Review Report

July 17, 2019
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) Lonsurf Combination Tablets T15 (2) Lonsurf Combination Tablets T20
Non-proprietary Name	Trifluridine and Tipiracil Hydrochloride (JAN*)
Applicant	Taiho Pharmaceutical Co., Ltd.
Date of Application	August 17, 2018
Dosage Form/Strength	(1) Each tablet contains 15 mg of trifluridine and 7.065 mg of tipiracil hydrochloride. (2) Each tablet contains 20 mg of trifluridine and 9.42 mg of tipiracil hydrochloride.
Application Classification	Prescription drug, (4) Drug with a new indication
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 the treatment of unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy, and that the product has acceptable safety in view of its benefits (see the Attachment).

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

Indications	Unresectable advanced or recurrent colorectal cancer <u>Unresectable advanced or recurrent gastric cancer progressing after cancer chemotherapy</u> (Underline denotes additions.)
Dosage and Administration	The usual initial adult dose of the combination product of trifluridine and tipiracil hydrochloride (FTD-TPI) is determined based on body surface area (BSA) and shown in the dosing table below, which presents predefined ranges of BSA and the corresponding initial doses (on the

basis of trifluridine at approximately 35 mg/m^2/dose). FTD-TPI is orally administered twice daily, after breakfast and after supper, in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles followed by a 14-day rest period.

The dose may be reduced according to the patient's condition.

Body surface area (m^2)	Initial dose (as trifluridine)
<1.07	35 mg/dose (70 mg/day)
1.07-<1.23	40 mg/dose (80 mg/day)
1.23-<1.38	45 mg/dose (90 mg/day)
1.38-<1.53	50 mg/dose (100 mg/day)
1.53-<1.69	55 mg/dose (110 mg/day)
1.69-<1.84	60 mg/dose (120 mg/day)
1.84-<1.99	65 mg/dose (130 mg/day)
1.99-<2.15	70 mg/dose (140 mg/day)
≥2.15	75 mg/dose (150 mg/day)

(No change)

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

June 5, 2019

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) Lonsurf Combination Tablets T15 (2) Lonsurf Combination Tablets T20
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Applicant	Taiho Pharmaceutical Co., Ltd.
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Dosage Form/Strength	(1) Each tablet contains 15 mg of trifluridine and 7.065 mg of tipiracil hydrochloride. (2) Each tablet contains 20 mg of trifluridine and 9.42 mg of tipiracil hydrochloride.
Proposed Indication(s)	Unresectable advanced or recurrent colorectal cancer <u>Unresectable advanced or recurrent gastric cancer</u>

(Underline denotes additions.)

Proposed Dosage and Administration

The usual initial adult dose of the combination product of trifluridine and tipiracil hydrochloride (FTD-TPI) is determined based on body surface area (BSA) and shown in the dosing table below, which presents predefined ranges of BSA and the corresponding initial doses (on the basis of trifluridine at approximately 35 mg/m^2/dose). FTD-TPI is orally administered twice daily, after breakfast and after supper, in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles followed by a 14-day rest period.

The dose may be reduced according to the patient's condition.

Body surface area (m^2)	Initial dose (as trifluridine)
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1.38-<1.53	50 mg/dose (100 mg/day)
1.53-<1.69	55 mg/dose (110 mg/day)
1.69-<1.84	60 mg/dose (120 mg/day)
1.84-<1.99	65 mg/dose (130 mg/day)
1.99-<2.15	70 mg/dose (140 mg/day)
≥2.15	75 mg/dose (150 mg/day)

(No change)

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

Lonsurf is a combination of trifluridine (FTD) and tipiracil hydrochloride (TPI) at a molar ratio of 2:1. FTD is an antineoplastic nucleoside analog discovered by Heidelberger, et al. at the University of Wisconsin. TPI is an inhibitor of the FTD-degrading enzyme, thymidine phosphorylase, and was discovered by the applicant. Combined TPI is expected to help maintain plasma FTD, which is incorporated into deoxyribonucleic acid (DNA) and inhibits tumor growth.

In Japan, FTD-TPI was approved for "the treatment of unresectable advanced or recurrent colorectal cancer (only if refractory to standard therapies)" in March 2014. The indication was revised to "the treatment of unresectable advanced or recurrent colorectal cancer" in March 2015.

1.2 Development history etc.

During the clinical development of FTD-TPI for the treatment of gastric cancer, the applicant conducted a global phase III study in patients with unresectable advanced or recurrent gastric cancer who had received ≥2 prior chemotherapies (Study 302) in February 2016.

Based on the results of Study 302 and other data, the applicant filed applications in the US in August 2018 and in the EU in October 2018. In the US, FTD-TPI was approved in February 2019 for the following indication: "LONSURF is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy." In the EU, the application is currently under review.

As of April 2019, the US is the only country that approved FTD-TPI for the treatment of gastric cancer.

In Japan, patient enrollment in Study 302 began in February 2016.
With the results of Study 302 serving as pivotal data, the applicant has recently filed a partial change approval application for FTD-TPI.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Because the present application is intended for a new indication, no additional data on the quality of FTD-TPI 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, no new data on non-clinical pharmacology have been submitted. The non-clinical pharmacology of FTD-TPI was evaluated during the review for the initial approval.

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

Although the present application is intended for a new indication, no new data on non-clinical pharmacokinetics have been submitted. The non-clinical pharmacokinetics of FTD-TPI were evaluated during the review for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present application is intended for a new indication, no toxicity data of FTD-TPI 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, no new data on biopharmaceutic studies and associated analytical methods and clinical pharmacology have been submitted. The biopharmaceutic studies and associated analytical methods and clinical pharmacology for FTD-TPI were evaluated during the review for the initial approval.

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

As Table 1 shows, the submitted efficacy and safety evaluation data are the results of the global phase III study.

Table 1. Summary of the clinical efficacy and safety study

Data type	Region	Study ID	Phase	Subjects	Number of patients enrolled	Dosage regimen	Main endpoints
Evaluation data	Global	302	III	Patients with unresectable advanced or recurrent gastric cancer who have received ≥2 chemotherapies	507 (a) 337 (b) 170	(a) FTD-TPI as 35 mg/m^2 of FTD or (b) placebo; orally administered twice daily in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles followed by a 14-day rest period.	Efficacy Safety

A summary of the clinical study is presented below. Common adverse events other than deaths reported in the study are detailed in Section “7.2 Adverse events reported in the clinical studies.”

7.1 Evaluation data

7.1.1 Global clinical study

7.1.1.1 Global phase III study (CTD 5.3.5.1.1, Study 302, ongoing since February 2016 [data cutoff, [redacted]; data cutoff for overall survival, [redacted]])

A double-blind, randomized, comparative study was conducted at 110 sites in 17 countries/regions including Japan to evaluate the efficacy and safety of FTD-TPI versus placebo in patients with unresectable advanced or recurrent gastric cancer[1)] who had received ≥2 chemotherapies[2)] (target sample size, 500 patients).

Each treatment cycle consisted of 28 days. A 5 consecutive-day treatment with oral FTD-TPI (35 mg/m^2 of FTD) or placebo twice daily with a subsequent 2-day rest period was repeated twice before a 14-day rest period. The treatment was continued until disease progression or a withdrawal criterion met.

All 507 enrolled and randomized patients (337 in the FTD-TPI group and 170 in the placebo group, including 46 and 27 Japanese patients, respectively) were included in the intention-to-treat (ITT) population and used for efficacy analyses. Of the 507 patients, 4 (2 in the FTD-TPI group and 2 in the placebo group) did not receive the study drug. Except these patients, the remaining 503 patients (335 in the FTD-TPI group and 168 in the placebo group, including 46 and 27 Japanese patients, respectively) were included in the safety analysis set.

The primary endpoint was overall survival (OS). An interim analysis was to be conducted aiming at benefit and futility evaluation when 192 events (50% of the target number of events, 384) had occurred. A Lan-DeMets α spending function of the O'Brien-Fleming type was used to control the probability of a type I error associated with the interim analysis.

Table 2 shows efficacy results based on the final OS analysis (data cut off, [redacted]), and Figure 1 is the Kaplan-Meier curves of OS. The results demonstrated the superiority of FTD-TPI in OS over placebo.

Table 2. Final OS analysis (ITT population [data cutoff, [redacted]])

	FTD-TPI	Placebo
Number of subjects	337	170
Number of events (%)	224 (72.4)	140 (82.4)
Median [95% CI] (months)	5.7 [4.8, 6.2]	3.6 [3.1, 4.1]
Hazard ratio [95% CI]*1	0.69 [0.56, 0.85]	
P-value (1-sided)*2	0.0003	

*1 Cox regression stratified by geographic region (Japan vs. rest of world), Eastern Cooperative Oncology Group (ECOG) performance status (PS) at baseline (0 vs. 1), and prior ramucirumab (with vs. without)
*2 Log-rank test stratified by geographic region (Japan vs. rest of world), ECOG PS at baseline (0 vs. 1), and prior ramucirumab (with vs. without), with a 1-sided significance level of 0.0215

1) The prior chemotherapy regimens must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan.
2) Including adenocarcinoma of the esophagogastric junction (whose center is within 5 cm proximal or distal of the esophagogastric junction) as defined by the American Joint Committee on Cancer (AJCC) staging classification (7th Ed., 2010).

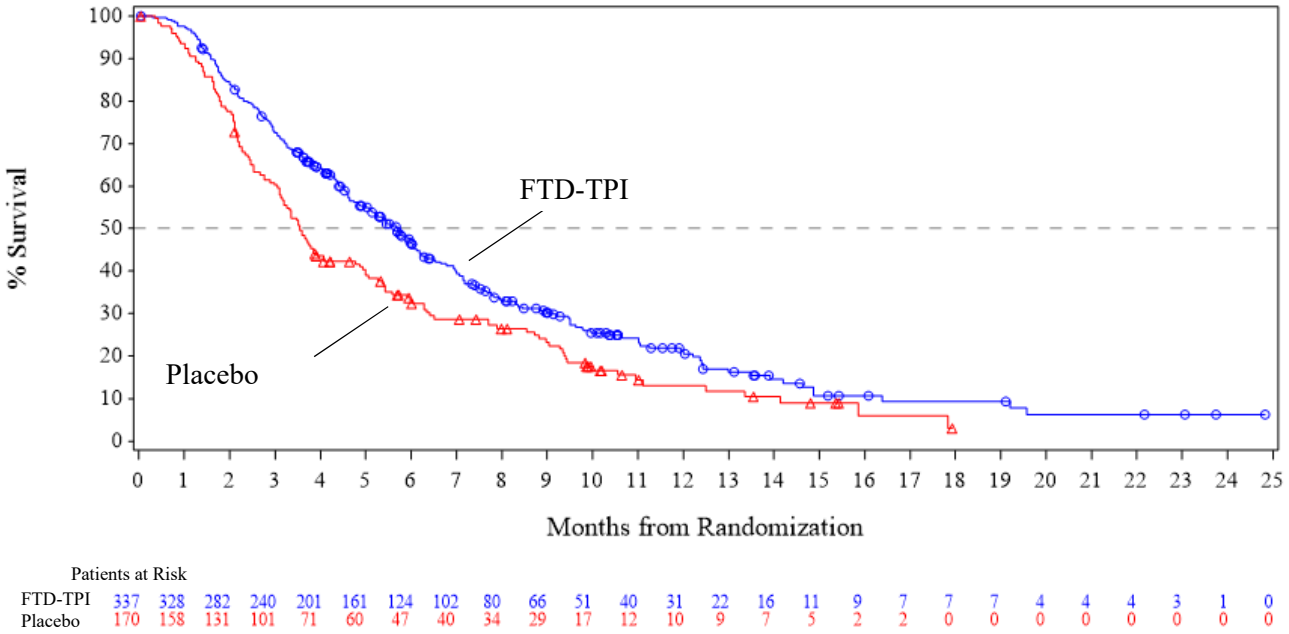

Figure 1. Kaplan-Meier curves for the final OS analysis (ITT population [data cutoff, [redacted], [redacted], [redacted]])

The safety analysis revealed deaths, during the treatment period or within 30 days after the last dose, of 62 of 335 patients (18.5%) in the FTD-TPI group and 42 of 168 patients (25.0%) in the placebo group. Causes of the deaths other than disease progression (47 in the FTD-TPI group and 40 in the placebo group) in the FTD-TPI group were septic shock in 3 patients, acute coronary syndrome and pulmonary embolism in 2 patients each, and intestinal sepsis, general physical health deterioration, organ failure, cerebral haemorrhage, transient ischaemic attack, pneumonia, gastrointestinal haemorrhage, and cardio-respiratory arrest in 1 patient each; while those in the placebo group were peritonitis bacterial and hepatitis toxic in 1 patient each. A causal relationship to the study drug could not be ruled out for the septic shock and cardio-respiratory arrest in 1 patient each in the FTD-TPI group, and the hepatitis toxic in 1 patient in the placebo group. (All of the deaths in Japanese patients [3 in the FTD-TPI group and 2 in the placebo group] were due to disease progression, for which a causal relationship to the study drug was ruled out.)

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

In principle, the efficacy of FTD-TPI was to be evaluated based on the submitted data from the entire study population of Study 302. Efficacy in Japanese patients was evaluated from a viewpoint of the consistency between the entire study population and the Japanese subpopulation of Study 302 according to “Basic Principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010 dated September 28, 2007), “Basic Principles on Global Clinical Trials (Reference Cases)” (Administrative Notice dated September 5, 2012), and Guidelines on General Principles for Planning and Design of Multi-Regional Clinical Trials” (PSEHB/PED Notification No. 0612-1 dated June 12, 2018).

Based on the discussion presented below, PMDA concluded that the efficacy of FTD-TPI had been demonstrated in patients with unresectable advanced or recurrent gastric cancer who had received ≥2 prior chemotherapies.

7.R.1.1 Control group selection, efficacy endpoints, and efficacy evaluation results

When Study 302 was being planned, there was no standard therapy established for the target patient population of the study in the National Comprehensive Cancer Network Clinical Practice Guidelines (NCCN guidelines) (v.3, 2015) or any other guidelines. Therefore, Study 302 was designed to verify the superiority of FTD-TPI in the primary endpoint of the study (OS) over placebo used as a control [see Section 7.1.1.1].

The results of the final OS analysis and the Kaplan-Meier curves of OS in the Japanese subpopulation of Study 302 are shown in Table 3 and Figure 2, respectively.

Table 3. Final OS analysis in Japanese patients (data cutoff, [redacted])

	FTD-TPI	Placebo
Number of subjects	46	27
Number of events (%)	38 (82.6)	25 (92.6)
Median [95% CI] (months)	6.3 [5.0, 9.0]	5.9 [3.6, 9.3]
Hazard ratio [95% CI]*	0.77 [0.46, 1.30]	

* Cox regression stratified by ECOG PS at baseline (0 vs. 1) and prior ramucirumab (with vs. without)

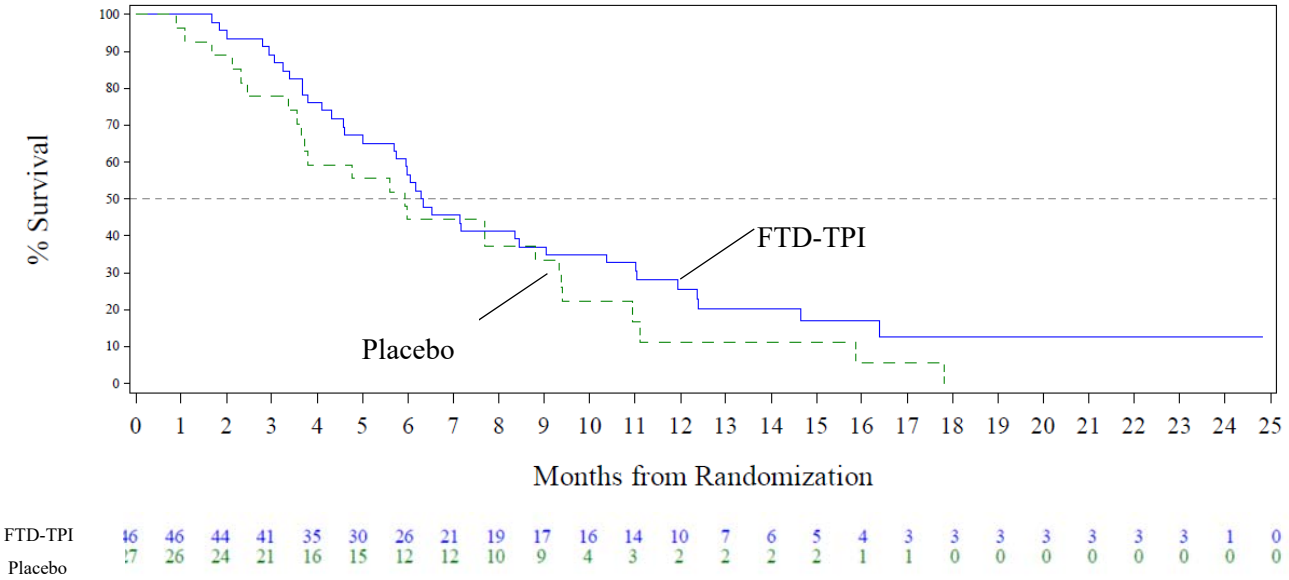

Figure 2. Kaplan-Meier curves for the final OS analysis in Japanese patients (data cutoff, [redacted])

PMDA's view:

PMDA concluded that FTD-TPI had been demonstrated to be effective in the target patient population of Study 302 (i.e., patients with unresectable advanced or recurrent gastric cancer who had received ≥2 prior chemotherapies) in view of the following facts and other data.

- The results of Study 302 demonstrated the superiority of FTP-TPI in the primary endpoint of OS over placebo.
- Although the small number of Japanese participants of Study 302 precluded precise evaluation of the efficacy of FTD-TPI in Japanese patients, the results from the Japanese subpopulation did not tend to clearly differ from those from the entire study population.

7.R.2 Safety [For adverse events, see "7.2 Adverse events reported in the clinical studies."]

PMDA's view:

According to the discussions in the subsections below, FTD-TPI therapy in patients with unresectable advanced or recurrent gastric cancer particularly requires attention to the onset of bone marrow suppression, infections, gastrointestinal symptoms (diarrhoea, nausea, vomiting, and decreased appetite), peripheral neuropathy, cardiac disorders, ileus, interstitial lung disease, and hepatic impairment. They were previously identified as attention-calling adverse events of FTD-TPI at its approval for the unresectable advanced or recurrent colorectal cancer (CRC) (see "Review Report for Lonsurf Combination Tablets T15, Lonsurf Combination Tablets T20 dated January 15, 2014"). Patients should be closely monitored for these events during FTD-TPI therapy for unresectable advanced or recurrent gastric cancer as well.

Although the use of FTD-TPI require attention to the above-mentioned adverse events, FTD-TPI is tolerable in patients with gastric cancer as well, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy through monitoring and management of adverse events, drug interruption or discontinuation, dose reduction, or other appropriate measures.

7.R.2.1 Safety profile

The applicant's explanation about the safety profile of FTD-TPI in patients with unresectable advanced or recurrent gastric cancer based on the safety data from Study 302:

Table 4 is a summary of the safety data from Study 302.

Table 4. Safety summary (Study 302)

	Number of subjects (%)	
	FTD-TPI N = 335	Placebo N = 168
All adverse events	326 (97.3)	157 (93.5)
Grade ≥3 adverse events	267 (79.7)	97 (57.7)
Adverse events resulting in death	45 (13.4)	19 (11.3)
Serious adverse events	143 (42.7)	70 (41.7)
Adverse events leading to drug discontinuation	43 (12.8)	28 (16.7)
Adverse events leading to drug interruption	193 (57.6)	37 (22.0)
Adverse events leading to dose reduction	36 (10.7)	2 (1.2)

The adverse events of any grade reported with a ≥5% higher incidence in the FTD-TPI group than in the placebo group were anaemia (44.5% [149 patients] in the FTD-TPI group, 19.0% [32 patients] in the placebo

group), neutropenia (38.5% [129 patients], 3.6% [6 patients]), nausea (37.0% [124 patients], 31.5% [53 patients]), fatigue (26.6% [89 patients], 20.8% [35 patients]), diarrhoea (22.7% [76 patients], 14.3% [24 patients]), leukopenia (17.0% [57 patients], 1.8% [3 patients]), neutrophil count decreased (15.2% [51 patients], 0.6% [1 patients]), thrombocytopenia (9.9% [33 patients], 1.2% [2 patients]), and white blood cell count decreased (6.9% [23 patients], 0%). Grade ≥3 adverse events reported with a ≥2% higher incidence in the FTD-TPI group than in the placebo group were neutropenia (23.3% [78 patients], 0%), anaemia (18.8% [63 patients], 7.7% [13 patients]), neutrophil count decreased (11.3% [38 patients], 0%), decreased appetite (8.7% [29 patients], 6.5% [11 patients]), leukopenia (6.9% [23 patients], 0%), white blood cell count decreased (2.7% [9 patients], 0%), thrombocytopenia (2.1% [7 patients], 0%), and pancytopenia (2.1% [7 of 335 patients], 0%). Serious adverse events reported with a ≥2% higher incidence in the FTD-TPI group than in the placebo group were vomiting (2.7% [9 patients], 0.6% [1 patients]) and pancytopenia (2.1% [7 patients], 0%). Adverse events that led to drug interruption with a ≥2% higher incidence in the FTD-TPI group than in the placebo group were neutropenia (25.4% [85 patients], 0%), neutrophil count decreased (11.6% [39 patients], 0.6% [1 patients]), anaemia (8.1% [27 patients], 1.8% [3 patients]), leukopenia (4.8% [16 patients], 0%), nausea (4.5% [15 patients], 2.4% [4 patients]), vomiting (3.3% [11 patients], 0.6% [1 patients]), and thrombocytopenia (2.4% [8 patients], 0%). Adverse events that led to dose reduction with a ≥2% higher incidence in the FTD-TPI group than in the placebo group were neutropenia (3.6% [12 patients], 0%) and anaemia (2.1% [7 patients], 0%). There were no adverse events that resulted in death or led to drug discontinuation with a ≥2% higher incidence in the FTD-TPI group than in the placebo group.

The applicant's explanation about differences in the safety profile of FTD-TPI between patients with gastric cancer (Study 302) and patients with unresectable advanced or recurrent CRC (Study 301):
Table 5 is a summary of the safety data from patients receiving FTD-TPI in Studies 302 and 301.

Table 5. Safety summary in patients with gastric cancer and those with CRC

	Number of subjects (%)	
	Gastric cancer	CRC
	Study 302 N = 335	Study 301 N = 533
All adverse events	326 (97.3)	524 (98.3)
Grade ≥3 adverse events	267 (79.7)	370 (69.4)
Adverse events resulting in death	45 (13.4)	17 (3.2)
Serious adverse events	143 (42.7)	158 (29.6)
Adverse events leading to drug discontinuation	43 (12.8)	55 (10.3)
Adverse events leading to drug interruption	193 (57.6)	289 (54.2)
Adverse events leading to dose reduction	36 (10.7)	72 (13.5)

The adverse event of any grade reported with a ≥10% higher incidence in patients with gastric cancer than in those with CRC was leukopenia (17.0% [57 patients] in patients with gastric cancer, 5.4% [29 patients] in patients with CRC). Grade ≥3 adverse events reported with a ≥3% higher incidence in patients with gastric cancer than in those with CRC were leukopenia (6.9% [23 patients], 2.4% [13 patients]), neutropenia (23.3% [78 patients], 20.1% [107 patients]), decreased appetite (8.7% [29 patients], 3.6% [19 patients]), fatigue

(6.9% [23 patients], 3.9% [21 patients]), and general physical health deterioration (6.6% [22 patients], 3.4% [18 patients]). The adverse event that resulted in death with a ≥3% higher incidence in patients with gastric cancer than in those with CRC was general physical health deterioration (5.1% [17 patients], 1.1% [6 patients]). The serious adverse event with a ≥3% higher incidence in patients with gastric cancer than in those with CRC was general physical health deterioration (6.3% [21 patients], 2.8% [15 patients]). Adverse events that led to drug discontinuation with a ≥3% higher incidence in patients with gastric cancer than in those with CRC were neutropenia (25.4% [85 patients], 19.5% [104 patients]), anaemia (8.1% [27 patients], 4.1% [22 patients]), leukopenia (4.8% [16 patients], 0.8% [4 patients]), and nausea (4.5% [15 patients], 1.5% [8 patients]). There were no adverse events that led to drug discontinuation or dose reduction with a ≥3% higher incidence in patients with gastric cancer than in those with CRC.

In addition, the post-marketing surveillance conducted in Japanese patients with unresectable advanced or recurrent CRC identified no new safety concerns.

PMDA's view:
All adverse events reported more frequently in the FTD-TPI group than in the placebo group in Study 302 and all of the adverse events reported more frequently in patients with gastric cancer than in patients with CRC are known adverse events of FTD-TPI. Therefore, FTD-TPI is tolerable in patients with gastric cancer as well as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy through monitoring and management of adverse events, drug interruption or discontinuation, dose reduction, or other appropriate measures.

7.R.2.2 Differences in the safety profile between Japanese and non-Japanese patients

The applicant's explanation about the differences in the safety of FTD-TPI between Japanese and non-Japanese patients:
Table 6 shows a summary of the safety data from Japanese and non-Japanese patients receiving FTD-TPI in Study 302.

Table 6. Safety summary in Japanese and non-Japanese patients (Study 302)

	Number of subjects (%)	
	Japanese N = 46	Non-Japanese N = 289
All adverse events	46 (100)	280 (96.9)
Grade ≥3 adverse events	37 (80.4)	230 (79.6)
Adverse events resulting in death	3 (6.5)	42 (14.5)
Serious adverse events	17 (37.0)	126 (43.6)
Adverse events leading to drug discontinuation	1 (2.2)	42 (14.5)
Adverse events leading to drug interruption	31 (67.4)	162 (56.1)
Adverse events leading to dose reduction	7 (15.2)	29 (10.0)

In the FTD-TPI group of Study 302, the adverse events of any grade reported with a ≥10% higher incidence in Japanese patients than in non-Japanese patients were decreased appetite (65.2% [30 patients] in Japanese

patients, 29.4% [85 patients] in non-Japanese patients), neutrophil count decreased (54.3% [25 patients], 9.0% [26 patients]), white blood cell count decreased (21.7% [10 patients], 4.5% [13 patients]), malaise (19.6% [9 patients], 0%), and pyrexia (17.4% [8 patients], 5.9% [17 patients]). Grade ≥3 adverse events reported with a ≥3% higher incidence in Japanese patients than in non-Japanese patients were neutrophil count decreased (43.5% [20 patients], 6.2% [18 patients]), anaemia (41.3% [19 patients], 15.2% [44 patients]), decreased appetite (19.6% [9 patients], 6.9% [20 patients]), white blood cell count decreased (6.5% [3 patients], 2.1% [6 patients]), febrile neutropenia (6.5% [3 patients], 1.0% [3 patients]), and platelet count decreased (4.3% [2 patients], 0.7% [2 patients]). Serious adverse events reported with a ≥3% higher incidence in Japanese patients than in non-Japanese patients were decreased appetite (17.4% [8 patients], 1.0% [3 patients]) and febrile neutropenia (4.3% [2 patients], 0.7% [2 patients]). Adverse events that led to drug interruption with a ≥3% higher incidence in Japanese patients than in non-Japanese patients were neutrophil count decreased (45.7% [21 patients], 6.2% [18 patients]), nausea (8.7% [4 patients], 3.8% [11 patients]), decreased appetite (8.7% [4 patients], 1.0% [3 patients]), and malaise (4.3% [2 patients], 0.7% [2 patients]). There were no adverse events that resulted in death, or led to drug discontinuation or dose reduction with a ≥3% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's view:

Because of the small number of Japanese patients with gastric cancer treated with FTD-TPI in Study 302, it is difficult to rigorously compare the safety of FTD-TPI between Japanese and non-Japanese patients. However, all adverse events more frequently reported in Japanese patients than in non-Japanese patients are known adverse events of FTD-TPI. Therefore, FTD-TPI is tolerable in both Japanese patients and non-Japanese patients with gastric cancer as long as appropriate measures, such as drug interruption or discontinuation, or dose reduction, are taken.

7.R.3 Clinical positioning and indication

The proposed indication was "unresectable advanced or recurrent gastric cancer." The proposed "Precautions for Indications" was described as follows:

- The efficacy and safety of FTD-TPI in first-line or second-line therapy have not been established.
- The efficacy and safety of FTD-TPI in adjuvant chemotherapy have not been established.
- Physicians should be acquainted with the prior treatment history of the patients enrolled in the clinical studies of FTD-TPI via information in the "Clinical Studies" section in order to fully understand the efficacy and safety of FTD-TPI before selecting eligible patients for FTD-TPI treatment.

PMDA's view:

Based on the reviews in Sections "7.R.1 Efficacy" and "7.R.2 Safety" and the subsection below, the appropriate indication of FTD-TPI should be "unresectable advanced or recurrent gastric cancer progressing after cancer chemotherapy," and the following statements should be presented in the "Precautions for Indications" section.

- The efficacy and safety of FTD-TPI in first-line or second-line therapy have not been established.
- The efficacy and safety of FTD-TPI in adjuvant therapy have not been established.

7.R.3.1 Clinical positioning and intended patient population

In representative clinical practice guidelines and representative textbooks for clinical oncology in and outside Japan, FTD-TPI therapy for gastric cancer is currently described as follows:

(Clinical practice guidelines)

- NCCN guidelines (v.1, 2019):
  FTD-TPI therapy is recommended for the treatment of patients with unresectable advanced or recurrent gastric cancer who have received ≥2 prior chemotherapies.
- Pan-Asian adopted ESMO Clinical Practice Guidelines (*Ann Oncol*. 2019;30:19-33):
  FTD-TPI therapy is a therapeutic option for the third-line or subsequent treatment of unresectable advanced or recurrent gastric cancer.

The applicant's explanation about the clinical positioning and indication of FTD-TPI:

Based on the results of Study 302, which demonstrated the clinical benefit of FTD-TPI, the product is expected to be recognized as a therapeutic option for patients with unresectable advanced or recurrent gastric cancer who have received ≥2 prior chemotherapies, who were the target of the study. However, the use of FTD-TPI in adjuvant therapy is not recommended due to no efficacy or safety data from clinical studies in such use.

Accordingly, the package insert of FTD-TPI would present the proposed indication of "unresectable advanced or recurrent gastric cancer," along with detailed prior treatment history of the patients enrolled in Study 302 in the "Clinical Studies" section and the following statements in the "Precautions for Indications" section.

- The efficacy and safety of FTD-TPI in first-line or second-line therapy have not been established.
- The efficacy and safety of FTD-TPI in adjuvant chemotherapy have not been established.
- Physicians should be acquainted with the prior treatment history of the patients enrolled in the clinical studies of FTD-TPI via information in the "Clinical Studies" section in order to fully understand the efficacy and safety of FTD-TPI before selecting eligible patients for FTD-TPI treatment.

Furthermore, there are no clinical study data on the efficacy and safety of FTD-TPI in comparison with nivolumab, which has been demonstrated to prolong OS in patients who would also have been eligible for Study 302 (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated August 22, 2017"). There is no clear standard for when to choose FTD-TPI or nivolumab at present. The choice of regimen should be made on a patient-by-patient basis according to their condition, with a good understanding of the efficacy and safety of each drug.

PMDA's view:

PMDA accepted the applicant's explanation in general. However, Study 302 enrolled patients with gastric cancer who had received ≥2 prior chemotherapies and did not include chemotherapy-näive patients or

patients with 1 prior chemotherapy. Therefore, the indication of FTD-TPI should make clear that the treatment is intended for patients with gastric cancer progressing after cancer chemotherapy.

Based on the above, the indication of FTD-TPI should be "unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy." Further, the following should be noted in the "Precautions for Indications" section of the package insert.

- The efficacy and safety of FTD-TPI in first-line or second-line therapy have not been established.
- The efficacy and safety of FTD-TPI in adjuvant therapy have not been established.

The advice on the selection of suitable patients with a good understanding of the efficacy and safety of FTD-TPI via the "Clinical Studies" section is not worth mentioning and thus is unnecessary to be presented in the "Precautions for Indications" section.

7.R.4 Dosage and administration

The applicant's explanation about the dosage and administration:

The efficacy and safety of FTD-TPI were demonstrated in Study 302, in which the dosage regimen and the dose adjustment criteria due to adverse drug reactions were the same as those for the approved indication. Therefore, the current application follows the descriptions of "Dosage and Administration" and "Precautions for Dosage and Administration" sections for the approved indication.

PMDA's conclusion:

The proposed "Dosage and Administration" and "Precautions for Dosage and Administration" sections are acceptable.

7.R.5 Post-marketing investigations

The applicant's explanation:

In view of the following outcomes, the study results have raised no new specific safety concerns, and it is not necessary to conduct post-marketing surveillance in patients treated with FTD-TPI for gastric cancer immediately after approval of the current application.

- The safety profile of FTD-TPI in Study 302 did not clearly differ from that in patients treated for the approved indication [see Section 7.R.2].
- A certain amount of safety data of FTD-TPI in Japanese patients are available from the post-marketing surveillance to evaluate the safety, etc. of FTD-TPI in patients with unresectable advanced or recurrent CRC, the approved indication. In addition, the surveillance raised no new safety concerns.

PMDA accepted the applicant's explanation.

7.2 Adverse events reported in clinical studies

Among the clinical study results submitted for the safety evaluation, death-related results are presented in "Section 7.1 Evaluation data," while other major adverse events are detailed below.

7.2.1 Global phase III study (Study 302)

Adverse events were reported in 326 of 335 patients (97.3%) in the FTD-TPI group and 157 of 168 patients (93.5%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 271 of 335 patients (80.9%) in the FTD-TPI group and 95 of 168 patients (56.5%) in the placebo group. Table 7 shows the adverse events reported with a ≥20% incidence in either treatment group.

Table 7. Adverse events with a ≥20% incidence in either treatment group

System Organ Class Preferred Term (MedDRA ver. 20.1)	Number of subjects (%)			
	FTD-TPI N = 335		Placebo N = 168	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	326 (97.3)	267 (79.7)	157 (93.5)	97 (57.7)
Blood and lymphatic system disorders				
Anaemia	149 (44.5)	63 (18.8)	32 (19.0)	13 (7.7)
Neutropenia	129 (38.5)	78 (23.3)	6 (3.6)	0
Gastrointestinal disorders				
Nausea	124 (37.0)	10 (3.0)	53 (31.5)	5 (3.0)
Vomiting	83 (24.8)	12 (3.6)	34 (20.2)	3 (1.8)
Diarrhoea	76 (22.7)	9 (2.7)	24 (14.3)	3 (1.8)
General disorders and administration site conditions				
Fatigue	89 (26.6)	23 (6.9)	35 (20.8)	10 (6.0)
Asthenia	65 (19.4)	16 (4.8)	40 (23.8)	11 (6.5)
Metabolism and nutrition disorders				
Decreased appetite	115 (34.3)	29 (8.7)	52 (31.0)	11 (6.5)

Serious adverse events were reported in 143 of 335 patients (42.7%) in the FTD-TPI group and 70 of 168 patients (41.7%) in the placebo group. Serious adverse events reported by ≥3 patients in the FTD-TPI group were general physical health deterioration in 21 patient (6.3%), anaemia in 13 patients (3.9%), decreased appetite in 11 patients (3.3%), vomiting in 9 patients (2.7%), abdominal pain in 8 patients (2.4%), pancytopenia in 7 patients (2.1%), diarrhoea and dysphagia in 6 patients (1.8%) each, pleural effusion and pulmonary embolism in 5 patients (1.5%) each, febrile neutropenia, neutropenia, gastrointestinal haemorrhage, intestinal obstruction, neutropenic sepsis, pneumonia, and dyspnoea in 4 patients (1.2%) each, and ascites, gastric haemorrhage, haematemesis, small intestinal obstruction, and septic shock in 3 patients (0.9%) each. Serious adverse events reported by ≥3 patients in the placebo group were general physical health deterioration in 15 patients (8.9%), ascites in 7 patients (4.2%), abdominal pain in 6 patients (3.6%), anaemia and decreased appetite in 4 patients (2.4%) each, and intestinal obstruction, gastric haemorrhage, asthenia, and back pain in 3 patients (1.8%) each. A causal relationship to the study drug could not be ruled out for the following events: the pancytopenia in 7 patients, anaemia and diarrhoea in 6 patients each, febrile neutropenia, neutropenia, and neutropenic sepsis in 4 patients each, vomiting and decreased appetite in 2 patients each, gastric haemorrhage, gastrointestinal haemorrhage, and general physical health deterioration in 1 patient each in the FTD-TPI group; and, anaemia in 2 patients in the placebo group.

Adverse events led to drug discontinuation in 43 of 335 patients (12.8%) in the FTD-TPI group and 28 of 168 patients (16.7%) in the placebo group. Adverse events that led to drug discontinuation in ≥2 patients in the FTD-TPI group were general physical health deterioration in 4 patients (1.2%), thrombocytopenia in 3 patients (0.9%), dysphagia, nausea, vomiting, diarrhoea, abdominal pain upper, fatigue, neutropenic sepsis, blood bilirubin increased, decreased appetite, cachexia, and pulmonary embolism in 2 patients (0.6%) each. Adverse events that led to drug discontinuation in ≥2 patients in the placebo group were general physical health deterioration in 4 patients (2.4%), malaise and decreased appetite in 3 patients (1.8%) each, and nausea, vomiting, ascites, and asthenia in 2 patients (1.2%) each. A causal relationship to the study drug could not be ruled out for thrombocytopenia in 3 patients, nausea, diarrhoea, and neutropenic sepsis in 2 patients each, and fatigue, general physical health deterioration, and decreased appetite in 1 patient each in the FTD-TPI group, and vomiting in 2 patients and nausea in 1 patient in the placebo group.

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

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection identified no obstacles to conducting its review based on the application documents submitted. At the same time, it also revealed errors at some study sites and the sponsor with minor impacts on the overall assessment of the study. The errors were notified to the heads of the study sites and the sponsor to request correction.

Findings requiring corrective actions

Study sites

- Protocol deviation (some study sites did not comply with the criteria for starting the next treatment cycle.)

Sponsor

- Some information on serious unexpected adverse drug reactions was not provided to the investigators and the heads of study sites in a timely manner.

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

On the basis of the data submitted, PMDA has concluded that FTD-TPI has efficacy in the treatment of unresectable advanced or recurrent gastric cancer progressing after cancer chemotherapy, and that FTD-TPI has acceptable safety in view of its benefits. FTD-TPI is clinically meaningful because it offers a new treatment option for patients with unresectable advanced or recurrent gastric cancer progressing after cancer chemotherapy. The indication, etc. of FTD-TPI should be further evaluated.

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

Review Report (2)

July 16, 2019

Product Submitted for Approval

Brand Name	Lonsurf Combination Tablets T15 Lonsurf Combination Tablets T20
Non-proprietary Name	Trifluridine and Tipiracil Hydrochloride
Applicant	Taiho Pharmaceutical Co., Ltd.
Date of Application	August 17, 2018

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

As a result of its review described in Section "7.R.1 Efficacy" of the Review Report (1), PMDA has concluded that the efficacy of the combination of trifluridine and tipiracil hydrochloride (FTD-TPI) has been demonstrated by the results of a global phase III study (Study 302) involving patients with unresectable advanced or recurrent gastric cancer who have received ≥2 prior chemotherapies, showing the superiority of FID-TPI in the primary endpoint (i.e., overall survival) over placebo.

At the Expert Discussion, the expert advisors supported PMDA's conclusion.

1.2 Safety

As a result of its review described in Section "7.R.2 Safety" of the Review Report (1), PMDA has concluded that particularly attention-calling adverse events of FTD-TPI therapy in patients with unresectable advanced or recurrent gastric cancer who have received ≥2 prior chemotherapies are bone marrow suppression, infections, gastrointestinal symptoms (diarrhoea, nausea, vomiting, and decreased appetite), peripheral neuropathy, cardiac disorders, ileus, interstitial lung disease, and hepatic impairment. They are known adverse events of FTD-TPI to which attention was called at its approval for unresectable advanced or recurrent CRC.

At the same time, PMDA has concluded that FTD-TPI, despite these attention calling adverse events, is tolerable in patients with gastric cancer as well, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy through monitoring and management of adverse events, drug interruption or discontinuation, dose reduction, or other appropriate measures.

At the Expert Discussion, the expert advisors supported PMDA's conclusion.

1.3 Clinical positioning and indication

As a result of its review described in Section "7.R.3 Clinical positioning and indication" of the Review Report (1), PMDA has concluded that the appropriate indication of FTD-TPI should be described as "unresectable advanced or recurrent gastric cancer progressing after cancer chemotherapy," along with the following cautionary statements presented in the "Precautions for Indications" section.

Precautions for Indications

- The efficacy and safety of FTD-TPI in first-line or second-line therapy have not been established.
- The efficacy and safety of FTD-TPI in adjuvant therapy have not been established.

At the Expert Discussion, the expert advisors supported PMDA's conclusion.

Based on the above, PMDA instructed the applicant to define the "Indications" and "Precautions for Indications" sections as above. The applicant agreed.

1.4 Dosage and administration

As a result of its review described in Section "7.R.4 Dosage and Administration" of the Review Report (1), PMDA has concluded that descriptions of the "Dosage and Administration" and the "Precautions for Dosage and Administration" sections for the treatment of gastric cancer should follow those for the approved indication (unresectable advanced or recurrent CRC).

At the Expert Discussion, the expert advisors supported PMDA's conclusion.

Based on the above, PMDA instructed the applicant to include the following statements in the "Dosage and Administration" and "Precautions for Dosage and Administration" sections of the package insert. The applicant agreed.

Dosage and Administration

The usual initial adult dose of the combination product of trifluridine and tipiracil hydrochloride (FTD-TPI) is determined based on body surface area (BSA) and shown in the dosing table below, which presents predefined ranges of BSA and the corresponding initial doses (on the basis of trifluridine at approximately 35 mg/m^2/dose). FTD-TPI is orally administered twice daily, after breakfast and after supper, in 28-day cycles,

each consisting of two 5 days on/2 days off treatment sub-cycles followed by a 14-day rest period. The dose may be reduced according to the patient's condition.

Precautions for Dosage and Administration

- The efficacy and safety of FTD-TPI in combination with other antitumor drugs have not been established.
- FTD-TPI should not be administered to patients in the fasted state because C_{max} of trifluridine is higher in the fasted state than in the postprandial state.
- Criteria for drug interruption, dose reduction, and drug discontinuation when adverse drug reactions develop
- When FTD-TPI is administered at a dose of 50 mg/day, 20 mg should be administered after breakfast and 30 mg after supper.

1.5 Risk management plan (draft)

In view of the discussion presented in Section "7.R.5 Post-marketing investigations" of the Review Report (1), PMDA has concluded that there is little necessity to conduct new post-marketing surveillance in patients with unresectable advanced or recurrent gastric cancer progressing after cancer chemotherapy immediately after approval and regular pharmacovigilance activities will suffice to gather safety data of FTD-TPI.

At the Expert Discussion, the expert advisors supported PMDA's conclusion.

In view of the discussion above, PMDA has concluded that the present draft risk management plan for FTD-TPI should include the safety and efficacy specifications presented in Table 8 and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 9. One of the important missing information of the safety specifications selected for the approved indication, "administration to patients with hepatic impairment" may be deleted, because the drug use-result data from patients with CRC, etc. have shown no marked differences in the incidence of adverse events by the presence or absence of hepatic impairment or its severity.

Table 8. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Bone marrow suppression • Infections	• Interstitial lung disease • Ileus • Cardiac disorders	• Administration to patients with renal impairment ~~• Administration to patients with hepatic impairment~~
Efficacy specifications		
Efficacy in patients with advanced or recurrent CRC in clinical practice		

Strikethrough denotes the safety specification to be deleted.

Table 9. Summary of additional pharmacovigilance activities, efficacy investigations or studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy investigations/studies	Additional risk minimization activities
None	None	• Preventive measures for administration errors

Underline denotes an activity to be performed for the new indication.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved with the proposed indication and the proposed dosage and administration modified as shown below with the following condition of approval, on the premise of the proper use of the product ensured by the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy and at medical institutions fully capable of responding to emergencies. The re-examination period for the present partial change approval application is the remainder of the ongoing re-examination period for the initial approval (until March 23, 2022).

Indications (Underline denotes additions.)

Unresectable advanced or recurrent colorectal cancer

Unresectable advanced or recurrent gastric cancer progressing after cancer chemotherapy

Dosage and Administration (No change)

The usual initial adult dose of the combination product of trifluridine and tipiracil hydrochloride (FTD-TPI) is determined based on body surface area (BSA) and shown in the dosing table below, which presents predefined ranges of BSA and the corresponding initial doses (on the basis of trifluridine at approximately 35 mg/m^2/dose). FTD-TPI is orally administered twice daily, after breakfast and after supper, in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles followed by a 14-day rest period.

The dose may be reduced according to the patient's condition.

Body surface area (m^2)	Initial dose (as trifluridine)
<1.07	35 mg/dose (70 mg/day)
1.07-<1.23	40 mg/dose (80 mg/day)
1.23-<1.38	45 mg/dose (90 mg/day)
1.38-<1.53	50 mg/dose (100 mg/day)
1.53-<1.69	55 mg/dose (110 mg/day)
1.69-<1.84	60 mg/dose (120 mg/day)
1.84-<1.99	65 mg/dose (130 mg/day)
1.99-<2.15	70 mg/dose (140 mg/day)
≥2.15	75 mg/dose (150 mg/day)

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Warnings (No change)

1. Cancer chemotherapy including FTD-TPI should be provided only under supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions fully capable of providing treatment in emergency. Patients or their family members should be thoroughly informed of the efficacy and risk of FTD-TPI, and informed consent should be obtained from them before starting treatment.
2. Caution should be exercised when FTD-TPI is used in combination treatment/therapy with fluoropyrimidines, fluoropyrimidine therapies including folinate/tegafur/uracil therapy; antifungal drug flucytosine; or antifolate drugs including methotrexate and pemetrexed sodium hydrate because serious adverse drug reactions such as bone marrow suppression may develop.

Contraindications (No change)

1. Patients with a history of serious hypersensitivities to any components of FTD-TPI
2. Pregnant women or women who may be pregnant

Precautions for Indications (Underline denotes additions and strikethrough denotes deletions.)

1. The efficacy and safety of FTD-TPI in first-line or second-line therapy have not been established.
2. The efficacy and safety of FTD-TPI in adjuvant therapy have not been established.
3. <u>For the treatment of unresectable advanced or recurrent colorectal cancer,</u> physicians should be acquainted with the prior treatment history of the patients enrolled in the clinical studies of FTD-TPI via information in the "Clinical Studies" section in order to fully understand the efficacy and safety of FTD-TPI before selecting eligible patients for FTD-TPI treatment.

Precautions for Dosage and Administration (No change)

1. The efficacy and safety of FTD-TPI in combination with other antitumor drugs have not been established.
2. FTD-TPI should not be administered to patients in the fasted state because C_{max} of trifluridine is higher in the fasted state than in the postprandial state.
3. During treatment with FTD-TPI, the criteria below should be referred to whenever dose reduction or treatment interruption is necessary.
   (1) FTD-TPI should not be administered to patients who do not meet the criteria for starting treatment at the beginning of each cycle. Treatment with FTD-TPI should be interrupted when adverse events develop and meet the criteria for treatment interruption, and should be restarted after the adverse events have subsided to the levels meeting the criteria for resuming treatment.

	Criteria for starting/resuming treatment	Criteria for treatment interruption
Hemoglobin	≥8.0 g/dL	<7.0 g/dL
Neutrophil count	≥1500/mm^3	<1000/mm^3
Platelet count	≥75,000/mm^3	<50,000/mm^3
Total bilirubin	≤1.5 mg/dL	>2.0 mg/dL
AST (GOT), ALT (GPT)	≤2.5 × UNL (≤5 × UNL for patients with liver metastasis)	>2.5 × UNL (>5 × UNL for patients with liver metastasis)
Creatinine	≤1.5 mg/dL	>1.5 mg/dL
Peripheral neuropathy	Grade ≤2	Grade ≥3
Toxicity other than hematotoxicity	Grade ≤1 (excluding alopecia, dysgeusia, pigmentation, and symptoms due to the tumor)	Grade ≥3

(CTCAE v3.0 grading)

(2) When adverse events meeting the criteria for dose reduction develop in the previous cycle (including the rest periods), the dose for the next cycle should be reduced by a unit of 10 mg/day. The daily dose should be 30 mg/day at minimum.

	Criteria for dose reduction
Neutrophil count	<500/mm^3
Platelet count	<50,000/mm^3

4. When FTD-TPI is administered at a dose of 50 mg/day, 20 mg should be administered after breakfast and 30 mg after supper.

Appendix

List of Abbreviations

AJCC	American Joint Committee on Cancer
BID	bis in die
CI	confidence interval
CRC	colorectal cancer
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
ITT	intent-to-treat
irinotecan	irinotecan hydrochloride hydrate
Japanese clinical practice guidelines	Gastric Cancer Treatment Guidelines, Revised in January 2018, Version 5, edited by the Japan Gastric Cancer Society
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Gastric Cancer
nivolumab	nivolumab (genetic recombination)
OS	overall survival
partial change application	application of partial change approval
PMDA	Pharmaceuticals and Medical Devices Agency
PS	performance status
ramucirumab	ramucirumab (genetic recombination)
Study 301	Study TPU-TAS-102-301
Study 302	Study TO-TAS-102-302