1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TS-ONE® OD Tablet 20
Each tablet contains 20 mg tegafur, 5.8 mg gimeracil and 19.6 mg oteracil potassium (equivalent to 15.8 mg oteracil free acid).

TS-ONE® OD Tablet 25
Each tablet contains 25 mg tegafur, 7.25 mg gimeracil and 24.5 mg oteracil potassium (equivalent to 19.7 mg oteracil free acid).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

TS-ONE® OD Tablet 20: 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: an orally disintegrating, pale orange tablet with a white disc inset centrally in one face, having a characteristic odor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TS-ONE® is indicated in adults

- For the treatment of advanced gastric cancer when given in combination with cisplatin.
- For postoperative adjuvant chemotherapy for locally advanced (stage II (excluding T1), IIIA or IIIB) gastric cancer.
- For the treatment of locally advanced or metastatic pancreatic cancer when given as monotherapy.
- For the treatment of locally advanced or metastatic non-small cell lung cancer when given in combination with carboplatin.
- 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 the treatment of HER2-negative metastatic breast cancer when given as monotherapy.
- For the postoperative adjuvant chemotherapy for hormone receptor (HR)-positive and human epidermal growth factor 2 (HER2)-negative breast cancer at high risk of recurrence.

4.2 Posology and method of administration

TS-ONE® should only be prescribed by a qualified physician experienced in treating cancer patients with anti-neoplastic medicinal products.

Posology

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 monotherapy or combination therapy 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 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.

Monotherapy

- For postoperative adjuvant chemotherapy for locally advanced (stage II (excluding T1), IIIA or IIIB) gastric cancer
- For the treatment of locally advanced or metastatic pancreatic cancer
- For the treatment of HER2-negative metastatic breast cancer

The standard initial recommended dose for TS-ONE® is based on the patient's BSA as per Table 1 and should be taken after meals twice daily, 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 3.

Combination Therapy

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 after meals twice daily, 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 locally advanced or metastatic non-small cell lung cancer when given in combination with carboplatin

The standard initial recommended dose of TS-ONE® is based on the patient's BSA as per Table 1. TS-ONE® should be given after meals twice daily, morning and evening, for 14 consecutive days in combination with carboplatin (AUC, 5 by Calvert) on Day 1. This treatment cycle is repeated every 3 weeks.

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.

When used in combination with oxaliplatin, TS-ONE® should be given after meals twice daily, 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 cycle is repeated every 3 weeks.

When used in combination with irinotecan, TS-ONE® should be given after meals twice daily, morning and evening, for 14 consecutive days, in combination with irinotecan 125 mg/m^2 on Day 1 and 15. This treatment is repeated every 4 weeks.

For postoperative adjuvant chemotherapy for HR-positive and HER2-negative breast cancer at high risk of recurrence *Note 1)*

The standard initial recommended dose for TS-ONE® is based on the patient's BSA as per Table 1. TS-ONE® should be taken after meals twice daily, morning and evening, for 14 consecutive days followed by a 7-day rest, in combination with endocrine therapy. This treatment cycle is repeated every 3 weeks. This is regarded as one course of the regimen and is continued for up to 1 year. The dose can be decreased or increased according to the patient's condition. The dose should not be increased more than the patient's initial dose.

Note 1) High risk of recurrence was defined as patients with the following (1) or (2) in the Phase III Clinical Study (POTENT study) protocol.

(1) Patients with axillary lymph node metastasis (positive axillary lymph node metastasis before drug therapy in patients undergoing preoperative or postoperative drug therapy).
(2) Patients who are negative for axillary lymph node metastasis and meet any of the following 1) to 3).
    1) No history of preoperative drug therapy: (i) invasion diameter of 3 cm or more, (ii) histological grade (HG) 3, (iii) evident vascular invasion, (iv) HG2 with an invasion diameter of 2 cm or more and less than 3 cm, (v) HG2, an invasion diameter of less than 2 cm and high proliferation markers*, or (vi) HG1, an invasion diameter of 2 cm or more and less than 3 cm and high proliferation markers*.
    2) A history of preoperative chemotherapy: Residual invasive cancer is observed in the surgical specimen of the primary tumor or axillary lymph node.
    3) History of preoperative endocrine therapy: (i) invasion diameter of 3 cm or more, (ii) HG3, (iii) evident vascular invasion, (iv) HG2 and invasion diameter of 2 cm or more in the surgical specimen <3 cm, (v) HG2, invasion diameter <2 cm and high proliferation marker*, or (vi) HG1, invasion diameter ≥2 cm and <3 cm and high proliferation marker*.
    *: Ki-67 labeling index ≥30% or if Ki-67 labeling index was ≥14% and <30% by central pathological assessment, Oncotype DX measurement will be performed, and patients with recurrence score (RS) ≥18 will be eligible.

If the creatinine clearance (CrCl) is 50 ml/min or greater and less than 80 ml/min, start the treatment cycle with the following dosage.

Table 2: TS-ONE® starting dose for postoperative adjuvant chemotherapy for HR-positive and HER2-negative breast cancer patients at high risk of recurrence, according to creatinine clearance values at the start of the cycle of treatment

Creatinine clearance (CrCl)*	Body surface area	Initial dose (tegafur equivalent)
≥ 50 ml/min, < 80 ml/min	< 1.25 m^2	20 mg in the morning 40 mg in the evening
	≥ 1.25 m^2, < 1.5 m^2	40 mg each time
	≥ 1.5 m^2	50 mg each time

* If there is no measured CrCl value using 24-hour pooled urine, an estimate will be calculated using the Cockcroft-Gault formula.
Cockcroft-Gault equation
CrCl estimate = ((140 - Age) x Weight (kg)) / (72 x Serum creatinine (mg/dL)) (For women, further, multiply the obtained value by 0.85)
Efficacy and safety in patients with CrCl less than 50 ml/min have not yet been established.

Adjustments during treatment

General

Toxicity due to TS-ONE® administration alone or in combination with cisplatin, oxaliplatin, irinotecan or carboplatin should be managed with symptomatic treatment and/or treatment interruption or dose reduction. Patients taking TS-ONE® alone or in combination with cisplatin, oxaliplatin, irinotecan or carboplatin 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.

TS-ONE® dose modification criteria

Dose modification for toxicity should be made according to Tables 3, 4, 5, 6 and 7. 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 3: TS-ONE® Dose reductions (expressed as tegafur content)

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

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

- *During the treatment cycle*

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 3 and Table 4, respectively.

Table 4: Dose reductions for cisplatin

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

For dose modification of irinotecan, oxaliplatin and carboplatin, refer to their SmPC respectively.

- *At the initiation of subsequent cycles of treatment*

  If a treatment delay is indicated for either TS-ONE® or the combination therapy anti-cancer drugs, 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 5: 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

[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 optimised prior to a 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 6: 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 4 as per patient's condition.
30 to 49 ml/min	Dose reduction 1 in Table 3	
<30 ml/min	Not recommended	

Dose modifications for haematologic toxicities

Table 7: Haematologic toxicities for which TS-ONE® treatment should be suspended

Units	Neutrophils	Platelets	Haemoglobin	TS-ONE® dose modification
IU	$<0.5x10^9$/l	$<25x10^9$/l	4.0 mmol/l	Suspend treatment until resumption criterion is met (see Table 8) and then resume dosing at one reduced dose level

Resumption criteria for TS-ONE® treatment

Table 8: Minimum criteria to resume TS-ONE® treatment following its suspension due to a toxicity

Non-haematologic	**Haematologic**
Baseline or Grade 1	Platelet count $\geq 100x10^9$/l
Calculated creatinine clearance ≥30 ml/min	Neutrophils $\geq 1.5x10^9$/l
	Haemoglobin ≥6.2 mmol/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 3 (See TS-ONE® dose modification criteria).

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

Elderly

No adjustment of the standard dose is recommended in patients >70 years old (see section 4.8).

Hepatic impairment

No adjustment of the standard dose is recommended for patients with hepatic impairment (see section 5.2).

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).

Precaution on Dosage and Administration

1. 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.

2. 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®. Laboratory tests should be performed frequently, particularly when one course of the regimen is conducted and the dose is increased.

3. 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.

4. Efficacy and safety of combination therapy with TS-ONE® and chest or abdominal radiation have not yet been established.

4.3 Contraindications

- Patients with a history of severe hypersensitivity to the ingredients of TS-ONE®
- Patients with severe bone marrow depression [Bone marrow depression may be aggravated]
- 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 section 5.2)]
- Patients with severe hepatic disorder [Hepatic disorder may be aggravated]

- Patients receiving treatment with other fluoropyrimidine-group anti-cancer drugs including combination therapies with them (see section 4.5)

- History of severe and unexpected reactions to fluoropyrimidine therapy

- Patients receiving treatment with flucytosine (see section 4.5)

- Pregnant women or women suspected of being pregnant (see section 4.6)

- Breastfeeding (see section 4.6)

- Known dihydropyrimidine dehydrogenase (DPD) deficiency

- Recent or concomitant treatment with brivudine

- For TS-ONE® in combination with cisplatin, refer to the cisplatin SmPC for contraindications of cisplatin

- For TS-ONE® in combination with oxaliplatin, refer to oxaliplatin SmPC for contraindications of oxaliplatin

- For TS-ONE® in combination with irinotecan, refer to irinotecan SmPC for contraindications of irinotecan

- For TS-ONE® in combination with carboplatin, refer to carboplatin SmPC for contraindications of carboplatin

4.4 Special warnings and precautions for use

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.

The dose-limiting toxicity (DLT) of TS-ONE® for Asian patients is bone marrow depression and for Caucasian patients is diarrhoea and dehydration (see section 4.8), in which is different from conventional oral fluorouracil-group drugs. Most adverse reactions are reversible and can be managed by symptomatic therapy, dose interruptions and dose reductions.

<u>Bone marrow suppression</u>

Treatment-related bone marrow suppression, including neutropaenia, leukopaenia, thrombocytopaenia, anaemia, and pancytopaenia, has been reported among patients treated with TS-ONE®. Patients with low white blood cell counts should be monitored carefully for infection and risk of other complications of neutropaenia and treated as medically indicated (e.g., with antibiotics, granulocyte-colony stimulating factor [G-CSF]). Patients with low platelet counts are at increased risk for bleeding and should be monitored carefully. The dose should be modified as recommended in Section 4.2.

Severe hepatic disorders

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 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.

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.

Diarrhoea

Patients with diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Prophylactic treatment for diarrhoea should be administered as indicated. Standard anti-diarrhoeal therapy (e.g., loperamide) and intravenous fluids/electrolytes should be initiated early when diarrhoea develops. Dose suspension/adjustment should be implemented with the occurrence of Grade 2 or higher diarrhoea if symptoms persist despite adequate treatment. Dose modification should be applied for the precipitating adverse reactions as necessary (see Section 4.2).

Dehydration

Dehydration and any associated electrolyte disturbances should be prevented or corrected at onset. Patients with anorexia, asthenia, nausea, vomiting, diarrhoea, stomatitis, and gastrointestinal obstruction should be monitored closely for signs of dehydration. Dehydration should be managed aggressively with rehydration and other appropriate measures. If Grade 2 (or higher) dehydration occurs, treatment should be immediately suspended and the dehydration corrected. Treatment should not be resumed until dehydration and its underlying causes are corrected or adequately controlled. Dose modifications should be applied for the precipitating adverse reactions as necessary (see Section 4.2).

Renal toxicity

Treatment with TS-ONE® in combination with cisplatin may be associated with a transient decline of glomerular filtration rate caused primarily by pre-renal factors (e.g., dehydration, electrolyte imbalance, etc). Adverse reactions of Grade 3 or higher such as increased blood creatinine, decreased creatinine clearance, toxic nephropathy, and acute kidney injury have all been reported in patients receiving TS-ONE® (see section 4.8). To detect early changes in renal function during treatment, renal parameters should be closely monitored (e.g., serum creatinine, CrCl).

Gimeracil increases 5-fluorouracil (5-FU) exposure by inhibiting DPD, the primary enzyme for metabolizing 5-FU. Gimeracil is primarily cleared by the kidney (see section 5.2); so in patients with renal insufficiency, gimeracil renal clearance is decreased and 5-FU exposure thus increased. Treatment-related toxicities can be expected to increase as 5-FU exposure increases (see section 5.2).

Dehydration and diarrhoea may increase the risk of renal toxicity for cisplatin. Hyperhydration (forced diuresis) should be administered according to the cisplatin SmPC to reduce the risk of renal toxicity associated with cisplatin therapy.

If deterioration of glomerular filtration rate is observed, TS-ONE® and/or cisplatin dose should be adjusted according to Table 6 and appropriate supportive measures taken (see Section 4.2).

Severe renal impairment
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, unless the benefits clearly outweigh the risks (see sections 4.2, 4.8 and 5.2).

Ocular toxicity

The most common treatment-related ocular disorders among patients in studies in Europe/United States of America (EU/USA) treated with TS-ONE® in combination with cisplatin were lacrimal disorders, including increased lacrimation, dry eye, and acquired dacryostenosis.

Most ocular reactions will resolve or improve with suspension of medicinal product and proper treatment (instillation of artificial tears, antibiotic eye drops, implantation of glass or silicone tubes in lacrimal punctas or canaliculi, and/or use of spectacles rather than contact lenses). Efforts should be made to ensure early detection of ocular reactions, including an early ophthalmologic consultation in the event of any persistent or vision-reducing ocular symptoms such as lacrimation or corneal symptoms.

Refer to the cisplatin SmPC for eye disorders observed with cisplatin therapy.

Coumarin-derivative anticoagulant

Patients receiving oral coumarin-derivative anticoagulant therapy must have their anticoagulant response (International Normalized Ratio for prothrombin time [INR] or prothrombin time [PT]) monitored closely and the anticoagulant dose adjusted accordingly (see section 4.5). The use of coumarin-derivative anticoagulant in clinical trials has been associated with elevated INR and gastrointestinal bleeding, bleeding tendency, haematuria, and anaemia in patients receiving TS-ONE® therapy.

Brivudine

Brivudine must not be administered concomitantly with TS-ONE®. Fatal cases have been reported following capecitabine interaction. There must be at least a 4-week waiting period between end of treatment with brivudine and start of TS-ONE® therapy. Treatment with brivudine can be started 24 hours after the last dose of TS-ONE® (see Section 4.3 and 4.5). In the event of accidental administration of brivudine to patients being treated with TS-ONE®, effective measures should be taken to reduce the toxicity of TS-ONE®. Immediate admission to hospital is recommended. All measures should be initiated to prevent systemic infections and dehydration.

DPD inducers

If DPD inducers were to be concomitantly administered with TS-ONE®, the exposure of 5-FU might not reach the efficacious level. However, since no DPD inducers are currently known, the interaction between a DPD inducer and TS-ONE® cannot be evaluated.

Microsatellite instability (MSI)

TS-ONE® has not been studied in gastric cancer patients with MSI. The association between 5-FU sensitivity and MSI in patients with gastric cancer is unclear and the association between TS-ONE® and MSI in gastric cancer is unknown.

Glucose/galactose intolerance/malabsorption

This medicinal product contains lactose. Patients with rare hereditory problems of galactose intolerance, the Lapp lactase deficiency or glucose/galactose malabasorption should not take this medicinal product.

Abnormal glucose tolerance may be aggravated.

Other oral fluoropyrimidines

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 Levofolinate and fluorouracil 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 section 4.5).

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 section 4.5).

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 section 4.5).

No clinical trials are available comparing TS-ONE® versus other oral 5-FU compounds. Therefore, TS-ONE® cannot be used as a substitute for other oral 5-FU products.

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.]

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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with other medicinal products

No interaction studies have been performed in adult or pediatric patients.

Other fluoropyrimidines

Co-administration of other fluoropyrimidines such as capecitabine, 5-FU, tegafur, or flucytosine can lead to additive toxicities, and is contraindicated. A minimum washout

period of 7 days is recommended between administration of TS-ONE® and other fluoropyrimidines. The washout period described in the SmPC of other fluoropyrimidine medicinal products should be followed if TS-ONE® is to be administered subsequent to other fluoropyrimidine medicinal products.

Brivudine

A clinically significant interaction between brivudine and fluoropyrimidines (e.g. capecitabine, 5-Fluorouracil, tegafur), resulting from the inhibition of dihydropyrimidine dehydrogenase by brivudine, has been described. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, brivudine must not be administered concomitantly with TS-ONE® (see section 2 and 3). There must be at least a 4-week waiting period between end of treatment with brivudine and start of TS-ONE® therapy. Treatment with brivudine can be started 24 hours after the last dose of TS-ONE®.

CYP2A6 inhibitors

As CYP2A6 is the major enzyme responsible for the conversion of tegafur to 5-FU, co-administration of a known CYP2A6 inhibitor and TS-ONE® should be avoided as effectiveness of TS-ONE® could be decreased (see section 5.2).

Folinate/folinic acid

No data are available on the concomitant use of folinic acid with TS-ONE®. However, metabolites of folinate/folinic acid will form a ternary structure with thymidylate synthase and fluorodeoxyuridine monophosphate (FdUMP), potentially increasing the cytotoxicity of 5-FU. Caution is advised as folinic acid is known to enhance the activity of 5-FU.

Nitroimidazoles, including metronidazole and misonidazole

No data are available on the concomitant use of nitroimidazoles with TS-ONE®. However, nitroimidazoles may reduce clearance of 5-FU and thus increase plasma levels of 5-FU. Caution is advised as co-administration may increase the toxicity of TS-ONE®.

Methotrexate

No data are available on the concomitant use of methotrexate with TS-ONE®. However, polyglutamated methotrexate inhibits thymidylate synthase and dihydrofolate reductase, potentially increasing cytotoxicity of 5-FU. Caution is advised as co-administration may increase the toxicity of TS-ONE®.

Clozapine

No data are available on the concomitant use of clozapine with TS-ONE®. However, due to possible additive pharmacodynamic effects (myelotoxicity), caution is advised as co-administration may increase the risk and severity of haematologic toxicity of TS-ONE®.

Cimetidine

No data are available on the concomitant use of cimetidine with TS-ONE®. However, co-administration may decrease clearance and, thus increase plasma levels of 5-FU. Caution is advised as co-administration may increase the toxicity of TS-ONE®.

Coumarin-derivative anticoagulant

The activity of coumarin-derivative anticoagulant was enhanced by TS-ONE®. Caution is advised as co-administration of TS-ONE® and coumarin-derivative anticoagulant therapy may increase the risk of bleeding.

Phenytoin

Fluoropyrimidines may increase phenytoin plasma concentration when administered concomitantly with phenytoin causing phenytoin toxicity. Frequent monitoring of phenytoin blood/plasma levels is advised when TS-ONE® and phenytoin are administered concomitantly. If indicated, the dose of phenytoin should be adjusted according to the phenytoin SmPC. If phenytoin toxicity develops, appropriate measures should be taken.

Other

Based on non-clinical data, allopurinol may decrease anti-tumour activity due to suppression of phosphorylation of 5-FU. Therefore, concurrent administration with TS-ONE® should be avoided.

Other forms of interaction

Food

Administration of TS-ONE® with a meal reduced exposure to oteracil and gimeracil, with a more pronounced effect for oteracil than for gimeracil (see section 5.2). TS-ONE® OD Tablet should be taken with or without water after a meal.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with this medicinal product.

Contraception in males and females

Contraceptive measures must be taken by both male and female patients during and up to 6 months after stopping treatment with TS-ONE®.

Pregnancy

TS-ONE® is contraindicated in pregnancy (see section 4.3). There have been some case reports of foetal abnormalities. Studies in animals have shown reproductive toxicity. As with other fluoropyrimidines, TS-ONE® administration caused embryolethality and teratogenicity in animals (see section 5.3). If the patient becomes pregnant while receiving TS-ONE®, treatment should be discontinued and the potential risk to the foetus must be explained. Genetic counseling should be considered.

Breastfeeding

TS-ONE® is contraindicated during breastfeeding (see section 4.3). It is not known whether TS-ONE® or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of TS-ONE® or its metabolites in milk (for details see section 5.3).

A risk to newborns/infants cannot be excluded. Breastfeeding should be discontinued while receiving treatment with TS-ONE®.

Fertility

No data are available on the effect of TS-ONE® on human fertility. Non-clinical studies demonstrated that TS-ONE® did not appear to affect male or female fertility in the rat (see section 5.3).

For combination therapy, refer to the respective SmPC of cisplatin, oxaliplatin, irinotecan and carboplatin for their effects on fertility, pregnancy and lactation.

4.7 Effects on ability to drive and use machines

TS-ONE® has a moderate influence on the ability to drive and use machines as fatigue, dizziness, blurred vision, and nausea are common adverse reactions of TS-ONE®.

4.8 Undesirable effects

Summary of safety profile

(i) For postoperative adjuvant chemotherapy for locally advanced (stage II (excluding T1), IIIA or IIIB) gastric cancer.

Table 9 shows the frequency of adverse events occurring in ≥ 5% of patients reported in the randomized study of postoperative 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 the 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 9: Frequency of adverse events occurring in ≥ 5% of patients in the randomized study of postoperative 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%
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%	5.3%	0.4%
glycosuria	7.0%	1.2%	4.2%	1.1%
Stomatitis	32.1%	0.2%	3.4%	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%	—	0.4%	—
Lacrimation	8.3%	0%	0%	0%
Taste abnormality	13.2%	0%	1.0%	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%
Nasopharyngitis	9.5%	0%	2.1%	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.

(ii) For the treatment of locally advanced or metastatic pancreatic cancer

Table 10 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 10: Frequency of common drug-related adverse events (> 10% incidence) in the randomized phase III study of gemcitabine versus TS-ONE® versus gemcitabine plus TS-ONE® in locally advanced or metastatic pancreatic cancer

AE term	GEM		TS-1		GEM + TS-1	
	N	(%)	N	(%)	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®

(iii) <u>For postoperative adjuvant chemotherapy for HR-positive and HER2-negative breast cancer at high risk of recurrence</u>

In the 954 patients included in the safety analysis of the TS-ONE and endocrine therapy combination group, the incidence of adverse events was 99.0% (944 patients). The most common adverse events were leukopenia 54.4%, hyperpigmentation 50.3%, increased ALT 42.9%, neutropenia 42.0%, increased blood bilirubin 40.8%, fatigue 39.1%, increased AST 38.6%, anemia 34.9%, nausea 34.5%, diarrhea 32.3%, and thrombocytopenia 32.2%.

4.8.1 Clinically significant adverse reactions

The overall safety profile of TS-ONE® is based on data from 751 patients treated with TS-ONE® postoperative adjuvant therapy in clinical studies for advanced or recurrent cancer and from postmarketing 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, anemia and thrombocytopenia (above mentioned incidence) 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®.

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.

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®.

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 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 (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.

   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.

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.

4.8.2 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

4.8.3 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 randomised study of postoperative adjuvant chemotherapy for gastric cancer, frequency of lacrimation (7.2%) was higher than in studies of advanced or recurrent cancer. In patients who were administered TS-ONE® in the postmarketing clinical study for unresectable or recurrent gastric cancer, the incidence of lacrimation was high (16.0%).

Incidence / *Classification*	*≥ 5%*	*0.1% to < 5%*	*incidence unknown*
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*	*Photosensitivity, DLE-like eruption*
Hypersensitivity	*Rash*	*Itching*	
Psychoneurologic	*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 overall safety profile of TS-ONE® in combination with cisplatin is based primarily on clinical study data from 593 patients with advanced gastric cancer treated with this regimen in a mainly Caucasian population (FLAGS study). Among 593 patients treated with TS-ONE® in combination with cisplatin, the most common severe adverse reactions (Grade 3 or higher with frequency of at least 10%) were neutropenia, anaemia and fatigue.

The following headings are used to rank the adverse reactions by frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data). The frequencies of very common, common, and uncommon adverse reactions are from 593 patients treated with TS-ONE® in combination with cisplatin in clinical trials. The frequencies of medically relevant rare and very rare adverse reactions are estimated from postmarketing surveillance of 866,000 patients in Asia (mostly Japanese) treated with TS-ONE® based therapy. Each term is presented in its most common category only and within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reactions reported by decreasing seriousness in each frequency grouping

System Organ Class[a]	Very Common	Common	Uncommon	Rare / Very Rare
Infections and Infestations			Neutropenic sepsis, septic shock, sepsis, infection, pneumonia, bacteremia, respiratory tract infection, upper respiratory tract infection, pyelonephritis acute, urinary tract infection, pharyngitis, nasopharyngitis, rhinitis, tooth infection, candidiasis, oral herpes, paronychia, furuncle	Hepatitis B reactivation
Neoplasms Benign, Malignant and Unspecified (Incl. cysts and polyps)			Tumour haemorrhage, cancer pain	
Blood and Lymphatic System Disorders	Neutropenia, leukopenia, anaemia, thrombo-cytopenia	Febrile neutropenia, lymphopenia	Pancytopenia, prothrombin time prolonged, international normalised ratio increased, hypoprothrombinaemia, prothrombin time shortened, granulocytosis, leukocytosis, eosinophilia, lymphocytosis, monocyte count decreased, monocyte count increased, thrombocythaemia	Disseminated intravascular coagulation
Immune System Disorders			Hypersensitivity	
Endocrine Disorders			Adrenal haemorrhage	
Metabolism and Nutrition Disorders	Anorexia	Dehydration, hypokalaemia, hyponatraemia, hypocalcaemia, hypomagnesaemia, hypoalbuminaemia, hyperkalaemia	Hyperglycaemia, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, hypophosphatemia, hypermagnesaemia, gout, hypoproteinaemia, hyperglobulinaemia, hyperlipidaemia, oral intake reduced	
Psychiatric Disorders		Insomnia	Confusional state, restlessness, personality disorder, hallucination, depression, anxiety, libido decreased,	

System Organ Class[a]	Very Common	Common	Uncommon	Rare / Very Rare
			sexual inhibition	
Nervous System Disorders	Peripheral neuropathy	Dizziness, headache, dysgeusia	Cerebrovascular accident, cerebellar infarction, cerebrovascular disorder, convulsion, ischaemic stroke, syncope, hemiparesis, aphasia, ataxia, metabolic encephalopathy, loss of consciousness, acoustic neuritis, memory impairment, balance disorder, somnolence, tremor, ageusia, parosmia, burning sensation, formication	Leukoenceph-alopathy, anosmia
Eye Disorders		Vision disorder, lacrimal disorder, conjunctivitis, corneal disorder[b]	Eye allergy, eyelid ptosis, erythema of eyelid	
Ear and Labyrinth Disorders		Hearing impairment, deafness	Vertigo, ear congestion, ear discomfort	
Cardiac Disorders			Cardiac failure, acute myocardial infarction, pericardial effusion, atrial fibrillation, angina pectoris, cardiac fibrillation, tachycardia, palpitations	
Vascular Disorders		Hypotension, deep vein thrombosis, hypertension	Iliac artery thrombosis, hypovolaemic shock, arterial limb thrombosis, thrombosis, flushing, pelvic venous thrombosis, thrombophlebitis, phlebitis, phlebitis superficial, orthostatic hypotension, haematoma, hyperaemia, hot flush	
Respiratory, Thoracic and Mediastinal Disorders		Dyspnoea, epistaxis, hiccups, cough	Pulmonary embolism, respiratory tract haemorrhage, exertional dyspnoea, pharyngolaryngeal pain, rhinorrhoea, pharyngeal erythema, rhinitis allergic, dysphonia, productive cough, nasal congestion	Interstitial lung disease
Gastro-intestinal Disorders	Diarrhoea, vomiting, nausea, constipation	Gastrointestinal haemorrhage, stomatitis, gastrointestinal inflammation, flatulence, abdominal pain, dysphagia, abdominal discomfort, dyspepsia, dry mouth	Gastrointestinal perforation, oesophagitis, gastrointestinal infection, ileus, gastrointestinal obstruction, ascites, lip oedema, oesophageal spasm, gastric ulcer, gastroesophageal reflux disease, reflux gastritis, retroperitoneal fibrosis, gastrointestinal disorder, anal haemorrhage, haemorrhoids, salivary hypersecretion, retching, salivary gland disorder, cheilitis, aerophagia, eructation, glossodynia, oral pain, teeth brittle	Acute pancreatitis, Terminal ileitis
Hepatobiliary Disorders		Hyperbilirubin-aemia, alanine aminotransferase increased, aspartate	Liver function test abnormal, gamma glutamyltransferase increased	Acute hepatic failure

System Organ Class[a]	Very Common	Common	Uncommon	Rare / Very Rare
		aminotransferase increased		
Skin and Subcutaneous Tissue Disorders		Palmar-plantar erythrodysaesthesia syndrome, rash, skin hyperpigmentation, dry skin, pruritus, alopecia	Exfoliative rash, skin exfoliation, necrolytic migratory erythema, blood blister, dermatitis allergic, skin reaction, dermatitis acneiform, erythema, increased tendency to bruise, purpura, hyperhidrosis, night sweats, nail atrophy, pigmentation disorder, skin discoloration, hypertrichosis	Toxic epidermal necrolysis, Stevens-Johnson syndrome, photosensitivity reaction, nail disorder
Musculo-skeletal and Connective Tissue Disorders		Musculoskeletal pain	Muscle spasms, arthralgia, pain in extremity, back pain, neck pain, bone pain, joint swelling, limb discomfort, muscle tightness, muscular weakness	Rhabdomyolysis
Renal and Urinary Disorders		Renal failure, blood creatinine increased, glomerular filtration rate decreased, blood urea increased	Toxic nephropathy, oligouria, haematuria, renal impairment, pollakiuria, blood creatinine increased, blood creatinine decreased	
Reproductive System and Breast Disorders			Erectile dysfunction, breast tenderness, nipple pain	
General Disorders and Administration Site Conditions	Fatigue, asthenia	Mucosal inflammation, pyrexia, weight decreased, peripheral oedema, chills	Multi-organ failure, performance status decreased, pain, oedema, chest pain, chest discomfort, generalized oedema, face oedema, local swelling, localized oedema, weight increased, early satiety, feeling cold, injection site reaction, malaise	
Injury, Poisoning and Procedural Complications			Contusion, medication error	

[a] Adverse reactions in the Investigations system organ class (SOC) have been reallocated to clinically appropriate SOCs related to their target organ.
Different MedDRA preferred terms that were considered clinically similar have been grouped into a single term.
[b] incl corneal epithelium defect, corneal erosion, corneal lesion, corneal opacity, corneal perforation, keratitis, punctate keratitis, ulcerative keratitis, limbal stem cell deficiency, visual acuity reduced, visual impairment, vision blurred.

Description of selected adverse reactions

Ocular toxicity

Terms for treatment-related ocular toxicities have been combined as follows. The only Grade 3 or higher adverse reaction was reduced visual acuity.

- Vision disorder includes adverse reactions of blurred vision, diplopia, photopsia, reduced visual acuity, and blindness;
- Lacrimal disorder includes adverse reactions of increased lacrimation, dry eye, and acquired dacryostenosis;
- Eye disorder includes adverse reactions of eye pruritus, ocular hyperaemia, eye irritation, eye disorder, and foreign body sensation in eyes.

Neuropathy

Central and peripheral neuropathy has been reported in patients treated with TS-ONE® in combination with cisplatin. The term peripheral neuropathy includes the following reported adverse reactions: peripheral sensory neuropathy, paraesthesia, hypoaesthesia, peripheral neuropathy, polyneuropathy, neurotoxicity, and dysaesthesia.

4.8.4 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

4.8.5 Special populations

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

Pediatric Use
No studies have been performed with TS-ONE® in pediatric patients.

Gender
There are no clinically significant differences in safety between males (N=382) and females (N=139) in the clinical study data from the Caucasian population (FLAGS study).

Patients with renal impairment
Comparison of 218 patients with mild renal impairment at baseline (CrCl 51 to 80 ml/min) to 297 patients with normal renal function at baseline (CrCl >80 ml/min) treated with TS-ONE® in combination with cisplatin in the FLAGS study indicated that there were no clinically significant differences in safety between patients with mild renal impairment and patients with normal renal function.

In a study performed in patients with renal impairment, the most common adverse reactions reported over all cycles across all cohorts were diarrhoea (57.6%), nausea (42.4%), vomiting (36.4%), fatigue (33.3%) and anaemia (24.2%). In this study, 7 patients with moderate renal impairment were treated with 20 mg/m^2 TS-ONE® twice daily, while 7 patients with severe renal impairment received TS-ONE® 20 mg/m^2 once daily. No dose limiting toxicities were observed in Cycle 1 in patients with moderate or severe renal impairment. The incidence of blood and lymphatic systems disorders adverse reactions observed across all cycles in the moderate and severe renal impairment patients were 28.6% and 44.4%, respectively. The dose for one patient in the severe cohort was reduced to 13.2 mg/m^2 once daily at the start of Cycle 12 due to an adverse reaction (Grade 2 diarrhoea) in Cycle 11.

4.9 Overdose

The highest single dose of TS-ONE® taken in an Asian patient was 200 mg (in an Asian phase I clinical trial). The highest single dose of TS-ONE® taken in a Caucasian patient was 1400 mg; this patient developed leukopenia (Grade 3). Manifestations of acute overdose reported include nausea, vomiting, diarrhoea, mucositis, gastrointestinal irritation, bleeding, bone marrow depression, and respiratory failure. Medical management of overdose should include customary therapeutic and supportive medical interventions aimed at correcting the presenting clinical manifestations and preventing their possible complications.
There is no known antidote available in case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, antimetabolites, ATC code: L01BC53.

Pharmacodynamic effects

TS-ONE® is an oral fluoropyrimidine anti-cancer medicinal product. It is a fixed dose combination of three active substances, tegafur, which after absorption is converted into the anti-cancer substance 5-FU; gimeracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor to prevent degradation of 5-FU by the body; and, oteracil, an orotate phosphoribosyltransferase (OPRT) inhibitor that decreases the activity of 5-FU in normal gastrointestinal mucosa. The combination of tegafur, gimeracil, and oteracil was set at 1:0.4:1 molar ratio as optimum in order to maintain 5-FU exposure and thus sustain anti-tumour activity while reducing toxicity associated with 5-FU alone.

Tegafur is a prodrug of 5-FU with good oral bioavailability. Following oral administration, tegafur is gradually converted to 5-FU *in vivo*, mainly by CYP2A6 enzyme activity in the liver. 5-FU is metabolised by the liver enzyme DPD. 5-FU is activated within cells by phosphorylation to its active metabolite, 5-fluoro-deoxyuridine-monophosphate (FdUMP). FdUMP and reduced folate are bound to thymidylate synthase leading to formation of a ternary complex which inhibits DNA synthesis. In addition, 5-fluorouridine-triphosphate (FUTP) is incorporated into RNA causing disruption of RNA functions.

Gimeracil inhibits the metabolism of 5-FU by reversibly and selectively inhibiting DPD, the primary metabolic enzyme for 5-FU, so that higher plasma concentrations of 5-FU are achieved with the administration of a lower dose of tegafur.

After oral administration, oteracil was distributed at high concentrations in normal gastrointestinal tract tissues while considerably lower concentrations were seen in blood and tumour tissue in animal studies.

5.2 Pharmacokinetic properties

Absorption

After single oral administration of TS-ONE® at recommended dose (32 - 40 mg/m^2, expressed as tegafur content, based on body surface area) in cancer patient (N=12) after a meal, the mean T_{max} for TS-ONE® components tegafur, gimeracil, and oteracil was 2.4, 2.1, and 2.3 hours, respectively, and the mean ± standard deviation (SD) AUC_{0-t} and C_{max} was 28217 ± 7771 ng.hr/ml and 1971 ± 269 ng/ml for tegafur, 1372 ± 574 ng.hr/ml and 285 ± 117 ng/ml for gimeracil, 366 ± 249 ng.hr/ml and 78 ± 58 ng/ml for oteracil. The median T_{max} for 5-FU was 3.5 hours and the mean AUC_{0-inf} and C_{max} was 724 ± 273 ng.hr/ml and 129 ± 42 ng/ml.

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. After multiple dose administration (32 - 40 mg/m^2, expressed as tegafur content, twice daily for 28 days; N=10), the median T_{max} of tegafur, gimeracil, and oteracil was 3.0, 2.6, and 2.6 hours, respectively, and the corresponding mean ± SD AUC_{0-t} and C_{max} was 80032 ± 20993 ng.hr/ml and 4166 ± 834 ng/ml for tegafur, 1364 ± 352 ng.hr/ml and 276 ± 142 ng/ml for gimeracil, and 550 ± 500 ng.hr/ml and 130 ± 190 ng/ml for oteracil. The mean T_{max} for 5-FU was 3.4 hours and the mean $AUC_{(0-12h)}$ and C_{max} was 609 ± 170 ng.hr/ml and 114 ± 41 ng/ml, respectively.

Administration of TS-ONE® under fed conditions resulted in decreased AUC_{0-inf} for oteracil of approximately 71% and gimeracil of approximately 25% relative to fasting administration. Concomitant administration of a proton pump inhibitor (PPI) reduced the effect of food on the pharmacokinetic profile of oteracil, but not by a sufficient margin to completely negate the food effect. There was a 15% decrease in AUC_{0-inf} for 5-FU under fed versus fasting conditions, and tegafur exposure was not altered by food.

Mean AUC_{0-inf} and C_{max} for 5-FU were approximately 3-fold greater following administration of TS-ONE® (50 mg expressed as tegafur content) than following administration of tegafur alone (800 mg), while AUC_{0-inf} and C_{max} values for the 5-FU metabolite α-fluoro-β-alanine (FBAL) were approximately 15- to 22-fold lower following administration of TS-ONE® than following administration of tegafur.

The oteracil component of TS-ONE® did not affect the pharmacokinetic profiles of 5-FU, tegafur, gimeracil, FBAL, or uracil. The gimeracil component did not affect the pharmacokinetic profile of tegafur.

Distribution

Oteracil, gimeracil, 5-FU, and tegafur were 8.4%, 32.2%, 18.4%, and 52.3% protein bound, respectively. The protein binding in human serum was not concentration-dependent over a range of 0.1 to 1.0 µg/ml for oteracil, gimeracil, and 5-FU and 1.2 to 11.8 µg/ml for tegafur.

There are no clinical data on the distribution of radiolabeled components of TS-ONE®. Although no intravenous data are available for TS-ONE® in humans, the volume of distribution could be roughly estimated from the apparent volume of distribution and urinary excretion data as 16 l/m^2, 17 l/m^2, and 23 l/m^2 for tegafur, gimeracil and oteracil, respectively.

Biotransformation

The main metabolic pathway for tegafur is through conversion to 5-FU via CYP2A6 in the liver, whereas gimeracil was stable in human liver homogenate (S9 fraction) with adenosine 3'-phosphate 5'-phosphosulfphate lithium salt (PAPS; a co-factor for sulfotransferase) or nicotinamide adenine dinucleotide phosphate (NADPH). Based on the results of *in vitro* studies, a part of oteracil is non-enzymatically degraded to 5-azauracil (5-AZU) by gastric fluid, and is then converted to cyanuric acid (CA) in the digestive tract. 5-AZU and CA do not inhibit OPRT enzyme activity. Only a small amount of oteracil is metabolised in the liver because of its low permeability.

In vitro evaluation using human liver microsomes indicated that neither tegafur, gimeracil nor oteracil showed any relevant inhibitory effects on enzyme activities of the cytochrome P450 isoforms tested (i.e., CYP1A1/2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4).

In vitro evaluation using primary cultures of human hepatocytes indicated that tegafur (0.7-70 μM), gimeracil (0.2-25 μM) and oteracil (0.04-4 μM) had little or no inductive effect on CYP1A2, CYP2B6 or CYP3A4/5 metabolic activities.

Using plasma uracil concentrations to assess DPD activity in clinical studies, no marked changes in plasma uracil concentrations were observed after administration of a single 800 mg dose of tegafur while plasma uracil concentrations increased markedly after administration of a single 50 mg dose of TS-ONE® (reflecting DPD inhibition by gimeracil). Following both single dose (50 mg) and multiple dose (30 mg/m^2 twice daily) administration of TS-ONE® in man, maximum uracil concentrations reflecting DPD inhibition were observed approximately 4 hours postdose. Similar inhibition was seen following single and multiple dosing. The plasma concentrations of uracil returned to baseline levels approximately 48 hours after dosing indicating reversibility of DPD inhibition by gimeracil.

Elimination

In man, the apparent terminal elimination half-life ($T_{1/2}$) of 5-FU observed after administration of TS-ONE® (containing tegafur, a 5-FU prodrug) was longer (1.9 ± 0.4 hours) than that previously reported after intravenous administration of 5-FU (10 to 20 minutes). Following a single dose of TS-ONE®, the mean $T_{1/2}$ values were 13.1 ± 3.1 hours for tegafur, 3.0 ± 0.5 hours for gimeracil, and 3.8 ± 1.6 hours for oteracil.

Urinary excretion within 12 hours after administration of TS-ONE® was 47.4% for gimeracil, 4.4% for tegafur, 7.0% for 5-FU, and 1.9% for oteracil. Urinary excretion within 72 hours was 52.8% for gimeracil, 7.8% for tegafur, 7.4% for 5-FU, and 2.2% for oteracil, indicating that urinary excretion was nearly completed by 12 hour.

Linearity/non-linearity

In a Japanese Phase I study that utilized 5 dose groups with doses ranging from 25 to 200 mg/body, there was a dose-proportional increase in exposure for tegafur, gimeracil and oteracil. However, the increase in 5-FU exposure tended to be greater than proportional to the increasing tegafur dose.

Pharmacokinetics in special populations

Population PK

A population PK analysis of TS-ONE® components and metabolites assessed the influence of various factors, including gender, age, food, ethnicity (Caucasian vs Asian), renal function, and hepatic function in 315 patients. Renal function, as reflected by creatinine clearance, was the primary factor that influenced gimeracil exposure and 5-FU exposure. As renal function decreased, there was an increase in 5-FU steady state exposure. This analysis also demonstrated that the trend in changes in TS-ONE® pharmacokinetics observed with increasing age was related to change in renal function as measured by creatinine clearance.

Renal impairment

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 (0-8hr)	
(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:

In men:

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

In women:

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

Phase I study of TS-ONE® investigated the 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 an 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. 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. However, it is to be noted that the exposure to 5-FU can be variable and unexpectedly higher in patients with severe renal impairment due to the impact of fluctuations in renal function in these patients.

Hepatic impairment

There were no significant differences in AUCs of 5-FU, tegafur, gimeracil or oteracil after either single or multiple dose administration of TS-ONE® 30mg/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.

Ethnic differences

During the clinical study of TS-ONE®, a difference was noted between the Asian and the Caucasian pharmacokinetic curves that showed the plasma concentration of tegafur and 5-FU. From the comparison of the pharmacokinetics curves, it was discovered that Asian patients showed slightly lower CYP2A6 activity compared to the Caucasian patients. CYP2A6 is the enzyme that metabolizes the active ingredient, tegafur in TS-ONE®. With a lower CYP2A6 activity, a slightly higher dose of tegafur would be required for Asian patients compared to Caucasian with similar body surface area in order to produce the same efficacy and safety results.

Pediatric population

No pharmacokinetic studies have been conducted with TS-ONE® in pediatric patients.

5.3 Preclinical safety data

Repeat-dose toxicity studies in rats, dogs and monkeys produced changes typically associated with administration of an anti-cancer medicinal product eliciting cytotoxic effects on populations of rapidly dividing cells, such as anaemia, decrease in the immune and digestive system function, disruption of spermatogenesis, and atrophy in male and female reproductive organs.

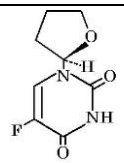
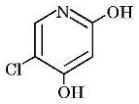
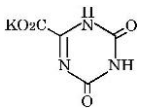
Treatment with TS-ONE® produced various skin effects in rat (keratosis of footpad and tail) and dog (skin crusts and erosions). In addition, hyperpigmentation in the skin and eyes and corneal opacity in dogs and cataracts in rats were observed following repeat dosing. These changes were reversible.

TS-ONE® does not appear to affect male or female fertility in the rat; however, administration at any time after conception resulted in a range of external, visceral, and skeletal foetal abnormalities in rat and rabbit. There is therefore a high risk for developmental toxicity at clinical doses, primarily due to tegafur (5-FU) and to oteracil to a lesser extent.

TS-ONE® was not carcinogenic in either the rat or the mouse. TS-ONE® was not found to be mutagenic when tested in the *in vitro* Ames assay. TS-ONE® was clastogenic *in vitro* using Chinese hamster lung cells and was weakly clastogenic *in vivo* in mouse bone marrow.

6. PHARMACEUTICAL PARTICULARS

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 rotation.	Gimeracil occurs as a white crystalline powder. It is soluble in sodium hydroxide test solution and *N*,*N*-dimethylformamide, sparingly soluble in methanol, slightly 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.

6.1 List of excipients

TS-ONE® OD Tablet 20

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

TS-ONE® OD Tablet 25

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from manufacturing date

6.4 Special precautions for storage

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

6.5 Nature and contents of container

56 tablets in press-through CPP/AL blister sheets (14 tablets x 2 sheets x 2 pouches)

6.6 Special precautions for disposal and other handling

Keep out of reach of children.
Hands should be washed after handling TS-ONE®.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRATION HOLDER

Zuellig Pharma Sdn Bhd
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8. DATE OF REVISION OF THE TEXT

July 2025