**Review Report**

October 18, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

| | |
|---|---|
| **Brand Name** | (1) TS-1 Combination Capsules T20 and TS-1 Combination Capsules T25<br>(2) TS-1 Combination Granules T20 and TS-1 Combination Granules T25<br>(3) TS-1 Combination OD Tablets T20 and TS-1 Combination OD Tablets T25<br>(4) S-1 Taiho Combination OD Tablets T20 and S-1 Taiho Combination OD Tablets T25 |
| **Non-proprietary Name** | Tegafur/Gimeracil/Oteracil Potassium (JAN*) |
| **Applicant** | Taiho Pharmaceutical Co., Ltd. for (1), (2), and (3); and Okayama Taiho Pharmaceutical Co., Ltd. for (4) |
| **Date of Application** | February 14, 2022 for (1), (2), and (3); and March 14, 2022 for (4) |
| **Dosage Form/Strength** | (1) Capsules: Each T20 capsule contains 20 of tegafur, 5.8 mg of gimeracil, and 19.6 mg of oteracil potassium. Each T25 capsule contains 25 mg of tegafur, 7.25 mg of gimeracil, and 24.5 mg of oteracil potassium.<br>(2) Granules: Each T20 sachet (0.2 g) contains 20 mg of tegafur, 5.8 mg of gimeracil, and 19.6 mg of oteracil potassium. Each T25 sachet (0.25 g) contains 25 mg of tegafur, 7.25 mg of gimeracil, and 24.5 mg of oteracil potassium.<br>(3) and (4) Orally disintegrating tablets: Each T20 OD tablet contains 20 mg of tegafur, 5.8 mg of gimeracil, and 19.6 mg of oteracil potassium. Each T25 OD tablet contains 25 mg of tegafur, 7.25 mg of gimeracil, and 24.5 mg of oteracil potassium. |
| **Application Classification** | Prescription drug; (4) Drug with a new indication and (6) Drug with a new dosage |
| **Items Warranting Special Mention** | None |
| **Reviewing Office** | Office of New Drug V |

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product has efficacy in adjuvant therapy for hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with a high risk of recurrence, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below.

**Indications**

Gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, biliary tract cancer, and adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with a high risk of recurrence

(Underline denotes additions.)

**Dosage and Administration**

***Gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, biliary tract cancer:***

The usual initial dose of TS-1 for adults is calculated according to body surface area, based on the recommended doses shown in the table below. TS-1 should be administered orally twice daily, after breakfast and after the evening meal, for 28 consecutive days, followed by a 14-day rest (1 treatment cycle). This treatment cycle is repeated.

| Body surface area | Recommended initial dose (expressed as tegafur equivalent) |
|---|---|
| $<1.25\ m^2$ | 40 mg twice daily |
| $\geq 1.25\ m^2$ and $<1.5\ m^2$ | 50 mg twice daily |
| $\geq 1.5\ m^2$ | 60 mg twice daily |

The dose may be adjusted according to the patient's condition. The dose should be increased or decreased gradually, with dose levels of 40 mg, 50 mg, 60 mg, and 75 mg twice daily. The recommended initial dose may be increased to the next dose level but to a maximum dose of 75 mg if the dose increase is considered to cause no safety problems, or no risk of drug-induced abnormalities in laboratory findings (hematological tests, liver and renal function tests) or gastrointestinal symptoms. Dose reduction by one dose level is recommended, but to a minimum dose of 40 mg.

***Adjuvant therapy for hormone receptor-positive and HER2-negative breast cancer with a high risk of recurrence:***

The usual initial dose of TS-1 for adults is calculated according to body surface area, based on the recommended doses shown in the table below. TS-1 should be administered orally twice daily in combination with endocrine therapy, after breakfast and after the evening meal, for 14 consecutive days, followed by a 7-day rest (1 treatment cycle). This treatment cycle is repeated for up to 1 year. The dose may be adjusted according to the patient's condition, but should not exceed their recommended initial dose.

| Body surface area | Recommended initial dose (expressed as tegafur equivalent) |
|---|---|
| $<1.25\ m^2$ | 40 mg twice daily |
| $\geq 1.25\ m^2$ and $<1.5\ m^2$ | 50 mg twice daily |
| $\geq 1.5\ m^2$ | 60 mg twice daily |

(Underline denotes additions.)

**Japanese Accepted Name (modified INN)*

**Attachment**

**Review Report (1)**

September 6, 2022

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

**Product Submitted for Approval**

**Brand Name** (1) TS-1 Combination Capsules T20 and TS-1 Combination Capsules T25
(2) TS-1 Combination Granules T20 and TS-1 Combination Granules T25
(3) TS-1 Combination OD Tablets T20 and TS-1 Combination OD Tablets T25
(4) S-1 Taiho Combination OD Tablets T20 and S-1 Taiho Combination OD Tablets T25

**Non-proprietary Name** Tegafur/Gimeracil/Oteracil Potassium

**Applicant** Taiho Pharmaceutical Co., Ltd., for (1), (2), and (3); and Okayama Taiho Pharmaceutical Co., Ltd. for (4)

**Date of Application** February 14, 2022 for (1), (2), and (3); and March 14, 2022 for (4)

**Dosage Form/Strength**
(1) Capsules: Each T20 capsule contains 20 mg of tegafur, 5.8 mg of gimeracil, and 19.6 mg of oteracil potassium. Each T25 capsule contains 25 mg of tegafur, 7.25 mg of gimeracil, and 24.5 mg of oteracil potassium.
(2) Granules: Each T20 sachet (0.2 g) contains 20 mg of tegafur, 5.8 mg of gimeracil, and 19.6 mg of oteracil potassium. Each T25 sachet (0.25 g) contains 25 mg of tegafur, 7.25 mg of gimeracil, and 24.5 mg of oteracil potassium.
(3) and (4) Orally disintegrating tablets: Each T20 OD tablet contains 20 mg of tegafur, 5.8 mg of gimeracil, and 19.6 mg of oteracil potassium. Each T25 OD tablet contains 25 mg of tegafur, 7.25 mg of gimeracil, and 24.5 mg of oteracil potassium.

**Proposed Indications**

Gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, biliary tract cancer, and adjuvant chemotherapy for breast cancer

(Underline denotes additions.)

**Proposed Dosage and Administration**

The usual initial dose of TS-1 for adults is calculated according to body surface area, based on the recommended doses shown in the table below. TS-1 should be administered orally twice daily, after breakfast and after the evening meal, for 28 consecutive days, followed by a 14-day rest (1 treatment cycle). This treatment cycle is repeated.

| Body surface area | Recommended initial dose (expressed as tegafur equivalent) |
|---|---|
| <1.25 $m^2$ | 40 mg twice daily |
| ≥1.25 $m^2$ and <1.5 $m^2$ | 50 mg twice daily |
| ≥1.5 $m^2$ | 60 mg twice daily |

The dose may be adjusted according to the patient's condition. ~~The dose should be increased or decreased gradually, with dose levels of 40 mg, 50 mg, 60 mg, and 75 mg twice daily.~~ The recommended initial dose may be increased to the next dose level but to a maximum dose of 75 mg if the dose increase is considered to cause no safety problems, or no risk of drug-induced abnormalities in laboratory findings (hematological tests, liver and renal function tests) or gastrointestinal symptoms. Dose reduction by one dose level is recommended~~, but to a minimum dose of 40 mg~~.

(Underline denotes additions. Strikethrough denotes deletions.)

**Table of Contents**



**List of Abbreviations**

See Appendix.

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

### 1.1 Outline of the proposed product

5-fluorouracil (5-FU) is a fluoropyrimidine anti-cancer agent, which is considered to inhibit tumor growth by blocking DNA synthesis.

TS-1 is a fixed-dose combination of 3 active substances (tegafur, a 5-FU prodrug; gimeracil, which inhibits the degradation of 5-FU by inhibiting dihydropyrimidine dehydrogenase; and oteracil potassium, which inhibits 5-FU phosphorylation by inhibiting the enzyme orotate phosphoribosyltransferase [in a molar ratio of 1:0.4:1]). It was developed to enhance anti-tumor activity by inhibiting the enzyme of 5-FU catabolism and to reduce gastrointestinal toxicity by inhibiting the enzyme for the phosphorylation of 5-FU.

In Japan, TS-1 was approved for the following indications: (1) gastric cancer in January 1999, (2) head and neck cancer in April 2001, (3) colorectal cancer in December 2003, (4) non-small cell lung cancer in December 2004, (5) inoperable or recurrent breast cancer in November 2005, (6) pancreatic cancer in August 2006, and (7) biliary tract cancer in August 2007.

### 1.2 Development history etc.

A Japanese phase III study in patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, resected breast cancer who met the definition of high risk of recurrence (the POTENT study) was initiated in February 2012 to evaluate the efficacy and safety of TS-1 in adjuvant therapy for breast cancer. The study was conducted at Kyoto University Hospital etc., with the status designated as an investigational medical care and then as an advanced medical care B clinical research (later classified as a specified clinical trial).

As of July 2022, TS-1 has not been approved for the indication of adjuvant therapy for breast cancer in any country or region.

The applicant has filed a partial change application for an additional indication and dosage and administration for adjuvant therapy for breast cancer, based on the results from the POTENT study as the pivotal data.

In the following sections, all doses of TS-1 are expressed as tegafur equivalent.

## 2. Quality and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, no quality data have been submitted.

## 3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although the present application is intended for a new indication and a new dosage, no new study data have been submitted because the non-clinical pharmacology data were previously evaluated for the initial application for TS-1 or subsequent submissions.

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application is intended for a new indication and a new dosage, no new study data have been submitted because the non-clinical pharmacokinetic data were previously evaluated for the initial application for TS-1.

## 5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, no toxicity data have been submitted.

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

Although the present application is intended for a new indication and a new dosage, no new study data have been submitted because the data on biopharmaceutic studies and associated analytical methods were previously evaluated for the initial application for TS-1 or subsequent submissions.

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the results from 1 Japanese phase III study presented in Table 1.

**Table 1. Efficacy and safety clinical study**

| Geographical location | Study ID | Phase | Study population | No. of subjects enrolled | Dosing regimen | Main endpoints |
|---|---|---|---|---|---|---|
| Japan | POTENT | III | Patients with ER-positive, HER2-negative, resected breast cancer at high risk of recurrence | 1,959<br>(1) 979<br>(2) 980 | (1) Endocrine therapy plus TS-1<br>TS-1 40-60 mg BID administered orally for 14 consecutive days, followed by a 7-day rest<br>(2) Endocrine therapy alone | Efficacy<br>Safety |

The clinical study is summarized below. The most common adverse events other than deaths reported in the clinical study are addressed in Section "7.2 Adverse events etc. reported in clinical studies."

### 7.1 Evaluation data

#### 7.1.1 Japanese study

##### 7.1.1.1 Japanese phase III study (CTD 5.3.5.1.1, POTENT study [February 2012 to August 2019])

A randomized, open-label, controlled study was conducted at 140 sites in Japan to evaluate the efficacy and safety of adjuvant TS-1 plus endocrine therapy versus endocrine therapy alone in patients with stage I to IIIB (at initial diagnosis), ER-positive, HER2-negative,[1)] resected breast cancer[2)] who were identified as being at

[1)] Needle biopsy or surgical samples before drug therapy were submitted for central pathological assessment, and subjects were enrolled based on the results of assessment. If the both samples were submitted, patients with an ER-positive result for either sample and those with HER2-negative results for the both samples were eligible.

[2)] Patients who had received prior neoadjuvant or adjuvant chemotherapy before enrollment were eligible if they had been treated with AC, EC, FAC, FEC, AC-T, EC-T, FAC-T, FEC-T, CMF, TC, or TAC. Patients who had received prior neoadjuvant endocrine therapy before enrollment were eligible if they had been treated with anastrozole, letrozole, exemestane, tamoxifen, toremifene, or the combination of an aromatase inhibitor and cyclophosphamide (combination with LH-RH agonist was also allowed). Patients must have completed adjuvant radiation therapy ≥2 weeks prior to enrollment. Concurrent radiation therapy with TS-1 or radiation therapy after the end of treatment with TS-1 was not allowed.

high risk of recurrence[3] (target sample size, 1,860 subjects). The study had the status previously designated as an investigational medical care and then as an advanced medical care B clinical research (later classified as a specified clinical trial). The clinical stage of breast cancer was to be determined based on the General Rules for Clinical and Pathological Recording of Breast Cancer (The 16th edition, the Japanese Breast Cancer Society [2008]).

Patients at high risk of recurrence were defined as (1) patients with positive axillary lymph node (patients with positive axillary lymph node before drug therapy if they had received prior neoadjuvant or adjuvant drug therapy), or (2) patients with negative axillary lymph node who meet any of the following criteria 1) to 3).

1) No prior neoadjuvant drug therapy: The surgical sample with (i) invasive tumor size ≥3 cm, (ii) histological grade (HG) 3, (iii) clear lymphovascular invasion, (iv) HG2 and invasive tumor size ≥2 cm and <3 cm, (v) HG2, invasive tumor size <2 cm and high proliferation marker,[4] or (vi) HG1, invasive tumor size ≥2 cm and <3 cm and high proliferation marker[4]
2) Prior neoadjuvant chemotherapy: Residual invasive cancer in the surgical sample from the breast or axillary lymph node
3) Prior neoadjuvant endocrine therapy: The surgical sample with (i) invasive tumor size ≥3 cm, (ii) HG3, (iii) clear lymphovascular invasion, (iv) HG2 and invasive tumor size ≥2 cm and <3 cm, (v) HG2, invasive tumor size <2 cm and high proliferation marker,[4] or (vi) HG1, invasive tumor size ≥2 cm and <3 cm and high proliferation marker[4]

A dose of TS-1 40 to 60 mg BID[5] determined according to creatinine clearance (Ccr) and body surface area was to be administered orally for 14 consecutive days, followed by a 7-day rest. This treatment cycle was to be repeated. The investigator's choice of standard endocrine therapy[6] was to be administered. Subjects were to receive a maximum of 5 years of endocrine therapy with or without a maximum of 1 year of TS-1 until the recurrence of the disease or a criterion for treatment discontinuation was met.

Of 1,959 subjects who were enrolled in the study and randomized to either treatment group (979 in the endocrine therapy plus TS-1 group, 980 in the endocrine therapy alone group [the control group]), 1,919 subjects (952 in the endocrine therapy plus TS-1 group, 967 in the endocrine therapy alone group) were included in the efficacy analysis population at the interim analysis. The remaining subjects, specifically 27 subjects who withdrew their consent (21 in the endocrine therapy plus TS-1 group, 6 in the endocrine therapy alone group), 1 ineligible subject (1 in the endocrine therapy plus TS-1 group, 0 in the endocrine therapy alone group), and 12 subjects without entered data (5 in the endocrine therapy plus TS-1 group, 7 in the endocrine therapy alone group) were excluded from the analysis. Among 1,959 subjects who were enrolled in

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[3] The protocol reads "intermediate to high risk of recurrence."

[4] Patients with Ki-67 labeling index ≥30% based on central pathological assessment were eligible. If Ki-67 labeling index was ≥14% and <30%, Oncotype DX was measured. Patients with a recurrence score (RS) ≥18 were eligible.

[5] A reduced initial dose of 60 to 100 mg/day was selected in patients with Ccr of ≥50 mL/min and <80 mL/min.

[6] Endocrine therapy agents were chosen from among the following. Patients who had received prior neoadjuvant endocrine therapy were to be treated for a total of 5 years (the neoadjuvant and adjuvant periods).

- Premenopausal patients: tamoxifen or toremifene. The concomitant use of goserelin or leuprorelin for 2 years was also allowed.
- Postmenopausal patients: anastrozole, letrozole, or exemestane. For patients ineligible for aromatase inhibitors, tamoxifen or toremifene was allowed.

the study and randomized to either treatment group by the time of the final analysis (979 in the endocrine therapy plus TS-1 group, 980 in the endocrine therapy alone group), 1,930 subjects (957 in the endocrine therapy plus TS-1 group, 973 in the endocrine therapy alone group) were included in the efficacy analysis population at the final analysis. The remaining subjects, specifically 28 subjects who withdrew their consent (21 in the endocrine therapy plus TS-1 group, 7 in the endocrine therapy alone group) and 1 ineligible subject (1 in the endocrine therapy plus TS-1 group, 0 in the endocrine therapy alone group) were excluded from the analysis. Among the subjects in the efficacy analysis population at the final analysis, 1,924 subjects (954 in the endocrine therapy plus TS-1 group, 970 in the endocrine therapy alone group) were included in the safety analysis population, and the remaining 6 subjects who did not receive study drug (3 in the endocrine therapy plus TS-1 group, 3 in the endocrine therapy alone group) were excluded from the safety analysis.

The primary endpoint for the study was invasive disease-free survival (IDFS) based on the investigator's assessment. At the start of the study, the target sample size was 1,400 subjects, and the interim and final analyses were planned for efficacy evaluation when approximately 165 and 248 IDFS events had been observed.

After the start of the study, the published articles and other data on adjuvant therapy for breast cancer except for the results of the POTENT study, indicated that the IDFS in the population of the POTENT study would be longer than expected at the time of designing the study. Thus, the target sample size was changed to 1,860 subjects, and then the analysis plan was changed as follows: the interim and final analyses were to be conducted for efficacy evaluation when approximately 221 and 332 IDFS events had been observed, respectively (Protocol Version 2.0 [as of July 1, 2014]). At the start of the study, the consent withdrawal form stated that in the event of consent withdrawal, consent to the use of data is also withdrawn, and the protocol stated that subjects with major protocol violations will be excluded from the efficacy analysis population. To define these rules, the exclusion of subjects who withdrew their consent and ineligible subjects from the efficacy analysis population was specified in the interim analysis plan (as of December 6, 2018). In addition, at the start of the study, the details of the interim analysis would be determined by the timing of the interim analysis, and the method of control of the type I error rate for multiplicity was not specified in the protocol or statistical analysis plan. However, the use of the Haybittle-Peto method to control the type I error rate for the interim analysis was mentioned in the interim analysis plan (as of December 6, 2018). The data were frozen for the interim analysis on December 17, 2018.

Efficacy data were analyzed. The results of the interim analysis of IDFS (data cutoff date of November 1, 2018) and the Kaplan-Meier curves are shown in Table 2 and Figure 1, respectively.

**Table 2. Results of interim analysis of IDFS**
**(Investigator's assessment, Efficacy analysis population, data cutoff date of November 1, 2018)**

| | Endocrine therapy plus TS-1 | Endocrine therapy alone |
|---|---|---|
| N | 952 | 967 |
| Number of events, n (%) | 91 (9.6) | 144 (14.9) |
| 3-year IDFS [95% CI] (%) | 92.91 [91.05, 94.40] | 88.71 [86.49, 90.58] |
| Hazard ratio [95% CI][*1] | 0.61 [0.47, 0.80] | |
| *P*-value (two-sided)[*2] | 0.0002 | |

*1: Unstratified Cox proportional hazards model, *2: Unstratified log-rank test, A two-sided significance level of 0.01

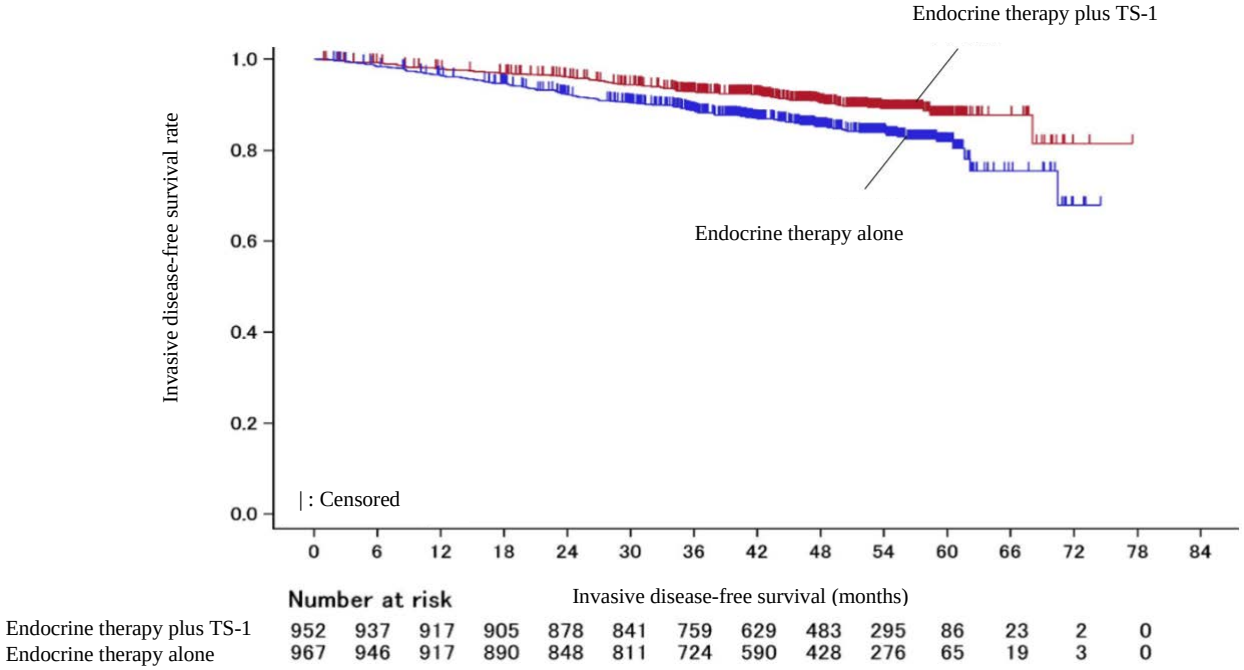


**Figure 1. Kaplan-Meier curves at the interim analysis of IDFS**
**(Investigator's assessment, Efficacy analysis population, data cutoff date of November 1, 2018)**

Safety data were analyzed. One of 954 subjects (0.1%) in the endocrine therapy plus TS-1 group and 1 of 970 subjects (0.1%) in the endocrine therapy alone group died during the study treatment or follow-up period.[7)] The causes of deaths were embolism (1 subject) in the endocrine therapy plus TS-1 group and cardio-respiratory arrest (1 subject) in the endocrine therapy alone group, and a causal relationship to study drug could not be ruled out for both cases.

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Efficacy

Based on the considerations presented in the subsections below, PMDA concluded that TS-1 was shown to have a certain level of efficacy in patients with ER-positive, HER2-negative, resected breast cancer at high risk of recurrence.

[7)] In the POTENT study, safety information was collected from randomization to 30 days after the last dose of study drug or the start of subsequent therapy, whichever was earlier. All safety information collected from the POTENT study through the database lock date (August 20, 2019) was entered.

### 7.R.1.1 Choice of control group and target population

The applicant's explanation about the reasons for the choice of the control group and study population of the POTENT study:

At the time of designing the POTENT study, the Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2009 (hereinafter referred to as the "St. Gallen International Expert Consensus [2009]"), the Japanese Breast Cancer Society clinical practice guidelines for breast cancer, 2007 edition (hereinafter referred to as the "Japanese clinical practice guidelines [2007]"), and other guidelines recommended adjuvant endocrine monotherapy with tamoxifen, an aromatase inhibitor, etc., or adjuvant endocrine therapy with tamoxifen plus luteinizing hormone-releasing hormone (LH-RH) agonist, according to menopausal status, for patients with ER-positive, HER2-negative, resected breast cancer. Thus, endocrine therapy was chosen as a control group.

At the time of designing the POTENT study, the St. Gallen International Expert Consensus (2009) proposed a treatment selection algorithm based on the risk of recurrence and recommended that a decision on whether perioperative drug therapy is indicated in patients with ER-positive, HER2-negative breast cancer should be made comprehensively, taking account of multiple risk factors of recurrence.[8)] Patients who had received prior perioperative drug therapy before enrollment in the POTENT study were eligible if they had been treated with the regimens specified in the protocol.[2)]

PMDA accepted the applicant's explanation.

### 7.R.1.2 Efficacy endpoint

The applicant's explanation about the appropriateness of the primary endpoint of IDFS based on the investigator's assessment for the POTENT study:

The primary endpoint of the POTENT study was IDFS based on the investigator's assessment, and IDFS events were defined as (1) invasive disease recurrence, (2) any second invasive cancer, or (3) death due to any cause.

In patients with resected breast cancer, recurrent breast cancer is not curable, except for local recurrence. When IDFS events are defined as the cases of the above (1), (2), and (3), an increase in the IDFS is considered clinically meaningful because longer time to recurrence of breast cancer is expected. For this and other reasons, IDFS chosen as the primary endpoint for the POTENT study is appropriate.

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8) According to the St. Gallen International Expert Consensus (2009), perioperative drug therapy should be considered if patients have any of the following risk factors of recurrence.
- Lower ER and PgR level
- HG3
- High proliferation marker (Ki-67 labeling index ≥30%, etc.)
- Four or more axillary lymph nodes involved
- Presence of extensive peritumoral vascular invasion
- Pathological tumor size >5 cm
- High score on multigene assays

PMDA's view:

While patients with cancer receive drug therapy with an expectation of survival benefit, patients with resected breast cancer are treated mainly to avoid recurrence. Thus, the above explanation by the applicant (an increase in the IDFS in the patient population of the POTENT study is clinically meaningful) is understandable to some extent.

Based on the above, the efficacy of TS-1 should be assessed comprehensively, by reviewing the results of overall survival (OS) and other outcomes, in addition to the results of the primary endpoint of IDFS, in the POTENT study.

### 7.R.1.3 Results of efficacy assessment

Table 3 shows the results of the primary endpoint of investigator-assessed IDFS at the interim analysis (data cutoff date of November 1, 2018) as the primary analysis time point in the POTENT study.

**Table 3. Results of interim analysis of IDFS**
**(Investigator's assessment, Efficacy analysis population, data cutoff date of November 1, 2018) (7.1.1.1, Table 2 relisted)**

| | Endocrine therapy plus TS-1 | Endocrine therapy alone |
|---|---|---|
| N | 952 | 967 |
| Number of events, n (%) | 91 (9.6) | 144 (14.9) |
| 3-year IDFS [95% CI] (%) | 92.91 [91.05, 94.40] | 88.71 [86.49, 90.58] |
| Hazard ratio [95% CI][*1] | 0.61 [0.47, 0.80] | |
| *P*-value (two-sided)[*2] | 0.0002 | |

*1: Unstratified Cox proportional hazards model, *2: Unstratified log-rank test, a two-sided significance level of 0.01

OS was a secondary endpoint. The hazard ratio of OS for endocrine therapy plus TS-1 vs. endocrine therapy alone [95% CI] at the interim analysis (data cutoff date of November 1, 2018) was 0.83 [0.49, 1.41]. Based on the results of the interim analysis, the independent data monitoring committee (IDMC) recommended early termination for efficacy. Thus, the final analysis of OS was conducted on the data cutoff date of January 31, 2019, which was earlier (at 3 years after enrollment of the last subject) than the pre-specified time point (when 332 IDFS events had been observed).[9)] The results of the final analysis of OS (data cutoff date of January 31, 2019) and the Kaplan-Meier curves are shown in Table 4 and Figure 2, respectively.

9) At the time of the final analysis, 256 IDFS events had been observed.

**Table 4. Results of final analysis of OS (Efficacy analysis population, data cutoff date of January 31, 2019)**

| | Endocrine therapy plus TS-1 | Endocrine therapy alone |
|---|---|---|
| N | 957 | 973 |
| Number of events, n (%) | 32 (3.3) | 36 (3.7) |
| 3-year OS [95% CI] (%) | 98.37 [97.31, 99.01] | 98.49 [97.46, 99.10] |
| Hazard ratio [95% CI]* | 0.90 [0.56, 1.44] | |

*: Unstratified Cox proportional hazards model

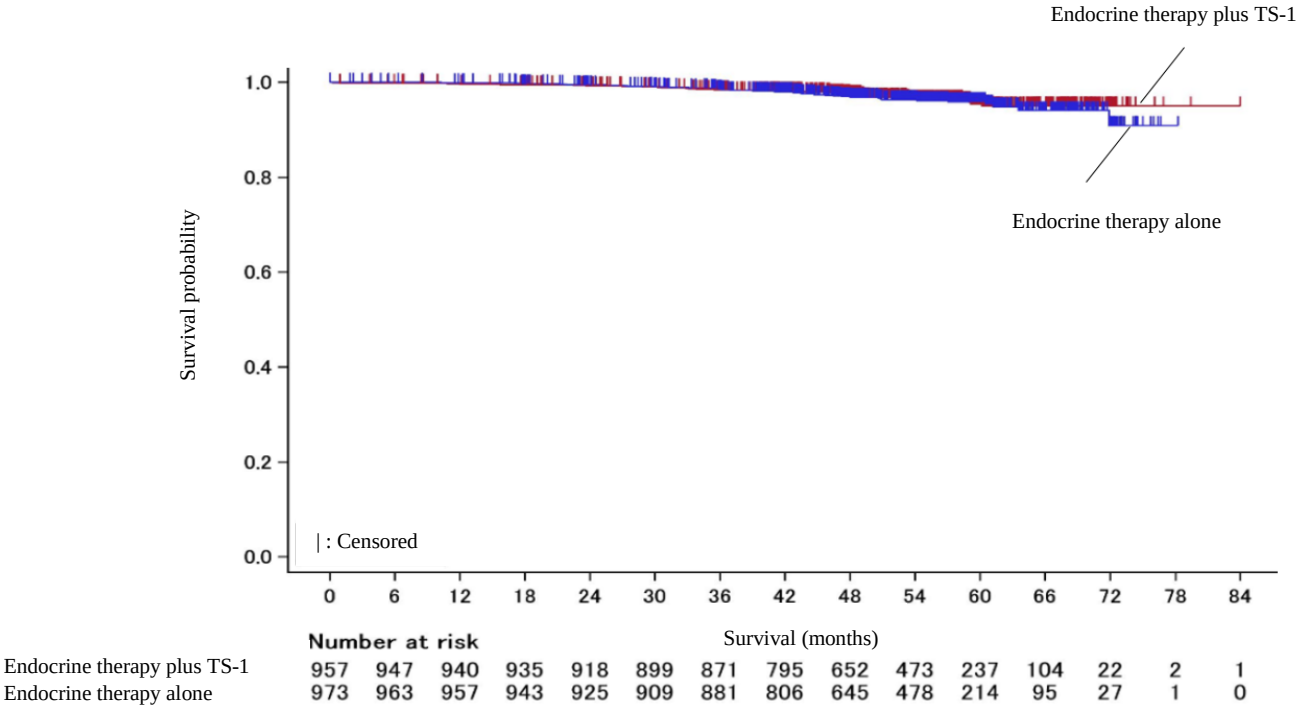


**Figure 2. Kaplan-Meier curves at the final analysis of OS (Efficacy analysis population, data cutoff date of January 31, 2019)**

PMDA asked the applicant to explain the original protocol or history of changes, the impact of the changes on the interpretation of the results, etc., in light of the following points: (1) The use of the Haybittle-Peto method to control the type I error rate for the interim analysis was not specified in the protocol etc. at the start of the study and was mentioned in the interim analysis plan after the data cutoff date for the interim analysis [see Section 7.1.1.1]; (2) Patients who withdrew their consent and patients without entered data were excluded from the efficacy analysis population; and (3) The applicant conducted the final analysis of OS at 3 years after enrollment of the last subject, instead of performing it at the planned completion of the study as specified at the start of the study (at 5 years after enrollment of the last subject) or when 332 IDFS events had been observed as specified in the amended protocol.

The applicant's explanation:

(1) Although the date of approval of the interim analysis plan that specified the method of control of the type I error rate for the interim analysis of the POTENT study (December 6, 2018) was later than the data cutoff date for the first interim analysis of IDFS (November 1, 2018), but was earlier than the date of data freezing for this analysis (December 17, 2018). Furthermore, if the Lan-DeMets O'Brien-Fleming α-spending function, which is commonly used in clinical trials, had been used to control the type I error rate

for the interim analysis, alpha would have been calculated to be 0.0154. Thus, there was no problem with an alpha of 0.01 chosen using the Haybittle-Peto method. Based on the above, the use of the Haybittle-Peto method to control the type I error rate for the interim analysis was specified after the data cutoff date for the interim analysis, which is unlikely to have a major impact on the interpretation of the efficacy results from the POTENT study.

(2) At the interim analysis of the POTENT study, 27 subjects who withdrew their consent (21 in the endocrine therapy plus TS-1 group, 6 in the endocrine therapy alone group) were excluded from the efficacy analysis population. In order to assess the impact of the excluded patients on the analysis, assuming that the 21 patients in the endocrine therapy plus TS-1 group had events at 0.26 months[10] and the 6 patients in the endocrine therapy alone group were event-free and censored at 74 months,[11] 1,946 patients including the 27 patients who withdrew their consent were analyzed for IDFS at the interim analysis. The hazard ratio of IDFS for endocrine therapy plus TS-1 vs. endocrine therapy alone [95% CI] was 0.77 [0.60, 0.98]. Data from 12 patients without entered data (5 in the endocrine therapy plus TS-1 group, 7 in the endocrine therapy alone group) were not reviewed but subjected to the interim analysis, despite the fact that there were no pre-defined rules for handling of patients without entered data at the database lock. Because new data became available from 10 of the 12 patients between the interim and final analyses, an additional analysis was performed using the data at the data cutoff date for the interim analysis (November 1, 2018).[12] The hazard ratio of IDFS for endocrine therapy plus TS-1 vs. endocrine therapy alone [95% CI] was 0.59 [0.46, 0.77]. For the above reasons, the exclusion of patients who withdrew their consent and patients without entered data from the analysis population is unlikely to have a major impact on the interpretation of the efficacy results from the POTENT study.

(3) According the protocol version 2.0 (dated July 1, 2014), the final analyses of the POTENT study (for IDFS and OS) were planned when 332 IDFS events had been observed [see Section 7.1.1.1]. However, based on the results of the interim analysis, the IDMC recommended early termination of the study for efficacy as of January 18, 2019 [see Section 7.1.1.1]. Thus, the final analysis of OS was to be conducted with the data cutoff date of January 31, 2019.[13] Then, an additional survey was planned as a follow-up study[14] as of January 31, 2021 (decided on February 15, 2019). The follow-up study was conducted in February 2021. Among 1,930 patients (957 in the endocrine therapy plus TS-1 group, 973 in the endocrine therapy alone group) in the efficacy analysis population at the final analysis, 1,593 patients (790 in the endocrine therapy plus TS-1 group, 803 in the endocrine therapy alone group) were evaluable for efficacy, because 8 patients who withdrew their consent (5 in the endocrine therapy plus TS-1 group, 3 in the

[10] The shortest time to event in 91 patients with events in the endocrine therapy plus TS-1 group at the interim analysis

[11] The longest follow-up time in 823 patients without events in the endocrine therapy alone group at the interim analysis

[12] An additional analysis was conducted on data from 1,928 patients (956 in the endocrine therapy plus TS-1 group and 972 in the endocrine therapy alone group) after adding 10 patients (4 in the endocrine therapy plus TS-1 group and 6 in the endocrine therapy alone group) out of12 patients without entered data at the interim analysis and excluding 1 patient who withdrew his/her consent after the interim analysis (1 in the endocrine therapy alone group). Because no data before November 1, 2018 were available for the remaining 2 patients without entered data at the interim analysis, these patients were not included in this analysis.

[13] Taking into account that the date of planned completion of the study specified at the start of the study (at 5 years after enrollment of the last subject) was January 31, 2021, the same day and month were chosen.

[14] In order to assess OS and other variables after the completion of the POTENT study, the included patients were to be surveyed altogether.

endocrine therapy alone group) and 329 patients from the study sites with the contract expired (162 in the endocrine therapy plus TS-1 group, 167 in the endocrine therapy alone group) were eventually excluded from the analysis. In the follow-up study, the hazard ratios of IDFS and OS for endocrine therapy plus TS-1 vs. endocrine therapy alone [95% CI] were 0.80 [0.64, 1.01] and 0.89 [0.61, 1.30], respectively. Based on the above findings, failure to conduct the final analysis at the time point specified in the protocol is unlikely to have a major impact on the interpretation of the efficacy results from the POTENT study.

PMDA's view:

The POTENT study was conducted as an open-label study using the primary endpoint of investigator-assessed IDFS. Since the following points were inappropriate in the study plan, it cannot be concluded that the POTENT study demonstrated the IDFS benefit of TS-1.

- The efficacy analysis population and the method of control of the type I error rate for the interim analysis had not been defined at the start of the study and were defined after the data cutoff date for the interim analysis.
- There were no pre-defined rules for handling of patients without entered data, and those patients were excluded *post-hoc* from the analysis population.

Moreover, while the procedure for conducting the interim analysis was inappropriate as described above, potentially leading to potential bias in the results, the final analysis was not conducted at the time point specified in the protocol etc. Further, only a fraction of subjects were evaluable in the follow-up study after the final analysis. Given these and other issues, concerns about potential bias in the results of the interim analysis cannot be resolved by the results of the final analysis and follow-up study.

However, based on the following points, a certain level of efficacy of TS-1 was demonstrated in the patient population of the POTENT study. The Japanese clinical practice guidelines strongly recommend the use of TS-1 in adjuvant therapy for HR-positive, HER2-negative breast cancer with a high risk of recurrence [see Section 7.R.3], and the use of TS-1 as adjuvant therapy is widely accepted among the Japanese experts. In view of these situations, TS-1 is clinically meaningful for the patient population of the POTENT study.

- There was a trend towards increased IDFS, the primary endpoint of the POTENT study, in the endocrine therapy plus TS-1 group compared with the endocrine therapy alone group [see Section 7.1.1.1]. The interim analysis, the additional analyses to assess the impact of exclusion of patients who withdrew their consent and other ineligible patients from the efficacy analysis population at the interim analysis, and the final analysis produced similar results.
- Although there are limitations to assessing the OS benefit of TS-1 in the POTENT study, there was no trend towards clearly shorter OS in the endocrine therapy plus TS-1 group than in the endocrine therapy alone group.

**7.R.2 Safety [for adverse events, see Section "7.2 Adverse events etc. reported in clinical studies"]**

PMDA's conclusion:

Based on the considerations presented in the subsection below, adverse events requiring particular attention

during and following the administration of TS-1 to patients with ER-positive, HER2-negative, resected breast cancer at high risk of recurrence are the following events that were defined as adverse events requiring attention at the time of the previous approvals of TS-1 (use for the approved indications) (see the Review Report on "TS-1 Capsules 20 and TS-1 Capsules 25" as of July 10, 2007, "the package inserts for TS-1 Combination Capsules T20 and TS-1 Combination Capsules T25, TS-1 Combination Granules T20 and Combination Granules T25, and TS-1 Combination OD Tablets T20 and TS-1 Combination OD Tablets T25," etc.).

- myelosuppression, hemolytic anemia, disseminated intravascular coagulation syndrome, severe hepatic disorder such as fulminant hepatitis, dehydration, severe enteritis, interstitial pneumonia, myocardial infarction, angina pectoris, arrhythmia, cardiac failure, severe stomatitis, gastrointestinal ulcer, gastrointestinal haemorrhage, gastrointestinal perforation, acute kidney injury, nephrotic syndrome, toxic epidermal necrolysis, oculomucocutaneous syndrome (Stevens-Johnson syndrome), psychoneurologic disorders including leukoencephalopathy, acute pancreatitis, rhabdomyolysis, anosmia, lacrimal duct obstruction, and hepatic cirrhosis

Although attention should be paid to the possible occurrence of the above adverse events during the use of TS-1, TS-1 is tolerable also in patients with ER-positive, HER2-negative, resected breast cancer at high risk of recurrence, as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g., monitoring for and management of adverse events and interruption of TS-1.

### 7.R.2.1 Safety profile

(1) Summary of safety data from the POTENT study

The applicant's explanation about the safety profile of TS-1 based on safety information from the POTENT study:

Safety data from the POTENT study are summarized in Table 5. Because there was no systematic collection of individual adverse events leading to study drug discontinuation, adverse events leading to study drug interruption, or adverse events leading to dose reduction of study drug in the endocrine therapy alone group, such information could not be collated.

**Table 5. Summary of safety data (Safety analysis population, database lock date of August 20, 2019[*1])**

| | n (%) | |
|---|---|---|
| | Endocrine therapy plus TS-1 N = 954 | Endocrine therapy alone N = 970 |
| All adverse events | 944 (99.0) | 769 (79.3) |
| Grade ≥3 adverse events | 154 (16.1) | 48 (4.9) |
| Adverse events leading to death | 1 (0.1) | 1 (0.1) |
| Serious adverse events | 24 (2.5) | 10 (1.0) |
| Adverse events leading to treatment discontinuation | 64 (6.7) | 3 (0.3) |
| Adverse events leading to study drug interruption | — | — |
| Adverse events leading to dose reduction of study drug | 283 (29.7) | — |

—: Not counted.

*1 In the POTENT study, safety information was collected from randomization to 30 days after the last dose of study drug or the start of subsequent therapy, whichever was earlier. All safety information collected from the POTENT study through the database lock date was collated.

In the POTENT study, adverse events of any grade reported at a ≥10% higher incidence in the endocrine therapy plus TS-1 group than in the endocrine therapy alone group were white blood cell count decreased (519

subjects [54.4%] in the endocrine therapy plus TS-1 group vs. 277 subjects [28.6%] in the endocrine therapy alone group), skin hyperpigmentation (480 subjects [50.3%] vs. 33 subjects [3.4%]), ALT increased (409 subjects [42.9%] vs. 197 subjects [20.3%]), neutrophil count decreased (401 subjects [42.0%] vs. 117 subjects [12.1%]), blood bilirubin increased (389 subjects [40.8%] vs. 69 subjects [7.1%]), fatigue (373 subjects [39.1%] vs. 88 subjects [9.1%]), AST increased (368 subjects [38.6%] vs. 134 subjects [13.8%]), anaemia (333 subjects [34.9%] vs. 151 subjects [15.6%]), nausea (329 subjects [34.5%] vs. 35 subjects [3.6%]), diarrhoea (308 subjects [32.3%] vs. 24 subjects [2.5%]), platelet count decreased (307 subjects [32.2%] vs. 83 subjects [8.6%]), decreased appetite (274 subjects [28.7%] vs. 36 subjects [3.7%]), stomatitis (261 subjects [27.4%] vs. 34 subjects [3.5%]), and taste disorder (101 subjects [10.6%] vs. 2 subjects [0.2%]). Grade ≥3 adverse events reported at a ≥2% higher incidence in the endocrine therapy plus TS-1 group than in the endocrine therapy alone group were neutrophil count decreased (72 subjects [7.5%] vs. 7 subjects [0.7%]). There were no adverse events leading to death or serious adverse events reported at a ≥2% higher incidence in the endocrine therapy plus TS-1 group than in the endocrine therapy alone group.

(2) Safety of TS-1 by combined endocrine therapy

The applicant's explanation about the safety of TS-1 by combined endocrine therapy, based on safety information from the endocrine therapy plus TS-1 group of the POTENT study:

In the endocrine therapy plus TS-1 group of the POTENT study, adverse events of any grade reported at a ≥10% higher incidence in patients receiving an aromatase inhibitor (N = 519) than in patients receiving endocrine therapy agents other than aromatase inhibitors (N = 435) were blood bilirubin increased (247 patients receiving an aromatase inhibitor [47.6%], 142 patients receiving endocrine therapy agents other than aromatase inhibitors [32.6%]). There were no Grade ≥3 adverse events, adverse events leading to death, or serious adverse events reported at a ≥5% higher incidence in patients receiving an aromatase inhibitor than in patients receiving endocrine therapy agents other than aromatase inhibitors. There were no adverse events of any grade reported at a ≥10% higher incidence in patients receiving endocrine therapy agents other than aromatase inhibitors than in patients receiving an aromatase inhibitor. There were no Grade ≥3 adverse events, adverse events leading to death, or serious adverse events reported at a ≥5% higher incidence in patients receiving endocrine therapy agents other than aromatase inhibitors than in patients receiving an aromatase inhibitor. There was no systematic collection of adverse events leading to discontinuation of any study drug, adverse events leading to interruption of TS-1, or adverse events leading to dose reduction of TS-1.

In the endocrine therapy plus TS-1 group of the POTENT study, there were no adverse events of any grade reported at a ≥10% higher incidence in patients receiving LH-RH agonist (N = 186) than in patients without LH-RH agonist use (N = 768). There were no Grade 3 adverse events, adverse events leading to death, or serious adverse events reported at a ≥5% higher incidence in patients receiving LH-RH agonist than in patients without LH-RH agonist use.

(3) Differences in safety from the previously approved indications

The applicant's explanation about differences in the safety profile of TS-1 between use in patients with ER-positive, HER2-negative, resected breast cancer at high risk of recurrence and use for the previously approved indications:

Table 6 shows the incidence of adverse events in the TS-1 group of the following clinical studies (i) to (v) that evaluated the efficacy and safety of TS-1 monotherapy (for (i), data from the endocrine therapy plus TS-1 group of the PTENT study were used).

(i) A Japanese phase III study in patients with ER-positive, HER2-negative, resected breast cancer at high risk of recurrence (the POTENT study)

(ii) A Japanese phase II study in patients with inoperable or recurrent breast cancer previously treated with chemotherapy (Study 10020230)

(iii) Japanese phase II studies in patients with biliary tract cancer (Studies 10020210 and 10020270 combined)

(iv) Japanese phase II studies in patients with pancreatic cancer (Studies 10020200 and 10020240 combined)

(v) A Japanese phase III study in patients with resected gastric cancer (the ACTS-GC study)

**Table 6. Summary of safety data from the above studies (i) to (v)[*1]**

| | n (%)[*2] | | | | |
|---|---|---|---|---|---|
| | (i) N = 954 | (ii) N = 55 | (iii) N = 59 | (iv) N = 59 | (v) N = 517 |
| All adverse events | 944 (99.0) | 55 (100) | 59 (100) | 59 (100) | 517 (100) |
| Grade ≥3 adverse events | 154 (16.1) | 28 (50.9) | 36 (61.0) | 38 (64.4) | 157 (30.4) |
| Adverse events leading to death | 1 (0.1) | — | — | — | — |
| Serious adverse events | 24 (2.5) | — | — | — | — |
| Adverse events leading to study drug discontinuation | 64 (6.7) | — | — | — | — |
| Adverse events leading to study drug interruption | — | — | — | — | — |
| Adverse events leading to dose reduction of study drug | 283 (29.7) | — | — | — | — |

—: Not counted.

*1 TS-1 40-60 mg BID was to be administered orally for 14 consecutive days, followed by a 7-day rest, and this treatment cycle was to be repeated in the POTENT study. In Studies 10020230, 10020210, 10020270, 10020200, and 10020240 and the ACTS-GC study, TS-1 40-60 mg BID was to be administered orally for 28 consecutive days, followed by a 14-day rest, and this treatment cycle was to be repeated.

*2 In all studies, events were re-coded to MedDRA ver.24.0 and counted.

Adverse events of any grade reported at a ≥10% higher incidence in the POTENT study (N = 954) than in the pooled studies (ii) to (v) (N = 690) were skin hyperpigmentation (480 subjects [50.3%] in the POTENT study, 0 subjects in the pooled studies), neutrophil count decreased (401 subjects [42.0%], 147 subjects [21.3%]), anaemia (333 subjects [34.9%], 3 subjects [0.4%]), and maculo-papular rash (123 subjects [12.9%], 0 subjects). On the other hand, adverse events of any grade reported at a ≥10% higher incidence in the pooled studies (ii) to (v) than in the POTENT study were haemoglobin decreased (0 subjects in the POTENT study, 579 subjects [83.9%] in the pooled studies), decreased appetite (274 subjects [28.7%], 438 subjects [63.5%]), fatigue (373 subjects [39.1%], 407 subjects [59.0%]), diarrhoea (308 subjects [32.3%], 386 subjects [55.9%]), pigmentation disorder (1 subject [0.1%], 317 subjects [45.9%]), rash (4 subjects [0.4%], 209 subjects [30.3%]), vomiting (80 subjects [8.4%], 186 subjects [27.0%]), red blood cell count decreased (1 subject [0.1%], 132 subjects [19.1%]), haematocrit decreased (0 subjects, 103 subjects [14.9%]), weight decreased (10 subjects [1.0%], 91 subjects [13.2%]), blood albumin decreased (0 subjects, 91 subjects [13.2%]), glucose urine present (0 subjects, 82 subjects [11.9%]), lymphocyte count decreased (0 subjects, 80 subjects [11.6%]), blood alkaline phosphatase

increased (6 subjects [0.6%], 79 subjects [11.4%]), and blood lactate dehydrogenase increased (2 subjects [0.2%], 78 subjects [11.3%]).

There were no Grade ≥3 adverse events reported at a ≥3% higher incidence in the POTENT study than in the pooled studies (ii) to (v). On the other hand, Grade ≥3 adverse events reported at a ≥3% higher incidence in the pooled studies (ii) to (v) than in the POTENT study were nausea (2 subjects [0.2%] in the POTENT study, 30 subjects [4.3%] in the pooled studies), lymphocyte count decreased (0 subjects, 25 subjects [3.6%]), and decreased appetite (3 subjects [0.3%], 64 subjects [9.3%]).

In the clinical studies other than the POTENT study, adverse events were collected, but there was no systematic collection of adverse events leading to death, serious adverse events, adverse events leading to treatment discontinuation, adverse events leading to treatment interruption, or adverse events leading to dose reduction.

Although the incidences of some adverse events were higher in patients with resected breast cancer than in use for the approved indications, all those events were known events or their incidences were substantially similar though the reported event terms were different. Thus, there should be no clear differences in the safety of TS-1 between use in patients with resected breast cancer and use for the approved indications.

PMDA's view:
In the POTENT study, there were adverse events including Grade ≥3 adverse events that were reported more frequently in the endocrine therapy plus TS-1 group than in the endocrine therapy alone group, but all those events were known adverse events with TS-1. Although there were adverse events including adverse events that were reported more frequently in patients with ER-positive, HER2-negative, resected breast cancer at high risk of recurrence than in use for the approved indications, all those events were known events with TS-1. Because safety information on some items was not collected from the clinical studies including the POTENT study [see Table 6], the assessment of these data has limitations. However, TS-1 is tolerable also in patients with ER-positive, HER2-negative, resected breast cancer at high risk of recurrence, as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g., monitoring for adverse events and dose reduction of TS-1.

### 7.R.3 Clinical positioning

TS-1 for the adjuvant treatment of breast cancer is described as follows in the major Japanese/foreign clinical practice guidelines and textbook of clinical oncology.
[Clinical practice guidelines]

- Japanese clinical practice guidelines (2022)
  - ➢ Adjuvant endocrine therapy plus TS-1 for HR-positive, HER2-negative breast cancer with a high risk of recurrence is strongly recommended.

The applicant's explanation about the clinical positioning of TS-1 and how to choose TS-1 or other drugs approved for adjuvant therapy for breast cancer (abemaciclib, olaparib):

The POTENT study in patients with ER-positive, HER2-negative, resected breast cancer at high risk of recurrence showed the clinical usefulness of TS-1 [see Sections 7.R.1 and 7.R.2].

The results of the interim analysis of IDFS by disease stage, menopausal status, and use of perioperative chemotherapy in the POTENT study are shown in Table 7, Table 8, and Table 9, respectively. At the interim analysis, perioperative chemotherapy was used in 528 subjects (55.5%) in the endocrine therapy plus TS-1 group and 541 subjects (55.9%) in the endocrine therapy alone group. In both groups, the use of perioperative chemotherapy was more frequent in the following subgroups of patients: younger age; premenopausal status; invasive tumor size ≥2 cm; positive axillary lymph node; total mastectomy; and the presence of nuclear pleomorphism, while the use of perioperative chemotherapy was infrequent in the subgroups of patients with invasive tumor size <2 cm or patients without lymphovascular invasion. There were no imbalances in the characteristics of patients with or without perioperative chemotherapy between the endocrine therapy plus TS-1 and endocrine therapy alone groups.

**Table 7. Results of interim analysis of IDFS by disease stage (Investigator's assessment, data cutoff date of November 1, 2018)**

| Stage [*1] | Treatment | N | Number of events | IDFS | |
|---|---|---|---|---|---|
| | | | | 3-year IDFS [95% CI] (%) | Hazard ratio [*2] [95% CI] |
| Stage I | Endocrine therapy plus TS-1 | 276 | 13 | 96.63 [93.64, 98.23] | 0.46 [0.24, 0.90] |
| | Endocrine therapy alone | 256 | 25 | 94.74 [91.11, 96.91] | |
| Stage II | Endocrine therapy plus TS-1 | 580 | 59 | 92.67 [90.18, 94.55] | 0.68 [0.49, 0.94] |
| | Endocrine therapy alone | 608 | 88 | 88.53 [85.65, 90.86] | |
| Stage III | Endocrine therapy plus TS-1 | 94 | 19 | 83.33 [73.88, 89.60] | 0.60 [0.34, 1.06] |
| | Endocrine therapy alone | 102 | 31 | 74.66 [64.82, 82.12] | |

*1 Three subjects with TXN0M0 according to the TNM classification (2 in the endocrine therapy plus TS-1 group and 1 in the endocrine therapy alone group) were unclassifiable and are not included in the above results.
*2 Unstratified Cox proportional hazards model

**Table 8. Results of interim analysis of IDFS by menopausal status (Investigator's assessment, data cutoff date of November 1, 2018)**

| Menopausal status | Treatment | N | Number of events | IDFS | |
|---|---|---|---|---|---|
| | | | | 3-year IDFS [95% CI] (%) | Hazard ratio [*] [95% CI] |
| Premenopausal | Endocrine therapy plus TS-1 | 455 | 45 | 91.52 [88.47, 93.79] | 0.62 [0.43, 0.90] |
| | Endocrine therapy alone | 476 | 73 | 89.17 [85.95, 91.69] | |
| Postmenopausal | Endocrine therapy plus TS-1 | 497 | 46 | 94.19 [91.68, 95.96] | 0.61 [0.42, 0.88] |
| | Endocrine therapy alone | 491 | 71 | 88.25 [84.97, 90.85] | |

* Unstratified Cox proportional hazards model

**Table 9. Results of interim analysis of IDFS by use of perioperative chemotherapy (Investigator's assessment, data cutoff date of November 1, 2018)**

| Perioperative chemotherapy | Treatment | N | Number of events | IDFS | |
|---|---|---|---|---|---|
| | | | | 3-year IDFS [95% CI] (%) | Hazard ratio [*] [95% CI] |
| Yes | Endocrine therapy plus TS-1 | 528 | 69 | 90.01 [87.06, 92.32] | 0.68 [0.50, 0.92] |
| | Endocrine therapy alone | 541 | 100 | 85.18 [81.84, 87.95] | |
| No | Endocrine therapy plus TS-1 | 424 | 22 | 96.56 [94.26, 97.95] | 0.48 [0.29, 0.80] |
| | Endocrine therapy alone | 426 | 44 | 93.34 [90.43, 95.39] | |

* Unstratified Cox proportional hazards model

Furthermore, efficacy data was analyzed by combined endocrine therapy ((1) aromatase inhibitors [N = 509], (2) others [N = 443]). The 3-year IDFS [95% CI] (%) at the interim analysis in the endocrine therapy plus TS-1 group was (1) 93.69 [91.14, 95.52] and (2) 92.01 [88.98, 94.23], showing no clear differences affecting the assessment of efficacy of TS-1 between the combined endocrine therapies.

The above findings suggest that TS-1 will become a treatment option for all patient subgroups in the POTENT study. On the other hand, there are no clinical study data showing the clinical usefulness of TS-1 in patients with resected breast cancer other than those with ER-positive, HER2-negative disease or patients with resected breast cancer who fail to meet the inclusion criterion concerning the risk of recurrence[3)] specified in the POTENT study [see Section 7.1.1.1]. Thus, TS-1 is not recommended in these patients.

Next, the following results have been obtained with regard to the use of abemaciclib and olaparib in patients with resected breast cancer including those with HR-positive, HER2-negative disease, i.e., the target population for TS-1.

- A global phase III study in patients with HR-positive, HER2-negative, resected breast cancer at high risk of recurrence (the monarchE study) demonstrated the superiority of endocrine therapy plus abemaciclib to endocrine therapy alone in the primary endpoint of IDFS (see the Review Report on Verzenio Tablets 50 mg, Verzenio Tablets 100 mg, and Verzenio Tablets 150 mg, dated November 12, 2021).
- A global phase III study in patients with germline *BRCA* (g*BRCA*) mutation-positive, HER2-negative breast cancer at high risk of recurrence who had received prior neoadjuvant or adjuvant chemotherapy (the OlympiA study) demonstrated the superiority of olaparib to placebo in the primary endpoint of IDFS (see the Review Report on Lynparza Tablets 100 mg and Lynparza Tablets 150 mg, dated July 1, 2022).

The applicant's opinion on how to choose TS-1, abemaciclib, or olaparib:
How to choose TS-1 or abemaciclib are currently unknown for patients who meet both of the definitions of high risk of recurrence used in the global phase III study (the monarchE study) and the POTENT study because there are no data from a clinical study comparing the efficacy and safety of abemaciclib versus TS-1. The appropriate drug will be chosen according to each patient's condition, by a physician with a full understanding of the efficacy, safety, duration of dosing, etc., of each drug.

In the POTENT study, testing for g*BRCA* mutation was not performed, and the efficacy and safety of TS-1 in patients with g*BRCA* mutation-positive breast cancer have not been determined. Thus, olaparib is likely to be chosen for patients with g*BRCA* mutation-positive breast cancer who have received prior neoadjuvant or adjuvant anthracycline or taxane chemotherapy, but the appropriate drug will be chosen according to each patient's condition, by a physician with a full understanding of the efficacy, safety, duration of dosing, etc., of each drug, in addition to the status of *BRCA* mutation and prior perioperative chemotherapy.

PMDA accepted the applicant's explanation.

### 7.R.4 Indication

After the submission of the present partial change application, the applicant explained that the proposed texts in the INDICATIONS and PRECAUTIONS CONCERNING INDICATIONS sections for breast cancer would be as shown in the left columns of Table 10 and Table 11, respectively.

Based on the considerations in Sections "7.R.1 Efficacy," "7.R.2 Safety," and "7.R.3 Clinical positioning" and the following subsection, PMDA concluded that the text provided in the right columns of Table 10 and Table 11 should be included in the INDICATIONS and PRECAUTIONS CONCERNING INDICATIONS sections for breast cancer, respectively.

**Table 10. Indications (draft) (A new indication is marked with underline.)**

| Applicant (draft) | PMDA (draft) |
|---|---|
| Inoperable or recurrent breast cancer<br><br><u>Adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with an intermediate to high risk of recurrence</u> | Inoperable or recurrent breast cancer<br><br><u>Adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with a high risk of recurrence</u> |

**Table 11. Precautions Concerning Indications (draft)**
**(Text with underline denotes additions to the current text in the package insert. Text with strikethrough denotes deletions from the current text in the package insert.)**

| Applicant (draft) | PMDA (draft) |
|---|---|
| ***Inoperable or recurrent breast cancer:***<br>● The efficacy and safety of TS-1 as neoadjuvant ~~or adjuvant~~ chemotherapy have not been established.<br>● TS-1 should be used in patients who had disease progression or recurrence after anthracycline- and taxane-based chemotherapy.<br>● The efficacy and safety of TS-1 in combination with other anti-neoplastic agents as the first-line chemotherapy have not been established.<br><br>***<u>Adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with an intermediate to high risk of recurrence:</u>***<br>● <u>Eligible patients must be selected by physicians who have a full understanding of the information presented in the CLINICAL STUDIES section, including the definition of intermediate to high risk of recurrence, and a thorough knowledge of the efficacy and safety of TS-1.</u><br>● <u>The efficacy and safety of TS-1 in combination with other anti-neoplastic agents (excluding endocrine therapy) have not been established.</u> | ***Inoperable or recurrent breast cancer:***<br>● ~~The efficacy and safety of TS-1 as neoadjuvant or adjuvant chemotherapy have not been established.~~<br>● TS-1 should be used in patients who had disease progression or recurrence after anthracycline- and taxane-based chemotherapy.<br>● ~~The efficacy and safety of TS-1 in combination with other anti-neoplastic agents as the first-line chemotherapy have not been established.~~<br><br>***<u>Adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with a high risk of recurrence</u>:***<br>● <u>The efficacy and safety of TS-1 as neoadjuvant therapy have not been established.</u><br>● <u>Eligible patients must be selected by physicians who have a full understanding of the information presented in the CLINICAL STUDIES section, including the definition of high risk of recurrence in patients enrolled in the clinical study, and a thorough knowledge of the efficacy and safety of TS-1.</u> |

#### 7.R.4.1 Indication for TS-1

The applicant's explanation about the indications and precautions concerning indications for TS-1:
The indication is proposed based on the POTENT study that showed the clinical usefulness of TS-1.

However, TS-1 will be indicated for HR-positive breast cancer for the following reason, though ER-positive patients were included in the POTENT study.

- A proposed indication of HR-positive breast cancer allows the use of TS-1 also in patients with ER-negative, progesterone receptor (PgR)-positive breast cancer, i.e., a subset of patients that were not included in the POTENT study. Given that both ER-positive patients and ER-negative, PgR-positive patients are handled as a patient population for whom the same treatment options are recommended (HR-positive) (the Japanese

clinical practice guidelines, etc.), patients with ER-negative, PgR-positive breast cancer who were not included in the POTENT study may be included in the indication for TS-1.

Although the phrase "an intermediate risk of recurrence" is used in the proposed indication, there is no unified definition of intermediate risk of recurrence in the Japanese or foreign clinical practice guidelines. For this reason, it is necessary to appropriately provide healthcare professionals in clinical practice with information on the definition of intermediate risk of recurrence used in the POTENT study [see Section 7.1.1.1]. Accordingly, the definition of intermediate risk of recurrence used in the POTENT study should be addressed in the CLINICAL STUDIES section of the package insert, and the PRECAUTIONS CONCERNING INDICATIONS section should advise that eligible patients must be selected, taking account of this information.

Furthermore, the following revisions and additions will be made.

- Since the POTENT study showed the efficacy and safety of TS-1 as adjuvant therapy, the statement reading that "The efficacy and safety of TS-1 as adjuvant chemotherapy have not been established" in the PRECAUTIONS CONCERNING INDICATIONS section for the approved indication of inoperable or recurrent breast cancer will be deleted. Instead, a modified statement reading that "The efficacy and safety of TS-1 as neoadjuvant chemotherapy have not been established" will be added.
- Another statement reading that "The efficacy and safety of TS-1 in combination with other anti-neoplastic agents (excluding endocrine therapy) have not been established" will also be added.

PMDA's view:
The applicant's explanation that the indication is proposed based on the POTENT study is acceptable.

However, the following revisions should be made to the text proposed by the applicant in the INDICATIONS and PRECAUTIONS CONCERNING INDICATIONS sections.

- The phrase "an intermediate to high risk of recurrence" in the proposed indication should be replaced with "a high risk of recurrence," taking into account that the Japanese clinical practice guidelines recommend TS-1 for patients at high risk of recurrence.
- The statement reading that "The efficacy and safety of TS-1 as neoadjuvant or adjuvant chemotherapy have not been established" in the PRECAUTIONS CONCERNING INDICATIONS section for the approved indication of inoperable or recurrent breast cancer should be deleted. The modified statement reading that "The efficacy and safety of TS-1 as neoadjuvant therapy have not been established" should be included in the PRECAUTIONS CONCERNING INDICATIONS section for an additional indication of adjuvant therapy for breast cancer in the present partial change application.
- The new statement reading that "The efficacy and safety of TS-1 in combination with other anti-neoplastic agents have not been established" and the statement for the approved indication of inoperable or recurrent breast cancer, reading that "The efficacy and safety of TS-1 in combination with other anti-neoplastic agents as the first-line chemotherapy have not been established" should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section because the both are precautionary statements concerning the dosage and administration of TS-1 [see Section 7.R.5].

### 7.R.5 Dosage and administration

After the submission of the present partial change application, the applicant explained that the proposed text in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections would be as shown in the left columns of Table 12 and Table 13, respectively.

Based on the considerations in Sections "7.R.1 Efficacy" and "7.R.2 Safety" and the following sections, PMDA concluded that the text provided in the right columns of Table 12 and Table 13 should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections, respectively. Although the applicant explained that revisions would be made also to the text other than that for adjuvant therapy for breast cancer in the present application, no data other than the POTENT study were submitted in the present partial change application, nor was any concrete evidence submitted to support these revisions. Thus, PMDA concluded that no changes can be made to the text other than that for adjuvant therapy for breast cancer, except for modifications associated with the present partial change application.

**Table 12. Dosage and administration (draft)**
**(Test with underline denote additions to the approved contents. Text with strikethrough denotes deletions from the approved contents.)**

<table>
<tr><th>Applicant (draft)</th><th>PMDA (draft)</th></tr>
<tr>
<td>
The usual initial dose of TS-1 for adults is calculated according to body surface area, based on the recommended doses shown in the table below. TS-1 should be administered orally twice daily, after breakfast and after the evening meal, for 28 consecutive days, followed by a 14-day rest (1 treatment cycle). This treatment cycle is repeated.<br><br>
<table>
<tr><th>Body surface area</th><th>Recommended initial dose (expressed as tegafur equivalent)</th></tr>
<tr><td><1.25m$^2$</td><td>40 mg twice daily</td></tr>
<tr><td>≥1.25 m$^2$ and <1.5 m$^2$</td><td>50 mg twice daily</td></tr>
<tr><td>≥1.5 m$^2$</td><td>60 mg twice daily</td></tr>
</table>
<br>
The dose may be adjusted according to the patient’s condition. ~~The doses should be increased or decreased gradually, with dose levels of 40 mg, 50 mg, 60 mg, and 75 mg twice daily.~~ The recommended initial dose may be increased to the next dose level but to a maximum dose of 75 mg if the dose increase is considered to cause no safety problems, or no risk of drug-induced abnormalities in laboratory findings (hematological tests, liver and renal function tests) or gastrointestinal symptoms. Dose reduction by one dose level is recommended~~, but to a minimum dose of 40 mg~~.<br><br>
For adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with an intermediate to high risk of recurrence, in the case of creatinine clearance ≥80 mL/min, TS-1 should be administered orally at the recommended initial dose twice daily in combination with endocrine therapy, after breakfast and after the evening meal, for 14 consecutive days, followed by a 7-day rest (1 treatment cycle). This treatment cycle is repeated for up to 1 year. The dose may be adjusted according to the patient’s condition, but should not exceed their recommended initial dose.
</td>
<td>
***Gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, biliary tract cancer:***<br>
The usual initial dose of TS-1 for adults is calculated according to body surface area, based on the recommended doses shown in the table below. TS-1 should be administered orally twice daily, after breakfast and after the evening meal, for 28 consecutive days, followed by a 14-day rest (1 treatment cycle). This treatment cycle is repeated.<br><br>
<table>
<tr><th>Body surface area</th><th>Recommended initial dose (expressed as tegafur equivalent)</th></tr>
<tr><td><1.25m$^2$</td><td>40 mg twice daily</td></tr>
<tr><td>≥1.25 m$^2$ and <1.5 m$^2$</td><td>50 mg twice daily</td></tr>
<tr><td>≥1.5 m$^2$</td><td>60 mg twice daily</td></tr>
</table>
<br>
The dose may be adjusted according to the patient’s condition. The dose should be increased or decreased gradually, with dose levels of 40 mg, 50 mg, 60 mg, and 75 mg twice daily. The recommended initial dose may be increased to the next dose level but to a maximum dose of 75 mg if the dose increase is considered to cause no safety problems, or no risk of drug-induced abnormalities in laboratory findings (hematological tests, liver and renal function tests) or gastrointestinal symptoms. Dose reduction by one dose level is recommended, but to a minimum dose of 40 mg.<br><br>
***Adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with a high risk of recurrence:***<br>
The usual initial dose of TS-1 for adults is calculated according to body surface area, based on the recommended doses shown in the table below. TS-1 should be administered orally twice daily in combination with endocrine therapy, after breakfast and after the evening meal, for 14 consecutive days, followed by a 7-day rest (1 treatment cycle). This treatment cycle is repeated for up to 1 year. The dose may be adjusted according to the patient’s condition, but should not exceed their recommended initial dose.<br><br>
<table>
<tr><th>Body surface area</th><th>Recommended initial dose (expressed as tegafur equivalent)</th></tr>
<tr><td><1.25 m$^2$</td><td>40 mg twice daily</td></tr>
<tr><td>≥1.25 m$^2$ and <1.5 m$^2$</td><td>50 mg twice daily</td></tr>
<tr><td>≥1.5 m$^2$</td><td>60 mg twice daily</td></tr>
</table>
</td>
</tr>
</table>

**Table 13. Precautions Concerning Dosage and Administration (draft)**
**(Text with underline denotes additions to the current text in the package insert. Text with strikethrough denotes deletions from the current text in the package insert.)**

<table>
<tr><th>Applicant (draft)</th><th>PMDA (draft)</th></tr>
<tr><td>

***All indications:***
- ~~Dose modifications~~
- Rest period
- To avoid serious adverse reactions including myelosuppression and fulminant hepatitis, 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, or discontinuing administration of TS-1.
- Administration after meals
- TS-1 in combination with radiation therapy

***Gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, biliary tract cancer:***
- The doses shown in the table below should be usually referenced when the dose is adjusted according to the patient's condition.

| Dose reduction | Recommended initial dose | Dose increase |
|---|---|---|
| drug rest | 40 mg BID | 50 mg BID |
| drug rest←40 mg BID | 50 mg BID | 60 mg BID |
| drug rest←40 mg BID←50 mg BID | 60 mg BID | 75 mg BID |

The dose may be increased to the next dose level after 1 treatment cycle.

***Non-small cell lung cancer:***
- The efficacy and safety of dosage regimens of TS-1 other than that used in a late phase II clinical study (TS-1 administered orally for 21 consecutive days in combination with cisplatin 60 mg/m$^2$ on Day 8) have not been established.

***Adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with an intermediate to high risk of recurrence:***
- For adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with an intermediate to high risk of recurrence, when administered in combination with endocrine therapy, the initial dose of TS-1 should be reduced per the table below in the case of creatinine clearance of ≥50 mL/min and <80 mL/min.

| Creatinine clearance* | Body surface area | Dose (expressed as tegafur equivalent) |
|---|---|---|
| <80 mL/min and ≥50 mL/min | <1.25 m$^2$ | 20 mg for morning 40 mg for evening |
| | ≥1.25 m$^2$ and <1.5 m$^2$ | 40 mg twice daily |
| | ≥1.5 m$^2$ | 50 mg twice daily |

* If measured creatinine clearance is not available, creatinine clearance value should be calculated from pretreatment serum creatinine, gender, age, and body weight using the following Cockcroft-Gault equation (Ccr estimate):
Ccr estimate = ([140 − age] × body weight [kg])/(72 × serum creatinine [mg/dL]) × 0.85 (if female)

Even in the case of creatinine clearance ≥80 mL/min, if there are residual effects of prior therapy or taking account of the patient's age or general condition, etc., the initial dose should be reduced to the next dose level if needed. The efficacy and safety of TS-1 in patients with creatinine clearance <50 mL/min have not been established (there are no clinical data).

</td><td>

***All indications:***
- ~~Dose modifications~~
- Rest period
- To avoid serious adverse reactions including myelosuppression and fulminant hepatitis, 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~~, or discontinuing administration of TS-1.
- Administration after meals
- TS-1 in combination with radiation therapy

***Gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, biliary tract cancer:***
- The doses shown in the table below should be usually referenced when the dose is adjusted according to the patient's condition.

| Dose reduction | Recommended initial dose | Dose increase |
|---|---|---|
| drug rest | 40 mg BID | 50 mg BID |
| drug rest←40 mg BID | 50 mg BID | 60 mg BID |
| drug rest←40 mg BID←50 mg BID | 60 mg BID | 75 mg BID |

The dose may be increased to the next dose level after 1 treatment cycle.

***Non-small cell lung cancer:***
- The efficacy and safety of dosage regimens of TS-1 other than that used in a late phase II clinical study (TS-1 administered orally for 21 consecutive days in combination with cisplatin 60 mg/m$^2$ on Day 8) have not been established.

***Inoperable or recurrent breast cancer:***
- The efficacy and safety of TS-1 in combination with other anti-neoplastic agents as the first-line chemotherapy have not been established.

***Adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with a high risk of recurrence:***
- The efficacy and safety of TS-1 in combination with other anti-neoplastic agents have not been established.
- In the case of creatinine clearance of ≥50 mL/min and <80 mL/min, the initial doses of TS-1 are listed in the table below.

| Creatinine clearance(Note) | Body surface area | Dose (expressed as tegafur equivalent) |
|---|---|---|
| ≥50 mL/min and <80 mL/min | <1.25 m$^2$ | 20 mg for morning 40 mg for evening |
| | ≥1.25 m$^2$ and <1.5 m$^2$ | 40 mg twice daily |
| | ≥1.5 m$^2$ | 50 mg twice daily |

Note) If measured creatinine clearance is not available, creatinine clearance value should be calculated from pretreatment serum creatinine, gender, age, and body weight using the following Cockcroft-Gault equation (Ccr estimate):
Cockcroft-Gault equation
Ccr estimate = ([140 − age] × body weight [kg])/(72 × serum creatinine [mg/dL]) (× 0.85 if female)
- The efficacy and safety of TS-1 in patients with creatinine clearance <50 mL/min have not been established.

</td></tr>
</table>

### 7.R.5.1 Dosage and administration and dose modifications of TS-1

The applicant's explanation about dosage and administration and dose modifications:

The dosage regimen of TS-1 for the POTENT study was selected, referring to the findings with the dosage regimens of TS-1 for other types of cancer as shown below, which had been available at the start of the POTENT study.

- In a clinical study that determined the feasible administration schedule of TS-1 for patients with head and neck cancer, the incidences of adverse events such as gastrointestinal toxicities were lower, and medication compliance was better with TS-1 40 to 60 mg BID administered orally for 14 consecutive days followed by a 7-day rest than with TS-1 40 to 60 mg BID administered orally for 28 consecutive days followed by a 14-day rest (*Br J Cancer*. 2005; 93: 884-9). Taking account of this report and other information, the schedule of 14-day administration of TS-1 followed by a 7-day rest was selected for the POTENT study, referring to the above study.
- In the ACTS-GC study that evaluated the usefulness of TS-1 as adjuvant chemotherapy for gastric cancer, 1 year of treatment with TS-1 improved relapse-free survival (*N Engl J Med*. 2007; 357: 1810-20). Thus, 1 year of treatment with TS-1 was selected for the POTENT study.

Since the POTENT study with the above administration schedule showed the clinical usefulness of TS-1 as adjuvant therapy in patients with ER-positive, HER2-negative, resected breast cancer at high risk of recurrence,[3)] the dosage regimen of TS-1 was selected based on the design of the POTENT study.

Unlike the approved dose modification guidelines, the initial dose was reduced to 60 to 100 mg/day[15)] in patients with Ccr ≥50 mL/min and <80 mL/min in the POTENT study. In the endocrine therapy plus TS-1 group of the POTENT study, the initial dose was reduced in 251 of 952 subjects, based on Ccr value or in the judgement of the investigator. The 3-year IDFS at the interim analysis was 92.82% in subjects who started treatment at the recommended initial dose, which was similar to 93.44% in subjects who started treatment at a reduced initial dose. Thus, considering that the initial dose of TS-1 should be reduced in patients with Ccr ≥50 mL/min and <80 mL/min, the relevant precautionary statement will be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section. Since there is no clinical experience with the use of TS-1 in patients with Ccr <50 mL/min, the package insert will advise that the efficacy and safety of TS-1 in these patients have not been established.

Moreover, the dose of TS-1 was increased in 10 patients in the POTENT study. In all of the 10 patients, the reduced dose of TS-1 was increased to their recommended initial dose determined according to body surface area, and their recommended initial doses were not exceeded. Thus, the following statement will be included in the DOSAGE AND ADMINISTRATION section: "The dose may be adjusted according to the patient's condition, but should not exceed their recommended initial dose."

15) This was based on data from the post-marketing surveillance of TS-1 in patients with gastric cancer, which reported a lower incidence of adverse drug reactions with a reduced initial dose than with the usual initial dose in patients with Ccr ≥50 mL/min and <80 mL/min.

PMDA's view:

PMDA accepted the above explanation by the applicant, and concluded that the following statements should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections after modifying the proposed text for the present partial change application.

**Dosage and Administration**

***Adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with a high risk of recurrence:***

The usual initial dose of TS-1 for adults is calculated according to body surface area, based on the recommended initial doses shown in the table below. TS-1 should be administered orally twice daily in combination with endocrine therapy, after breakfast and after the evening meal, for 14 consecutive days, followed by a 7-day rest (1 treatment cycle). This treatment cycle is repeated for up to 1 year. The dose may be adjusted according to the patient's condition, but should not exceed their recommended initial dose.

| Body surface area | Recommended initial dose (expressed as tegafur equivalent) |
|---|---|
| <1.25 $m^2$ | 40 mg twice daily |
| ≥1.25 $m^2$ and <1.5 $m^2$ | 50 mg twice daily |
| ≥1.5 $m^2$ | 60 mg twice daily |

**Precautions Concerning Dosage and Administration**

***All indications:***

- Rest period
- To avoid serious adverse reactions including myelosuppression and fulminant hepatitis, if any abnormal findings are observed, appropriate measures should be taken, such as prolongation of the drug rest period, dosage reduction, or discontinuing administration of TS-1.
- Administration after meals
- TS-1 in combination with radiation therapy

***Adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with a high risk of recurrence:***

- The efficacy and safety of TS-1 in combination with other anti-neoplastic agents have not been established.
- In the case of creatinine clearance of ≥50 mL/min and <80 mL/min, the initial doses of TS-1 are listed in the table below.

| Creatinine clearance[Note)] | Body surface area | Dose (expressed as tegafur equivalent) |
|---|---|---|
| ≥50 mL/min and <80 mL/min | <1.25 $m^2$ | 20 mg for morning<br>40 mg for evening |
| | ≥1.25 $m^2$ and <1.5 $m^2$ | 40 mg twice daily |
| | ≥1.5 $m^2$ | 50 mg twice daily |

Note) If measured creatinine clearance is not available, creatinine clearance value should be calculated from pretreatment serum creatinine, gender, age, and body weight using the following Cockcroft-Gault equation (Ccr estimate):
Cockcroft-Gault equation
Ccr estimate = ([140 − age] × body weight [kg])/(72 × serum creatinine [mg/dL]) (× 0.85 if female)

- The efficacy and safety of TS-1 in patients with creatinine clearance <50 mL/min have not been established.

### 7.R.5.2 Endocrine therapy to be combined with TS-1

The applicant's explanation about endocrine therapy to be combined with TS-1:

The initiation of TS-1 in combination with endocrine therapy is recommended for the patient population of the POTENT study, because the POTENT study showed the clinical usefulness of TS-1 in combination with standard endocrine therapy (tamoxifen, an aromatase inhibitor, etc., alone or in combination with LH-RH agonist) [see Sections 7.R.1 and 7.R.2]. Thus, endocrine therapy agents used in the POTENT study should be listed in the CLINICAL STUDIES section of the package insert.

PMDA accepted the applicant's explanation.

### 7.R.6 Post-marketing investigations

The applicant's explanation:

The applicant will collect safety information through routine pharmacovigilance practices, because (1) no new safety concerns have been identified in the present partial change application, and (2) there is currently no need to conduct post-marketing surveillance to evaluate the safety and other aspects of TS-1 in adjuvant therapy for HR-positive, HER2-negative breast cancer with a high risk of recurrence, immediately after obtaining approval. This opinion is based on the following and other reasons:

- In the POTENT study, some adverse events were reported more frequently in the endocrine therapy plus TS-1 group than in the endocrine therapy alone group, but all those events were known adverse events with TS-1. There were no clear differences in the safety profile of TS-1 between the POTENT study and the approved indications [see Section 7.R.2].
- No new safety concerns have been identified based on safety information and other data collected from post-marketing surveillance for the approved indications.

PMDA accepted the applicant's explanation.

## 7.2 Adverse events etc. reported in clinical studies

Among clinical study data submitted for safety evaluation, deaths are described in Section "7.1 Evaluation data." The main adverse events other than deaths are described below.

### 7.2.1 Japanese phase III study (the POTENT study)

Adverse events occurred in 944 of 954 subjects (99.0%) in the endocrine therapy plus TS-1 group and 769 of 970 subjects (79.3%) in the endocrine therapy alone group. Since information on the assessment of the relatedness to study drug was collected for some events[16)] only, adverse events for which a causal relationship to study drug could not be ruled out could not be counted. Table 14 shows adverse events reported in ≥5% of subjects in either treatment group.

[16)] Information on the assessment of relatedness to study drug was collected for adverse events leading to death and serious adverse events only, but not for other events.

**Table 14. Adverse events reported in ≥5% of subjects in either group**

| SOC<br>PT<br>(MedDRA/J ver.23.1) | n (%) | | | |
|---|---|---|---|---|
| | Endocrine therapy plus TS-1<br>N = 954 | | Endocrine therapy alone<br>N = 970 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Any adverse event | 944 (99.0) | 154 (16.1) | 769 (79.3) | 48 (4.9) |
| Blood and lymphatic system disorders | | | | |
| Anaemia | 333 (34.9) | 3 (0.3) | 151 (15.6) | 0 |
| Eye disorders | | | | |
| Lacrimation increased | 87 (9.1) | 2 (0.2) | 0 | 0 |
| Gastrointestinal disorders | | | | |
| Diarrhoea | 308 (32.3) | 18 (1.9) | 24 (2.5) | 0 |
| Nausea | 329 (34.5) | 2 (0.2) | 35 (3.6) | 0 |
| Stomatitis | 261 (27.4) | 4 (0.4) | 34 (3.5) | 0 |
| Vomiting | 80 (8.4) | 1 (0.1) | 20 (2.1) | 0 |
| General disorders and administration site conditions | | | | |
| Fatigue | 373 (39.1) | 6 (0.6) | 88 (9.1) | 0 |
| Malaise | 53 (5.6) | 0 | 7 (0.7) | 0 |
| Pyrexia | 49 (5.1) | 0 | 3 (0.3) | 0 |
| Investigations | | | | |
| ALT increased | 409 (42.9) | 6 (0.6) | 197 (20.3) | 10 (1.0) |
| AST increased | 368 (38.6) | 1 (0.1) | 134 (13.8) | 5 (0.5) |
| Blood bilirubin increased | 389 (40.8) | 10 (1.0) | 69 (7.1) | 3 (0.3) |
| Blood creatinine increased | 134 (14.0) | 0 | 137 (14.1) | 1 (0.1) |
| Haemoglobin increased | 53 (5.6) | 3 (0.3) | 69 (7.1) | 3 (0.3) |
| Neutrophil count decreased | 401 (42.0) | 72 (7.5) | 117 (12.1) | 7 (0.7) |
| Platelet count decreased | 307 (32.2) | 5 (0.5) | 83 (8.6) | 4 (0.4) |
| White blood cell count decreased | 519 (54.4) | 15 (1.6) | 277 (28.6) | 2 (0.2) |
| Metabolism and nutrition disorders | | | | |
| Decreased appetite | 274 (28.7) | 3 (0.3) | 36 (3.7) | 0 |
| Musculoskeletal and connective tissue disorders | | | | |
| Arthralgia | 89 (9.3) | 2 (0.2) | 97 (10.0) | 0 |
| Nervous system disorders | | | | |
| Taste disorder | 101 (10.6) | 0 | 2 (0.2) | 0 |
| Skin and subcutaneous tissue disorders | | | | |
| Rash maculo-papular | 123 (12.9) | 1 (0.1) | 32 (3.3) | 0 |
| Skin hyperpigmentation | 480 (50.3) | 0 | 33 (3.4) | 0 |
| Vascular disorders | | | | |
| Hot flush | 31 (3.2) | 0 | 79 (8.1) | 0 |

Serious adverse events occurred in 24 of 954 subjects (2.5%) in the endocrine therapy plus TS-1 group and 10 of 970 subjects (1.0%) in the endocrine therapy alone group. The serious adverse events reported in the endocrine therapy plus TS-1 group were diarrhoea (6 subjects [0.6%]); pneumonitis (3 subjects [0.3%]); fracture (2 subjects [0.2%]); embolism (2 subjects [0.2%]); and enteritis, nausea, malaise, haemophagocytic lymphohistiocytosis, appendicitis, wound infection, soft tissue infection, device related infection, ovarian neoplasm, cerebral ischaemia, ovarian cyst, bullous dermatitis, and haematoma (1 subject each [0.1%]). The serious adverse events reported in the endocrine therapy alone group were pneumonitis (3 subjects [0.3%]); and cardio-respiratory arrest, inguinal hernia, herpes zoster, fracture, cerebral infarction, mood disorder due to a general medical condition, and heavy menstrual bleeding (1 subject each [0.1%]). A causal relationship to study drug could not be ruled out for diarrhoea (6 subjects); pneumonitis (3 subjects); embolism (2 subjects); and enteritis, nausea, malaise, haemophagocytic lymphohistiocytosis, bullous dermatitis, device related infection, and cerebral ischaemia (1 subject each) in the endocrine therapy plus TS-1 group and pneumonitis,

cardio-respiratory arrest, inguinal hernia, and heavy menstrual bleeding (1 subject each) in the endocrine therapy alone group.

Adverse events leading to study drug discontinuation occurred in 64 of 954 subjects (6.7%) in the endocrine therapy plus TS-1 group and 3 of 970 subjects (0.3%) in the endocrine therapy alone group. There was no systematic collection of individual adverse events leading to study drug discontinuation.

## 8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

## 9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that TS-1 has a certain level of efficacy in adjuvant therapy for HR-positive, HER2-negative breast cancer with a high risk of recurrence, and that TS-1 has acceptable safety in view of its benefits. TS-1 as adjuvant therapy is clinically meaningful because it offers a new treatment option for patients with HR-positive, HER2-negative, resected breast cancer at high risk of recurrence. PMDA considers that the efficacy, clinical positioning, indication, etc. of TS-1 need to be further discussed.

PMDA has concluded that TS-1 may be approved if TS-1 is not considered to have any particular problems based on comments from the Expert Discussion.

**Review Report (2)**

October 17, 2022

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | (1) TS-1 Combination Capsules T20 and TS-1 Combination Capsules T25<br>(2) TS-1 Combination Granules T20 and TS-1 Combination Granules T25<br>(3) TS-1 Combination OD Tablets T20 and TS-1 Combination OD Tablets T25<br>(4) S-1 Taiho Combination OD Tablets T20 and S-1 Taiho Combination OD Tablets T25 |
| **Non-proprietary Name** | Tegafur/Gimeracil/Oteracil Potassium |
| **Applicant** | Taiho Pharmaceutical Co., Ltd. for (1), (2), and (3); and Okayama Taiho Pharmaceutical Co., Ltd. for (4) |
| **Date of Application** | February 14, 2022 for (1), (2), and (3); and March 14, 2022 for (4) |

**List of Abbreviations**

See Appendix.

## 1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

### 1.1 Efficacy

PMDA's conclusion:

Based on the considerations in Section "7.R.1 Efficacy" in the Review Report (1), the following results of a Japanese phase III study in patients with ER-positive, HER2-negative, resected breast cancer at high risk of recurrence (the POTENT study) showed a certain level of efficacy of TS-1 in this patient population.

- In the POTENT study, there was a trend towards increased investigator-assessed IDFS in the endocrine therapy plus TS-1 group compared with the endocrine therapy alone group, and the interim analysis, the additional analyses to assess the impact of excluding patients who withdrew their consent and other ineligible patients from the efficacy analysis population at the interim analysis, and the final analysis produced similar results. However, it cannot be concluded that the POTENT study with the primary endpoint of investigator-assessed IDFS demonstrated the IDFS benefit of TS-1, because of the following issues:
  - ➢ At the interim analysis, (1) the efficacy analysis population and the method of control of the type I error rate for the interim analysis had not been defined at the start of the study and were defined after

the data cutoff date for the interim analysis, and (2) there were no pre-defined rules for handling of patients without entered data, and those patients were excluded post-hoc from the analysis population. These were not appropriate, leading to potential bias in the results.

- Although there are limitations to assessing the OS benefit of TS-1 in the POTENT study, there was no trend towards clearly shorter OS in the endocrine therapy plus TS-1 group than in the endocrine therapy alone group.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

### 1.2 Safety

PMDA's conclusion:

Based on the considerations in "7.R.2 Safety" in the Review Report (1), adverse events that require particular attention during and following the administration of TS-1 in patients with ER-positive, HER2-negative, resected breast cancer at high risk of recurrence are the events that were identified as requiring attention at the time of the previous approvals of TS-1 (for use in the approved indications) (myelosuppression, hemolytic anemia, disseminated intravascular coagulation syndrome, severe hepatic disorder such as fulminant hepatitis, dehydration, severe enteritis, interstitial pneumonia, myocardial infarction, angina pectoris, arrhythmia, cardiac failure, severe stomatitis, gastrointestinal ulcer, gastrointestinal haemorrhage, gastrointestinal perforation, acute kidney injury, nephrotic syndrome, toxic epidermal necrolysis, oculomucocutaneous syndrome [Stevens-Johnson syndrome], psychoneurologic disorders including leukoencephalopathy, acute pancreatitis, rhabdomyolysis, anosmia, lacrimal duct obstruction, and hepatic cirrhosis).

Although attention should be paid to the possible occurrence of the above adverse events during the use of TS-1, TS-1 is tolerable also in patients with ER-positive, HER2-negative, resected breast cancer at high risk of recurrence, as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g., monitoring for and management of adverse events and interruption of TS-1.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

### 1.3 Clinical positioning and indication

Based on the considerations in Sections "7.R.3 Clinical positioning" and "7.R.4 Indication" in the Review Report (1), PMDA has concluded that the text provided in the table below should be included in the INDICATIONS and PRECAUTIONS CONCERNING INDICATIONS sections for adjuvant therapy for HR-positive, HER2-negative breast cancer with a high risk of recurrence.

| Indications | Precautions Concerning Indications |
|---|---|
| Adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with a high risk of recurrence | ● The efficacy and safety of TS-1 as neoadjuvant therapy have not been established.<br>● Eligible patients must be selected by physicians who have a full understanding of the information presented in the CLINICAL STUDIES section, including the definition of high risk of recurrence in patients enrolled in the clinical study, and a thorough knowledge of the efficacy and safety of TS-1. |

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

Based on the above conclusion, PMDA instructed the applicant to include the above statements in the INDICATIONS and PRECAUTIONS CONCERNING INDICATIONS sections, and the applicant agreed.

### 1.4 Dosage and administration

Based on the considerations in Section "7.R.5 Dosage and administration" in the Review Report (1), PMDA has concluded that the text provided in the table below should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections for adjuvant therapy for HR-positive, HER2-negative breast cancer with a high risk of recurrence.

<table>
<tr><th>Dosage and administration</th><th>Precautions Concerning Dosage and Administration</th></tr>
<tr><td>The usual initial dose of TS-1 for adults is calculated according to body surface area, based on the recommended doses shown in the table below. TS-1 should be administered orally twice daily in combination with endocrine therapy, after breakfast and after the evening meal, for 14 consecutive days, followed by a 7-day rest (1 treatment cycle). This treatment cycle is repeated for up to 1 year. The dose may be adjusted according to the patient's condition, but should not exceed their recommended initial dose.
<table>
<tr><th>Body surface area</th><th>Recommended initial dose (expressed as tegafur equivalent)</th></tr>
<tr><td><1.25 m$^2$</td><td>40 mg twice daily</td></tr>
<tr><td>≥1.25 m$^2$ and <1.5 m$^2$</td><td>50 mg twice daily</td></tr>
<tr><td>≥1.5 m$^2$</td><td>60 mg twice daily</td></tr>
</table>
</td><td>
● The efficacy and safety of TS-1 in combination with other anti-neoplastic agents have not been established.<br>
● In the case of creatinine clearance of ≥50 mL/min and <80 mL/min, the initial doses of TS-1 are listed in the table below.
<table>
<tr><th>Creatinine clearance[Note)]</th><th>Body surface area</th><th>Dose (expressed as tegafur equivalent)</th></tr>
<tr><td rowspan="3">≥50 mL/min and <80 mL/min</td><td><1.25 m$^2$</td><td>20 mg for morning<br>40 mg for evening</td></tr>
<tr><td>≥1.25 m$^2$ and <1.5 m$^2$</td><td>40 mg twice daily</td></tr>
<tr><td>≥1.5 m$^2$</td><td>50 mg twice daily</td></tr>
</table>
Note) If measured creatinine clearance is not available, creatinine clearance value should be calculated from pretreatment serum creatinine, gender, age, and body weight using the following Cockcroft-Gault equation (Ccr estimate):<br>
Cockcroft-Gault equation<br>
Ccr estimate = ([140 − age] × body weight [kg])/(72 × serum creatinine [mg/dL]) (× 0.85 if female)<br>
● The efficacy and safety of TS-1 in patients with creatinine clearance <50 mL/min have not been established.
</td></tr>
</table>

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

Based on the above conclusion, PMDA instructed the applicant to include the above statements in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections, and the applicant agreed.

### 1.5 Risk management plan (draft)

Based on the considerations in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA has concluded that there is little need to conduct post-marketing surveillance to evaluate the safety and other aspects of TS-1 in adjuvant therapy for HR-positive, HER2-negative breast cancer with a high risk of recurrence, immediately after obtaining marketing approval, and that the applicant may collect safety information through routine pharmacovigilance activities.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

## 2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indications and dosage and administration as shown below, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is appropriately disseminated in the post-marketing setting, and provided that the proper use of the product is ensured under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care.

**Indications** (Underline denotes additions.)

Gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, biliary tract cancer, and adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with a high risk of recurrence

**Dosage and Administration** (Underline denotes additions.)

***Gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, biliary tract cancer:***

The usual initial dose of TS-1 for adults is calculated according to body surface area, based on the recommended doses shown in the table below. TS-1 should be administered orally twice daily, after breakfast and after the evening meal, for 28 consecutive days, followed by a 14-day rest (1 treatment cycle). This treatment cycle is repeated.

| Body surface area | Recommended initial dose (expressed as tegafur equivalent) |
|---|---|
| $<1.25\ m^2$ | 40 mg twice daily |
| $\geq 1.25\ m^2$ and $<1.5\ m^2$ | 50 mg twice daily |
| $\geq 1.5\ m^2$ | 60 mg twice daily |

The dose may be adjusted according to the patient's condition. The dose should be increased or decreased gradually, with dose levels of 40 mg, 50 mg, 60 mg, and 75 mg twice daily. The recommended initial dose may be increased to the next dose level but to a maximum dose of 75 mg if dose increase is considered to cause no safety problems, or no risk of drug-induced abnormalities in laboratory findings (hematological tests, liver and renal function tests) or gastrointestinal symptoms. Dose reduction by one dose level is recommended, but to a minimum dose of 40 mg.

***Adjuvant treatment of hormone receptor-positive, HER2-negative breast cancer with a high risk of recurrence:***

The usual initial dose of TS-1 for adults is calculated according to body surface area, based on the recommended initial doses shown in the table below. TS-1 should be administered orally twice daily in combination with endocrine therapy, after breakfast and after the evening meal, for 14 consecutive days, followed by a 7-day rest (1 treatment cycle). This treatment cycle is repeated for up to 1 year. The dose may be adjusted according to the patient's condition, but should not exceed their recommended initial dose.

| Body surface area | Recommended initial dose (expressed as tegafur equivalent) |
|---|---|
| <1.25 $m^2$ | 40 mg twice daily |
| ≥1.25 $m^2$ and <1.5 $m^2$ | 50 mg twice daily |
| ≥1.5 $m^2$ | 60 mg twice daily |

**Warnings** (Underline denotes additions. Strikethrough denotes deletions.)

1. Chemotherapy containing TS-1 should be administered only to patients eligible for this therapy, under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. Eligible patients should be carefully selected with reference to ~~the package insert~~ the electronic package insert of each concomitant drug. Prior to initiation of treatment, patients or their families should be fully informed of its efficacy and risks, and their consent should be obtained.
2. The dose-limiting toxicity (DLT) of TS-1 is myelosuppression, which is different from that of conventional oral fluorouracil drugs. Because of this, adequate attention should be paid to changes in the laboratory data. Laboratory tests should be conducted frequently.
3. Since severe hepatic disorders such as fulminant hepatitis may occur, patients should be closely monitored by periodic hepatic function tests to detect hepatic disorder early. Adequate attention should be paid to the possible occurrence of symptoms such as malaise accompanied by anorexia, which are thought to be signs or subjective symptoms of hepatic disorder. If jaundice (yellow ocular coloring) appears, TS-1 should be discontinued immediately, and appropriate measures should be taken.
4. Co-administration of TS-1 with other fluoropyrimidine anti-neoplastic agents, combination therapies containing these agents (such as folinate plus tegafur-uracil combination therapy), or the antifungal flucytosine is contraindicated because adverse reactions such as severe blood disorder may occur.

**Contraindications** (No change)

1. Patients with a history of severe hypersensitivity to any of the components of TS-1
2. Patients with severe myelosuppression [Myelosuppression may be aggravated.]
3. Patients with severe renal disorder [A marked decrease in the urinary excretion of gimeracil, a catabolic enzyme inhibitor of fluorouracil, may lead to increased blood fluorouracil concentrations, thereby resulting in the enhancement of adverse reactions such as myelosuppression.]
4. Patients with severe hepatic disorder [Hepatic disorder may be aggravated.]
5. Patients receiving other fluoropyrimidine anti-neoplastic agents (including combination therapies containing these agents)
6. Patients receiving flucytosine
7. Pregnant women or women who may be pregnant

**Precautions Concerning Indications** (Underline denotes additions. Strikethrough denotes deletions.)

***Colorectal cancer, head and neck cancer, pancreatic cancer, biliary tract cancer:***

1. The efficacy and safety of TS-1 as adjuvant chemotherapy have not been established.

***Non-small cell lung cancer:***

2. The efficacy and safety of TS-1 as adjuvant chemotherapy have not been established.
3. The efficacy and safety of TS-1 monotherapy have not been established.

***Inoperable or recurrent breast cancer:***

~~4. The efficacy and safety of TS-1 as neoadjuvant or adjuvant chemotherapy have not been established.~~

4~~5~~. TS-1 should be used in patients who had disease progression or recurrence after anthracycline- and taxane-based chemotherapy.

~~6. The efficacy and safety of TS-1 in combination with other anti-neoplastic agents as the first-line chemotherapy have not been established.~~

***Adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with a high risk of recurrence:***

5. The efficacy and safety of TS-1 as neoadjuvant therapy have not been established.
6. Eligible patients must be selected by physicians who have a full understanding of the information presented in the CLINICAL STUDIES section, including the definition of high risk of recurrence in patients enrolled in the clinical study, and a thorough knowledge of the efficacy and safety of TS-1.

**Precautions Concerning Dosage and Administration**

(Underline denotes additions. Strikethrough denotes deletions.)

***All indications:***

~~1. The doses shown in the table below should be usually referenced when the dose is adjusted according to the patient's condition.~~

| ~~Dose reduction~~ | ~~Recommended initial dose~~ | ~~Dose increase~~ |
|---|---|---|
| ~~drug rest~~ | ~~40 mg twice daily~~ | ~~50 mg twice daily~~ |
| ~~drug rest←40 mg twice daily~~ | ~~50 mg twice daily~~ | ~~60 mg twice daily~~ |
| ~~drug rest←40 mg twice dialy←50 mg twice daily~~ | ~~60 mg twice daily~~ | ~~75 mg twice daily~~ |

~~The dose may be increased to the next dose level after 1 treatment cycle.~~

1~~2~~. If a drug rest period therapeutically needs to be shortened, do so after confirming that the shortened drug rest period causes no safety problems, or no risk of drug-induced abnormalities in laboratory findings (hematological tests, liver and renal function tests) or gastrointestinal symptoms. In this case, however, a drug rest period of at least 7 days must be provided. The safety of TS-1 in the case of the shortened drug rest period in therapy for inoperable or recurrent breast cancer have not been established (there is no clinical data).

2~~3~~. To avoid serious adverse reactions such as myelosuppression and fulminant hepatitis, if any abnormal findings are observed, appropriate measures should be taken, such as prolongation of the drug rest period, dose reduction ~~according to the above~~, or discontinuation of TS-1.

3~~4~~. Basic investigations (in rats) have revealed that the bioavailability of oteracil potassium changes when the drug is administered in the fasting state. This finding suggests that phosphorylation of fluorouracil is inhibited more in the fasting than fed state and that its antitumor effect is reduced. Thus, TS-1 should be administered after meals.

4~~5~~. The efficacy and safety of TS-1 in combination with thoracic or abdominal radiation therapy have not been established.

***Gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, biliary tract cancer:***

5. The doses shown in the table below should be usually referenced when the dose is adjusted according to the patient's condition.

| Dose reduction | Recommended initial dose | Dose increase |
|---|---|---|
| drug rest | 40 mg twice daily | 50 mg twice daily |
| drug rest←40 mg twice daily | 50 mg twice daily | 60 mg twice daily |
| drug rest←40 mg twice dialy←50 mg twice daily | 60 mg twice daily | 75 mg twice daily |

The dose may be increased to the next dose level after 1 treatment cycle.

***Non-small cell lung cancer:***

6. The efficacy and safety of dosage regimens of TS-1 other than that used in a late phase II clinical study (TS-1 administered orally for 21 consecutive days in combination with cisplatin 60 mg/m$^2$ on Day 8) have not been established.

***Inoperable or recurrent breast cancer:***

7. The efficacy and safety of TS-1 in combination with other anti-neoplastic agents as the first-line chemotherapy have not been established.

***Adjuvant therapy for hormone receptor-positive, HER2-negative breast cancer with a high risk of recurrence:***

8. The efficacy and safety of TS-1 in combination with other anti-neoplastic agents have not been established.
9. In the case of creatinine clearance of ≥50 mL/min and <80 mL/min, the initial doses of TS-1 are listed in the table below.

| Creatinine clearance[Note)] | Body surface area | Dose (expressed as tegafur equivalent) |
|---|---|---|
| ≥50 mL/min and <80 mL/min | <1.25 m$^2$ | 20 mg for morning<br>40 mg for evening |
| | ≥1.25 m$^2$ and <1.5 m$^2$ | 40 mg twice daily |
| | ≥1.5 m$^2$ | 50 mg twice daily |

Note) If measured creatinine clearance is not available, creatinine clearance value should be calculated from pretreatment serum creatinine, gender, age, and body weight using the following Cockcroft-Gault equation (Ccr estimate):
Cockcroft-Gault equation
Ccr estimate = ([140 − age] × body weight [kg])/(72 × serum creatinine [mg/dL]) (× 0.85 if female)

10. The efficacy and safety of TS-1 in patients with creatinine clearance <50 mL/min have not been established.

**Appendix**

**List of Abbreviations**

| | |
|---|---|
| AC | the combination of doxorubicin and cyclophosphamide |
| AC-T | sequential AC and taxane |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BID | bis in die |
| *BRCA* gene | breast cancer susceptibility gene |
| Ccr | creatinine clearance |
| CI | confidence interval |
| CMF | the combination of cyclophosphamide, methotrexate, and 5-FU |
| cyclophosphamide | cyclophosphamide hydrate |
| docetaxel | docetaxel or docetaxel hydrate |
| doxorubicin | doxorubicin hydrochloride |
| EC | the combination of epirubicin and cyclophosphamide |
| EC-T | sequential EC and taxane |
| epirubicin | epirubicin hydrochloride |
| ER | estrogen receptor |
| FAC | the combination of 5-FU, doxorubicin, and cyclophosphamide |
| FAC-T | sequential FAC and taxane |
| FEC | the combination of 5-FU, epirubicin, and cyclophosphamide |
| FEC-T | sequential FEC and taxane |
| 5-FU | fluorouracil |
| g*BRCA* mutation | germline *BRCA* mutation |
| goserelin | goserelin acetate |
| HER2 | human epidermal growth factor receptor 2 |
| HG | histological grade |
| HR | hormone receptor (estrogen receptor or progesterone receptor) |
| IDFS | invasive disease-free survival |
| IDMC | independent data monitoring committee |
| Japanese clinical practice guidelines | the Japanese Breast Cancer Society clinical practice guidelines for breast cancer |
| leuprorelin | leuprorelin acetate |
| LH-RH | luteinizing hormone-releasing hormone |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OS | overall survival |
| partial change application | an application for partial change of marketing approval |
| PgR | progesterone receptor |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PT | preferred term |
| SOC | system organ class |
| St. Gallen International Expert Consensus | Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2009 |
| TAC | the combination of docetaxel, doxorubicin, and cyclophosphamide |
| tamoxifen | tamoxifen citrate |
| taxane | taxanes (paclitaxel or docetaxel) |
| TC | the combination of docetaxel and cyclophosphamide |
| The product | A fixed-dose combination formulation of tegafur, gimeracil, and oteracil potassium |
| toremifene | toremifene citrate |