi), keratitis, konjungtivitis, terkelupasnya sebagian lapisan permukaan mata (erosi korneal), nyeri mata, kepekaan penglihatan menurun, mata kering.
- **Lainnya**: demam, perasaan panas pada tubuh secara umum, kandungan gula pada urin, kadar gula darah tinggi, edema, nyeri otot, peningkatan CK (CPK), nyeri sendi, perubahan pada tes darah (peningkatan atau penurunan kadar natrium, kalium, kalsium dan klorida), penurunan berat badan.

Efek samping yang jarang terjadi juga bisa meliputi:

- anemia hemolitik
- gangguan berat pada hati
- dehidrasi
- cedera ginjal akut
- perforasi lambung, usus kecil dan usus besar, pankreatitis akut (gejala utamanya berupa nyeri perut atau peningkatan serum amilase)
- nyeri dada, sinkop, palpitasi (berdebar-debar), infark miokard, angina pectoris, aritmia (termasuk takikardia ventrikular) dan gagal jantung
- rasa sakit serius dengan melepuhnya kulit, mulut, mata dan alat kelamin [*sindroma muko-kutaneous-okular (sindrom steven-johnson) dan nekrolisis epidermal toksik (sindrom Lyell)*], alergi terhadap sinar matahari
- penyakit yang mempengaruhi *white matter* dari otak (*leukoencelopati* dengan gejala utama antara lain: *cerebellar ataxia*, gangguan kesadaran dan gejala mirip demensia), somnolen, gangguan kesadaran, gangguan bicara, disorientasi, *hypomnesia*, gejala ekstrapiramidal, gangguan pola gerak, *quadriplegia*, inkontinensia urin atau gangguan sensoris, perasaan kepala ringan, kehilangan fungsi penciuman, neuropati perifer
- ulkus kornea,sumbatan pada saluran lakrimal, opasitaskorneal, defisiensi sel punca limbal
- kerusakan otot (*rhabdomyolysis*: dengan gejala utama melibatkan nyeri otot, peningkatan CK (CPK) dan peningkatan mioglobin baik dalam darah maupun urin)

Bila anda mengalami salah satu dari efek samping yang di atas, mohon informasikan kepada dokter.

Bila salah satu efek samping yang terjadi menjadi semakin serius, hentikan pemakaian TS-ONE®dan informasikan ke dokter anda langsung.

Cara Penyimpanan Obat

Penyimpanan:

- Jauhkan dari jangkauan anak-anak
- Simpan dalam suhu di bawah 30°C. Setelah dibuka jauhkkan dari kelembaban.

Pembuangan obat:

Obat tidak boleh dibuang begitu saja sebagai limbah air maupun limbah sampah rumah tangga. Tanyakan pada apoteker anda bagaimana membuang obat yang sudah tidak diperlukan lagi. Langkah-langkah ini diperlukan untuk menjaga kebersihan lingkungan.

Informasi lebih lanjut

Untuk informasi lebih lanjut, mohon hubungi dokter, apoteker ataupun tenaga medis profesional anda lainnya.

Lembaran informasi ini dibuat oleh Taiho Pharmaceutical Co., Ltd.

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