HIGHLIGHTS OF PACKAGE INSERT

These highlights do not include all the information needed to use Lonsurf® safely and effectively. See full package insert for Lonsurf®.

Lonsurf® (trifluridine and tipiracil) film-coated tablets, for oral use

INDICATIONS AND USAGE

Lonsurf® is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of adult patients with:

- metastatic colorectal cancer as a single agent or in combination with bevacizumab who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. (1.1)
- metastatic gastric or gastroesophageal junction adenocarcinoma who have been 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. (1.2)

DOSAGE AND ADMINISTRATION

- Recommended dosage: 35 mg/m^2/dose orally twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. (2.1)
- Take Lonsurf® within 1 hour after completion of morning and evening meals. (2.1)

DOSAGE FORMS AND STRENGTHS

Film-coated Tablets:

- 15 mg trifluridine/6.14 mg tipiracil (as 7.065 mg tipiracil hydrochloride) (3)
- 20 mg trifluridine/8.19 mg tipiracil (as 9.420 mg tipiracil hydrochloride) (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Severe Myelosuppression: Obtain complete blood counts prior to and on Day 15 of each cycle. Withhold and resume at next lower Lonsurf® dosage as recommended. (2.2, 5.1)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.2, 7.1, 7.3)
- Gastrointestinal Toxicity: Careful monitoring required. Withhold and resume at next lower Lonsurf® dosage as recommended. (2.2, 5.3)

ADVERSE REACTIONS

The most common adverse reactions or laboratory abnormalities for single agent Lonsurf® (≥ 10%) are neutropenia, anemia, thrombocytopenia, fatigue, nausea, decreased appetite, diarrhea, vomiting, abdominal pain and pyrexia. (6.1)

The most common adverse reactions or laboratory abnormalities for Lonsurf® in combination with bevacizumab (≥20%) are neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased AST, increased ALT, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain, and decreased appetite. (6.1)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (7.2)
- Geriatric Use: For Lonsurf® as single agent, Grade 3 or 4 neutropenia and Grade 3 or 4 thrombocytopenia and Grade 3 anemia occurred more commonly in patients 65 years old or older. (7.5) For Lonsurf® in combination with bevacizumab, Grade 3 or 4 neutropenia and Grade 3 or 4 thrombocytopenia occurred more commonly in patients 65 years or older. (7.5)
- Hepatic Impairment: Do not initiate Lonsurf® in patients with baseline moderate or severe hepatic impairment. (7.6)
- Renal Impairment: Reduce dose of Lonsurf® in patients with severe renal impairment. (7.7)

See 14 for PATIENT COUNSELING INFORMATION

Revised: May 2024

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1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer

Lonsurf®, as a single agent or in combination with bevacizumab, is indicated for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

1.2 Metastatic Gastric Cancer

Lonsurf® is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma who have been 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of Lonsurf® as a single agent or in combination with bevacizumab is 35 mg/m^2 up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily within one hour of completion of morning and evening meals on Days 1 through 5 and Days 8 through 12 of each 28-day cycle until disease progression or unacceptable toxicity. Round dose to the nearest 5 mg increment.

Refer to the Prescribing Information for bevacizumab dosing information.

Instruct patients to swallow Lonsurf® tablets whole.

Instruct patients not to retake doses of Lonsurf® that are vomited or missed and to continue with the next scheduled dose.

Table 1 shows the calculated initial daily dose based on body surface area (BSA).

Table 1: Recommended Dosage According to Body Surface Area (BSA)

BSA (m^2)	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15 mg/6.14 mg	20 mg/8.19mg
< 1.07	70	35	1	1
1.07 – 1.22	80	40	0	2
1.23 – 1.37	90	45	3	0
1.38 – 1.52	100	50	2	1
1.53 – 1.68	110	55	1	2
1.69 – 1.83	120	60	0	3
1.84 – 1.98	130	65	3	1

1.99 – 2.14	140	70	2	2
2.15 – 2.29	150	75	1	3
≥ 2.30	160	80	0	4

2.2 Dosage Modifications for Adverse Reactions

Obtain complete blood cell counts prior to and on Day 15 of each cycle. *[*see *Warnings and Precautions (5.1)]*

Do not initiate the cycle of Lonsurf® until:

- Absolute neutrophil count (ANC) is greater than or equal to 1,500/mm^3 or febrile neutropenia is resolved
- Platelets are greater than or equal to 75,000/mm^3
- Grade 3 or 4 non-hematological adverse reactions are resolved to Grade 0 or 1

Within a treatment cycle, withhold Lonsurf® for any of the following:

- Absolute neutrophil count (ANC) less than 500/mm^3 or febrile neutropenia
- Platelets less than 50,000/mm^3
- Grade 3 or 4 non-hematological adverse reaction

After recovery, resume Lonsurf® after reducing the dose by 5 mg/m^2/dose from the previous dose, if the following occur:

- Febrile neutropenia
- Uncomplicated Grade 4 neutropenia (which has recovered to greater than or equal to 1,500/mm^3) or thrombocytopenia (which has recovered to greater than or equal to 75,000/mm^3) that results in more than 1 week delay in start of next cycle
- Non-hematologic Grade 3 or Grade 4 adverse reaction except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication

A maximum of 3 dose reductions are permitted. Permanently discontinue Lonsurf® in patients who are unable to tolerate a dose of 20 mg/m^2 orally twice daily. Do not escalate Lonsurf® dosage after it has been reduced.

Refer to the bevacizumab prescribing information for dose modifications for adverse reactions associated with bevacizumab.

2.3 Recommended Dosage for Renal Impairment

Severe Renal Impairment

In patients with severe renal impairment [creatinine clearance (CLcr) of 15 to 29 mL/min as determined by the Cockcroft-Gault formula], the recommended dosage is 20 mg/m^2 (based on the trifluridine component) orally twice daily within one hour of completion of morning and evening meals on Days 1 through 5 and Days 8 through 12 of each 28-day cycle (Table 2). *[*see *Use in Specific Populations (7.7), Clinical Pharmacology (10.3)]* Reduce dose to 15 mg/m^2 twice daily in patients with severe renal

impairment who are unable to tolerate a dose of 20 mg/m^2 twice daily (Table 2). Permanently discontinue Lonsurf® in patients who are unable to tolerate a dose of 15 mg/m^2 twice daily.

Table 2: Recommended Dosage for Severe Renal Impairment According to BSA

BSA (m^2)	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15 mg/6.14 mg	20 mg/8.19mg
For a dose of 20 mg/m^2 twice daily:				
< 1.14	40	20	0	1
1.14 – 1.34	50	25*	2 in the evening*	1 in the morning*
1.35 – 1.59	60	30	2	0
1.60 – 1.94	70	35	1	1
1.95 – 2.09	80	40	0	2
2.10 – 2.34	90	45	3	0
≥ 2.35	100	50	2	1
For a dose of 15 mg/m^2 twice daily:				
< 1.15	30	15	1	0
1.15 – 1.49	40	20	0	1
1.50 – 1.84	50	25*	2 in the evening*	1 in the morning*
1.85 – 2.09	60	30	2	0
2.10 – 2.34	70	35	1	1
≥ 2.35	80	40	0	2

* For a total daily dose of 50 mg, instruct patients to take 1 × 20 mg/8.19 mg tablet in the morning and 2 × 15 mg/6.14 mg tablets in the evening.

3 DOSAGE FORMS AND STRENGTHS

Lonsurf® Film-coated Tablet 15 mg/6.14 mg (15 mg trifluridine/6.14 mg tipiracil as 7.065 mg tipiracil hydrochloride) is a white, biconvex, round, film-coated tablet, imprinted with ‘15’ on one side, and ‘102’ and ‘15 mg’ on the other side, in gray ink.

Lonsurf® Film-coated Tablet 20 mg/8.19 mg (20 mg trifluridine/8.19 mg tipiracil as 9.420 mg tipiracil hydrochloride) is a pale red, biconvex, round, film-coated tablet, imprinted with ‘20’ on one side, and ‘102’ and ‘20 mg’ on the other side, in gray ink.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Myelosuppression

In the 1114 patients who received Lonsurf® as a single agent, Lonsurf® caused severe or life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (38%), anemia (17%), thrombocytopenia (4%) and febrile neutropenia (3%). Three patients (0.3%) died due to neutropenic infection/sepsis and four other patients (0.5%) died due to septic shock. Serious infections have been reported following treatment with Lonsurf®. Given that the majority were reported in the context of bone marrow suppression, the patient's condition should be monitored closely, and appropriate measures, such as antimicrobial agents and granulocyte-colony stimulating factor, should be administered as clinically indicated. A total of 14% of Lonsurf®-treated patients received granulocyte-colony stimulating factors. In the 246 patients who received Lonsurf® in combination with bevacizumab, Lonsurf® caused severe or life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (52%), anemia (5%), thrombocytopenia (4%) and febrile neutropenia (0.4%). One patient (0.4%) died due to abdominal sepsis and two other patients (0.8%) died due to septic shock. A total of 29% of patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on Day 15 of each cycle of Lonsurf® and more frequently as clinically indicated. Withhold Lonsurf® for severe myelosuppression and resume at the next lower dosage. *[*see *Dosage and Administration (2.2)]*

5.2 Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, Lonsurf® can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dosage levels resulting in exposures lower than those achieved at the recommended dosage of 35 mg/m^2 twice daily.

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with Lonsurf® and for at least 6 months after the final dose. *[*see *Use in Specific Populations (7.1, 7.3)]*

5.3 Gastrointestinal Toxicity

Lonsurf® caused an increase in the incidence of gastrointestinal toxicities including nausea, vomiting and diarrhea.

Patients with nausea, vomiting, diarrhea and other gastrointestinal toxicities should be carefully monitored, and anti-emetic, anti-diarrheal and other measures, such as fluid/electrolyte replacement therapy, should be administered as clinically indicated. Dose modifications (delay and/or reduction) should be applied as necessary. *[*see *Dosage and Administration (2.2)]*

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in detail in other sections of the package insert:

- Severe Myelosuppression *[*see *Warnings and Precautions (5.1)]*
- Gastrointestinal Toxicity *[*see *Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions section and below reflect exposure to Lonsurf® at the recommended dose in 533 patients with metastatic colorectal cancer in the RECOURSE study, 246 patients with metastatic colorectal cancer treated with Lonsurf® as monotherapy in SUNLIGHT and 335 patients with metastatic gastric cancer in the TAGS study. Among the 1114 patients who received Lonsurf® as a single agent, 12% were exposed for 6 months or longer and 1% were exposed for 12 months or longer. The most common adverse reactions or laboratory abnormalities (≥ 10%) were neutropenia, anemia, thrombocytopenia, fatigue, nausea, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

Among the 246 patients with metastatic colorectal cancer treated with Lonsurf® in combination with bevacizumab in SUNLIGHT, 39% were exposed for 6 months or longer, and 14% were exposed for 12 months or longer. The most common adverse reactions or laboratory abnormalities (≥20%) were neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased AST, increased ALT, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain, and decreased appetite.

Metastatic Colorectal Cancer

Lonsurf® as a single agent

The data described below are from the RECOURSE study, a randomized (2:1), double-blind, placebo-controlled trial in which 533 patients (median age 63 years; 61% men; 57% White, 35% Asian, 1% Black) with previously treated metastatic colorectal cancer received Lonsurf® as a single agent at a dose of 35 mg/m^2/dose administered twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. The mean duration of Lonsurf® therapy was 12.7 weeks.

The most common adverse reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with Lonsurf® at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

In the RECOURSE study, 3.6% of patients discontinued Lonsurf® for an adverse reaction and 13.7% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

Tables 3 and 4 list the adverse reactions and laboratory abnormalities (graded using CTCAE v4.03) observed in the RECOURSE study respectively.

Table 3: Adverse Reactions (≥ 5%) in Patients Receiving Lonsurf® and at a Higher Incidence (> 2%) than in Patients Receiving Placebo in RECOURSE study

Adverse Reactions	Lonsurf® (N=533)		Placebo (N=265)	
	All Grades (%)	Grades 3-4* (%)	All Grades (%)	Grades 3-4* (%)
Gastrointestinal disorders				
Nausea	48	1.9	24	1.1
Diarrhea	32	3	12	0.4
Vomiting	28	2.1	14	0.4
Abdominal pain	21	2.4	19	3.8
Stomatitis	8	0.4	6	0
General disorders and administration site conditions				
Asthenia/fatigue	52	7	35	9
Pyrexia	19	1.3	14	0.4
Metabolism and nutrition disorders				
Decreased appetite	39	3.6	29	4.9
Infections†	27	7	16	4.9
Nervous system disorders				
Dysgeusia	7	0	2.3	0
Skin and subcutaneous tissue disorders				
Alopecia	7	0	1.1	0

*No Grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

†Incidence reflects 64 preferred terms in the Infections and Infestations system organ class.

Table 4: Laboratory Abnormalities in RECOURSE study

Laboratory Parameter*	Lonsurf®		Placebo	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Blood and lymphatic system disorders				
Anemia	77	18#	33	3
Neutropenia	67	38	0.8	0
Thrombocytopenia	42	5	8	0.4

* Worst Grade at least one grade higher than baseline, with percentages based on number of patients with post-baseline samples, which may be less than 533 (Lonsurf®) or 265 (placebo)

One Grade 4 anemia adverse reaction based on clinical criteria was reported

In the RECOURSE study, pulmonary emboli occurred more frequently in Lonsurf®-treated patients (2%) compared to no patients on placebo.

Lonsurf® in combination with bevacizumab

The safety of Lonsurf® in combination with bevacizumab was evaluated in SUNLIGHT, an international, randomized, open label study in patients with previously treated metastatic colorectal cancer *[see Clinical Studies (12.1)]*.

The study population characteristics were: median age 63 years (20 to 90 years); 52% male; 88% White, 1.4% Black, 0.2% Asian, 0.2% American Indian or Alaska Native, and 9.6% were unknown; and baseline ECOG performance status 0 (46%), 1 (54%), or 2 (0.2%).

Serious adverse reactions occurred in 25% of patients. The most frequent serious adverse reactions (≥2%) were intestinal obstruction (2.8%), and COVID-19 (2%). Fatal adverse reactions occurred in 1.2% of patients who received Lonsurf® in combination with bevacizumab, including rectal fistula (0.4%), bowel perforation (0.4%) and atrial fibrillation (0.4%).

Permanent treatment discontinuation due to an adverse reaction occurred in 13% of patients. The adverse reaction which resulted in permanent treatment discontinuation in ≥2% of patients was fatigue.

Dosage reductions due to an adverse reaction or laboratory abnormality occurred in 7% of patients. At least one dose reduction in 3.7% of patients was required for neutropenia.

Dosage interruptions due to an adverse reaction occurred in 11% of patients who received Lonsurf® in combination with bevacizumab. The adverse reaction that required dosage interruption in ≥2% of patients was nausea.

The most common adverse reactions or laboratory abnormalities (≥20% in incidence) in patients treated with Lonsurf® in combination with bevacizumab were neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased aspartate aminotransferase, increased alanine aminotransferase, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain, and decreased appetite. Table 5 and Table 6 list the adverse reactions and laboratory abnormalities, respectively, observed in SUNLIGHT.

Table 5: Adverse Reactions (≥5%) in SUNLIGHT

Adverse Reactions	**Lonsurf® + Bevacizumab (N=246) (%)**		**Lonsurf® (N=246) (%)**	
	All Grades	**Grade 3 or 4**	**All Grades**	**Grade 3 or 4**
Gastrointestinal disorders				
Nausea	37	1.6	27	1.6
Diarrhea*	21	1.2	19	2.4
Abdominal pain*	20	2.8	18	3.7
Vomiting*	19	0.8	15	1.6
Stomatitis*	13	<0.4	4.1	0
Constipation	11	0	11	0.8
General disorders and administration site conditions				

Fatigue*	45	5	37	8
Pyrexia	4.9	0	6	0.4
Infections and infestations*	31	8	24	8
Metabolism and nutrition disorders				
Decreased appetite	20	<0.8	15	1.2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	18	1.2	11	2
Nervous system disorder				
Headache	8	0	3.7	0
Vascular disorders				
Hypertension*	11	6	2	1.2
Hemorrhage*	10	1.2	3.7	0.8
Renal and urinary disorders				
Proteinuria	6	0.8	1.2	0

*Represents a composite of multiple related terms

Table 6: Select Laboratory Abnormalities (≥10%) in SUNLIGHT

Laboratory parameters	**Lonsurf® + Bevacizumab[a]**		**Lonsurf® [a]**	
	All Grades (%)	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Hematology				
Neutrophils decreased	80	52	68	39
Hemoglobin decreased	68	5	73	11
Platelets decreased	54	4.1	29	0.8
Chemistry				
Aspartate aminotransferase increased	34	2.1	28	1.2
Alanine aminotransferase increased	33	3.3	23	0.4
Alkaline phosphatase increased	31	0.8	36	1.2
Sodium decreased	25	2.1	20	3.3
Potassium increased	17	0	15	0
Potassium decreased	12	0.8	12	2.5
Creatinine increased	12	0.8	15	0

[a]Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Lonsurf® + bevacizumab group (n=242 patients) and Lonsurf® group (range: 240 to 242 patients).

Metastatic Gastric Cancer

The data described below are from the TAGS study, a randomized (2:1), double-blind, placebo-controlled trial in which 503 patients (median age 63 years (24 to 89 years); 73% male; 70% White, 16% Asian, 1% Black) with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma who were previously treated with at least 2 prior chemotherapy regimens for advanced disease, received Lonsurf® as a single agent at a dose of 35 mg/m^2/dose (n=335) or placebo (n=168) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle with best supportive care. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. In the TAGS study, 10% of patients received Lonsurf® for more than 6 months and 0.9% of patients received Lonsurf® for more than 1 year.

The most common adverse reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with Lonsurf® at a rate that exceeds the rate in patients receiving placebo were neutropenia, anemia, nausea, decreased appetite, thrombocytopenia, vomiting, and diarrhea.

In the TAGS study, 13% of patients discontinued Lonsurf® for an adverse reaction and 11% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, and diarrhea.

Tables 7 and 8 list the adverse reactions and laboratory abnormalities (graded using CTCAE v4.03) observed in the TAGS study respectively.

Table 7: Adverse Reactions (≥ 5%) in Patients Receiving Lonsurf® and at a Higher Incidence (> 2%) than in Patients Receiving Placebo in TAGS study

Adverse Reactions	Lonsurf® (N=335)		Placebo (N=168)	
	All Grades (%)	Grades 3-4* (%)	All Grades (%)	Grades 3-4* (%)
Gastrointestinal disorders				
Nausea	37	3	32	3
Vomiting	25	4	20	2
Diarrhea	23	3	14	2
Metabolism and nutrition disorders				
Decreased appetite	34	9	31	7
Infections†	23	5	16	5

*No Grade 4 definition for nausea in NCI CTCAE, version 4.03.

†Incidence reflects 46 preferred terms in the Infections and Infestations system organ class.

Table 8: Laboratory Abnormalities in TAGS study

Laboratory Parameter*	Lonsurf®		Placebo	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Blood and lymphatic system disorders				
Neutropenia	66	38	4	0
Anemia	63	19	38	7
Thrombocytopenia	34	6	9	0

* Worst Grade at least one grade higher than baseline, with percentages based on number of patients with post-baseline samples, which may be less than 335 (Lonsurf®) or 168 (placebo)

In the TAGS study, pulmonary emboli occurred more frequently in Lonsurf®-treated patients (3.1%) compared to 1.8% for patients on placebo.

6.2 Additional Clinical Experience

Interstitial lung disease was reported in fifteen (0.2%) patients, three of which were fatal, among approximately 7,000 patients exposed to Lonsurf® in clinical studies and clinical practice settings in Asia.

7 USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action *[*see *Clinical Pharmacology (10.1)]*, Lonsurf® can cause fetal harm. Lonsurf® caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to human exposures at the recommended clinical dose *(*see *Data).* There are no available data on Lonsurf® use in pregnant women. Advise pregnant women of the potential risk to a fetus.

Data

Animal Data

Trifluridine/tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50, and 150 mg/kg [trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses greater than or equal to 50 mg/kg (approximately 0.33 times the FTD exposure at the clinical dose of 35 mg/m^2 twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m^2 twice daily), embryolethality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies) were observed.

7.2 Lactation

Risk Summary

There are no data on the presence of trifluridine, tipiracil or its metabolites in human milk or its effects on the breastfed child or on milk production. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk *(*see *Data)*. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Lonsurf® and for one day following the final dose.

Data

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing ^{14}C-FTD or ^{14}C-tipiracil (TPI). Levels of FTD-derived radioactivity were as high as approximately 50% of the exposure in maternal plasma an hour after dosing with trifluridine/tipiracil and were approximately the same as those in maternal plasma for up to 12 hours following dosing. Exposure to TPI-derived radioactivity was higher in milk than in maternal plasma beginning 2 hours after dosing and continuing for at least 12 hours following administration of trifluridine/tipiracil.

7.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating Lonsurf®. *[*see *Use in Specific Populations (7.1)]*

Contraception

Females

Lonsurf® can cause fetal harm when administered to a pregnant woman. *[*see *Use in Specific Populations (7.1)]*

Advise females of reproductive potential to use effective contraception during treatment with Lonsurf® and for at least 6 months after the final dose. It is currently unknown whether Lonsurf® may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier contraceptive method.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with Lonsurf® and for up to 6 months after the final dose. *[*see *Nonclinical Toxicology (11.1)]*

7.4 Pediatric Use

Safety and effectiveness of Lonsurf® in pediatric patients have not been established.

Juvenile Animal Toxicity Data

Dental toxicity including whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in rats treated with trifluridine/tipiracil at doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily).

7.5 Geriatric Use

Of the 1114 patients with metastatic colorectal cancer or gastric cancer who received single agent Lonsurf® in clinical studies, 45% were 65 years of age or over, while 11% were 75 and over. In the 246 patients who received Lonsurf® in combination with bevacizumab; 41% were 65 years of age or over, and 10% were 75 and over. While these studies were not designed to detect a difference in efficacy, no overall differences were observed in patients 65 years or older versus younger patients with either Lonsurf® as a single agent or Lonsurf® in combination with bevacizumab.

Patients 65 years of age or older who received Lonsurf® as a single agent had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (46% vs. 32%), Grade 3 anemia (20% vs. 14%), and Grade 3 or 4 thrombocytopenia (6% vs. 3%). Patients 65 years of age or older who received Lonsurf® in combination with bevacizumab had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (60% vs 46%) and Grade 3 or 4 thrombocytopenia (5% vs 4%).

7.6 Hepatic Impairment

No adjustment to the starting dosage of Lonsurf® is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to the upper limit of normal (ULN) and aspartate aminotransferase (AST) greater than ULN or total bilirubin greater than 1 to 1.5 times ULN and any AST). Do not initiate Lonsurf® in patients with baseline moderate or severe (total bilirubin greater than 1.5 times ULN and any AST) hepatic impairment. *[*see *Clinical Pharmacology (10.3)]*

7.7 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min as determined by the Cockcroft-Gault formula). Reduce the dose of Lonsurf® for patients with severe renal impairment (CLcr of 15 to 29 mL/min). *[*see *Dosage and Administration (2.3)]* The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

7.8 Ethnicity

There were no clinically meaningful differences in the RECOURSE and TAGS studies between Western and Asian subgroups with respect to overall incidence of adverse events or ≥ Grade 3 adverse events in either the Lonsurf® or placebo groups.

8 OVERDOSAGE

The highest dose of Lonsurf® administered in clinical studies was 180 mg/m^2 per day.

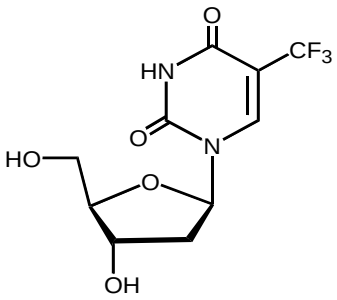
There is no known antidote for Lonsurf® overdosage.

9 DESCRIPTION

Lonsurf® contains trifluridine and tipiracil hydrochloride at a molar ratio of 1:0.5.

Trifluridine

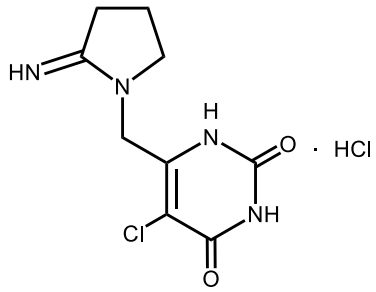
Trifluridine, an antineoplastic thymidine-based nucleoside analogue, is described chemically as 2'-deoxy-5-(trifluoromethyl) uridine, and has the following structural formula:



Trifluridine has a molecular formula $C_{10}H_{11}F_3N_2O_5$ and a molecular weight of 296.20. Trifluridine is a white crystalline powder, soluble in water, ethanol, 0.01 mol/L hydrochloric acid, 0.01 mol/L sodium hydroxide solution; freely soluble in methanol, acetone; sparingly soluble in 2-propanol, acetonitrile; slightly soluble in diethyl ether; and very slightly soluble in isopropyl ether.

Tipiracil hydrochloride

Tipiracil hydrochloride, a thymidine phosphorylase inhibitor, is described chemically as 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1*H*,3*H*)-dione monohydrochloride or 2,4(1*H*,3*H*)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (1:1), and has the following structural formula:



Tipiracil hydrochloride has a molecular formula $C_9H_{11}ClN_4O_2$•HCl and a molecular weight of 279.12. Tipiracil hydrochloride is a white crystalline powder, soluble in water, 0.01 mol/L hydrochloric acid, and 0.01 mol/L sodium hydroxide; slightly soluble in methanol; very slightly soluble in ethanol; and practically insoluble in acetonitrile, 2-propanol, acetone, diisopropyl ether, and diethyl ether.

Lonsurf® Film-coated Tablet 15 mg/6.14 mg

Each Lonsurf® Film-coated Tablet 15 mg/6.14 mg, for oral use, contains 15 mg of trifluridine and 6.14 mg of tipiracil equivalent to 7.065 mg of tipiracil hydrochloride as active ingredients. Lonsurf® Film-coated Tablet 15 mg/6.14 mg contains the following inactive ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, and magnesium stearate.

Lonsurf® Film-coated Tablet 20 mg/8.19 mg

Each Lonsurf® Film-coated Tablet 20 mg/8.19 mg, for oral use, contains 20 mg of trifluridine and 8.19 mg of tipiracil equivalent to 9.420 mg of tipiracil hydrochloride as active ingredients. Lonsurf® Film-coated Tablet 20 mg/8.19 mg contains the following inactive ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, ferric oxide (red), and magnesium stearate.

Both Lonsurf® Film-coated Tablet 15 mg/6.14 mg and Lonsurf® Film-coated Tablet 20 mg/8.19 mg are imprinted with ink containing shellac, ferric oxide (red), ferric oxide (yellow), titanium dioxide, FD&C Blue No. 2 – Lakes, carnauba wax, and talc.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Lonsurf® consists of a thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil hydrochloride, at a molar ratio 1:0.5 (weight ratio, 1:0.471). Inclusion of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase.

Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation. Trifluridine/tipiracil demonstrated anti-tumor activity against *KRAS* wild-type and mutant human colorectal cancer xenografts in mice.

10.2 Pharmacodynamics

Cardiac Electrophysiology

Lonsurf® administered to 42 patients with advanced solid tumors at the recommended dosage had no large effect (i.e. > 20 msec) in the mean QTc interval when compared to placebo and no evident exposure-QT relationship was identified. Two of 42 patients (4.8%) had QTc greater than 500 msec and 2.4% had a QTc increase from baseline greater than 60 msec.

10.3 Pharmacokinetics

After twice daily dosing of Lonsurf®, systemic exposure (area under the concentration curve, AUC) of trifluridine increased more than dose-proportionally over the dose range of 15 mg/m^2 (0.43 times the recommended dose) to 35 mg/m^2.

The accumulation of trifluridine was 3-fold for $AUC_{0\text{-}12hr}$ and 2-fold for peak plasma concentration (C_{max}) at steady state while no accumulation was observed for tipiracil.

Administration of a single dose of Lonsurf® 35 mg/m^2 increased the mean $AUC_{0\text{-}last}$ of trifluridine by 37-fold and C_{max} by 22-fold with reduced variability compared to administration of a single dose of trifluridine 35 mg/m^2 alone.

Absorption

Following a single oral administration of Lonsurf® at 35 mg/m^2 in patients with cancer, the mean time to peak plasma concentration (T_{max}) of trifluridine was around 2 hours.

Food Effect

A standardized high-fat, high-calorie meal decreased trifluridine C_{max}, tipiracil C_{max} and AUC by approximately 40%, but did not change trifluridine AUC compared to those in a fasting state in patients with cancer following administration of a single dose of Lonsurf® 35 mg/m^2. It is recommended to take Lonsurf® within 1 hour after completion of the morning and evening meals based on the observed correlation between the increase in the C_{max} of trifluridine and the decrease in neutrophil counts.

Distribution

Trifluridine mainly binds to human serum albumin. The *in vitro* protein binding of trifluridine in human plasma is greater than 96%, independent of drug concentration and presence of tipiracil. Plasma protein binding of tipiracil is below 8%.

Elimination

After administration of Lonsurf® 35 mg/m^2, the mean elimination half-life ($t_{1/2}$) of trifluridine was 1.4 hours and of tipiracil was 2.1 hours after a single dose. The mean elimination half-life at steady state of trifluridine was 2.1 hours and of tipiracil was 2.4 hours.

Metabolism

Trifluridine and tipiracil are not metabolized by cytochrome P450 (CYP) enzymes. Trifluridine is mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, 5-(trifluoromethyl) uracil (FTY). No other major metabolites were detected in plasma or urine.

Excretion

After single oral administration of Lonsurf® (60 mg) with [^{14}C]-trifluridine, the total cumulative excretion of radioactivity was 60% of the administered dose. The majority of recovered radioactivity was eliminated into urine (55% of the dose) as FTY and trifluridine glucuronide isomers within 24 hours, and the excretion into feces and expired air was less than 3% for both. The unchanged trifluridine was less than 3% of administered dose recovered in the urine and feces.

After single oral administration of Lonsurf® (60 mg) with [^{14}C]-tipiracil hydrochloride, recovered radioactivity was 77% of the dose, which consisted of 27% urinary excretion and 50% fecal excretion. Tipiracil was the major component and 6-hydroxymethyluracil (6-HMU) was the major metabolite in urine, and feces.

Specific Populations

Age, Sex, and Race

Based on the population pharmacokinetic analysis, there is no clinically relevant effect of age, sex, or race (White or Asian) on the pharmacokinetics of trifluridine or tipiracil.

Renal Impairment

In a dedicated renal impairment study, all patients received Lonsurf® 35 mg/m^2 twice daily except for patients with severe renal impairment who received 20 mg/m^2 twice daily. Mild renal impairment (CLcr of 60 to 89 mL/min as determined by the Cockcroft-Gault formula) had no clinically important effect

on steady-state $AUC_{0\text{-last}}$ of trifluridine and tipiracil. Moderate renal impairment (CLcr of 30 to 59 mL/min) increased steady-state $AUC_{0\text{-last}}$ of trifluridine by 56% and tipiracil by 139% compared to normal renal function (CLcr ≥ 90 mL/min). Severe renal impairment (CLcr of 15 to 29 mL/min) increased the dose-normalized steady-state $AUC_{0\text{-last}}$ of trifluridine by 140% and tipiracil by 614% compared to normal renal function. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

Hepatic Impairment

In a pharmacokinetic trial of patients with hepatic impairment, no clinically important differences in the mean exposures of trifluridine and tipiracil were observed between patients with mild hepatic impairment (total bilirubin less than or equal to the ULN and AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN and any AST) to moderate hepatic impairment (total bilirubin greater than 1.5 to 3 times ULN and any AST) and patients with normal hepatic function (total bilirubin and AST less than or equal to the ULN). However, 5 of 6 patients with moderate hepatic impairment experienced Grade 3 or 4 increased bilirubin levels. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with severe hepatic impairment (total bilirubin greater than 3 times ULN and any AST). *[*see *Dosage and Administration (2.2), Use in Specific Populations (7.6)]*

Drug Interaction Studies

Trifluridine is a substrate of thymidine phosphorylase, and is not metabolized by cytochrome P450 (CYP) enzyme. Tipiracil is not metabolized in either human liver or hepatocytes.

In vitro studies indicated that trifluridine, tipiracil, and FTY did not inhibit the CYP enzymes and had no inductive effect on CYP1A2, CYP2B6, or CYP3A4/5.

In vitro studies indicated that trifluridine was not an inhibitor of or substrate for human uptake and efflux transporters.

11 NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies evaluating the carcinogenic potential of trifluridine/tipiracil in animals have been performed. Trifluridine/tipiracil was genotoxic in a reverse mutation test in bacteria, a chromosomal aberration test in mammalian-cultured cells, and a micronucleus test in mice.

Animal studies did not indicate an effect of trifluridine/tipiracil on male fertility in rats. Dose-related increases in the corpus luteum count and implanted embryo count were observed, but female fertility was not affected.

12 CLINICAL STUDIES

12.1 Metastatic Colorectal Cancer

Previously treated metastatic colorectal cancer (single agent Lonsurf®)
RECOURSE Study

The clinical efficacy and safety of Lonsurf® were evaluated in an international, randomized, double-blind, placebo-controlled study conducted in patients with previously treated metastatic colorectal cancer (CRC).

A total of 800 patients were randomized 2:1 to receive Lonsurf® (N = 534) plus best supportive care (BSC) or matching placebo (N = 266) plus BSC. Randomization was stratified by *KRAS* status (wild-type vs. mutant), time since diagnosis of first metastasis (< 18 months vs. ≥ 18 months), and region (Japan vs. US, Europe and Australia). Key eligibility criteria included prior treatment with at least 2 lines of standard chemotherapy for metastatic CRC, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1, absence of brain metastasis, and absence of ascites requiring drainage in the past four weeks. Patients received 35 mg/m^2 Lonsurf® or matching placebo orally twice daily after meals on Days 1 – 5 and 8 – 12 of each 28-day cycle until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival (OS) and an additional efficacy outcome measure was progression-free survival (PFS). The median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, and all patients had baseline ECOG PS of 0 or 1. The primary site of disease was colon (62%) or rectum (38%). *KRAS* status was wild-type (49%) or mutant (51%) at study entry. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received bevacizumab, and all but two patients with *KRAS* wild-type tumors received panitumumab or cetuximab.

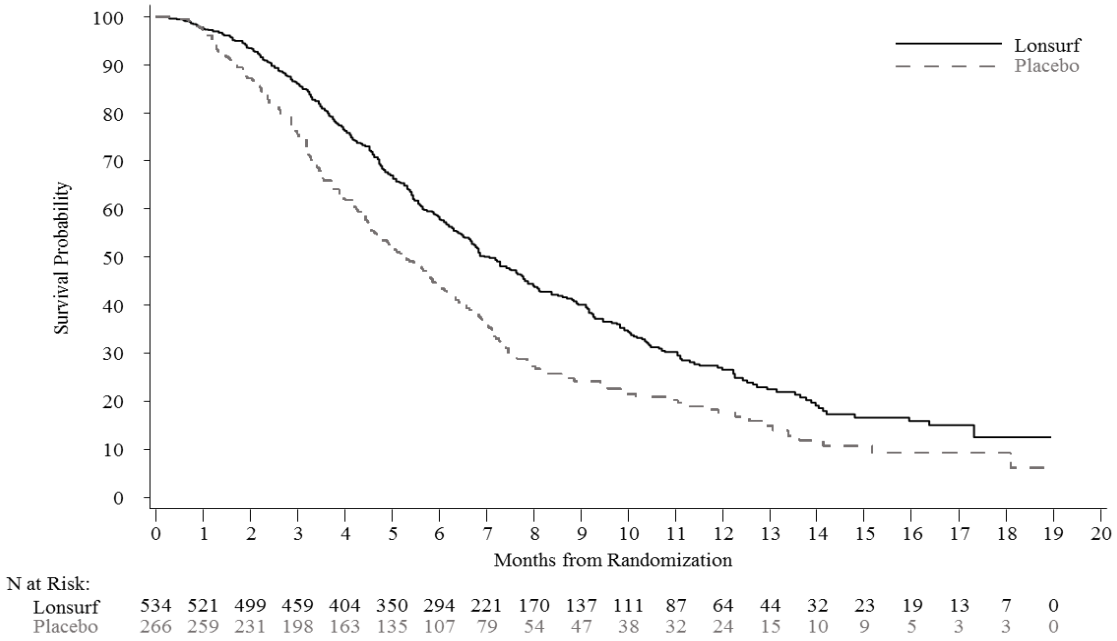
A statistically significant improvement in overall survival and progression-free survival were demonstrated in patients in the Lonsurf® plus BSC arm compared to those who received placebo plus BSC *(*see *Table 9 and Figure 1)*.

Table 9: Efficacy Results from RECOURSE study

	Lonsurf® (N=534)	**Placebo (N=266)**
Overall Survival		
Number of deaths, N (%)	364 (68)	210 (79)
Median OS (months)[a] [95% CI][b]	7.1 [6.5, 7.8]	5.3 [4.6, 6.0]
Hazard ratio [95% CI]	0.68 [0.58, 0.81]	
P-value[c]	< 0.001	
Progression-Free Survival		
Number of Progression or Death, N (%)	472 (88)	251 (94)
Hazard ratio [95% CI]	0.47 [0.40, 0.55]	
P-value[c]	< 0.001	

[a] Kaplan-Meier estimates
[b] Methodology of Brookmeyer and Crowley
[c] Stratified log-rank test (strata: *KRAS* status, time since diagnosis of first metastasis, region), 2-sided

Figure 1: Kaplan-Meier Curves of Overall Survival in RECOURSE study



Previously treated metastatic colorectal cancer (Lonsurf® in combination with bevacizumab)

SUNLIGHT

The efficacy of Lonsurf® in combination with bevacizumab was evaluated in SUNLIGHT (NCT 04737187), an international, randomized (1:1), open label study in patients with previously treated metastatic colorectal cancer. Patients were required to have received no more than 2 prior treatments for advanced disease, including a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody (optional) and an anti-EGFR monoclonal antibody for patients with RAS wild-type. Other key eligibility criteria included ECOG performance status (PS) 0-1, absence of symptomatic brain metastases, absence of ascites requiring drainage in the past 4 weeks, absence of uncontrolled hypertension, absence of non-healing wound, and absence of deep venous thromboembolic event in the past 4 weeks. Patients were randomized to receive Lonsurf® 35 mg/m^2 administered orally twice daily on Days 1 to 5 and 8 to 12 of each 28-day cycle with or without bevacizumab 5 mg/kg administered intravenously every 2 weeks (on Day 1 and Day 15) of each 4-week cycle until disease progression or unacceptable toxicity. Randomization was stratified by geographic region (North America, European Union, Rest of the World), time since diagnosis of metastatic disease (<18 months, ≥18 months) and RAS status (wild-type, mutant). The major efficacy outcome was overall survival (OS), and an additional efficacy outcome measure was progression-free survival (PFS).

A total of 492 patients were randomized to receive Lonsurf® in combination with bevacizumab (N=246) or Lonsurf® as a single agent (N=246). The trial population characteristics were as follows: median age 63 years, 52% male, 88% White, 1.4% Black, 0.2% Asian, 0.2% American Indian or Alaska Native, and 9.6% were unknown, 46% had ECOG PS 0 and 54% had ECOG PS 1. The primary site of disease was colon (73%) or rectum (27%). Seventy-one percent of patients had a RAS mutant status. A total of 92% of patients received 2 prior anticancer treatment regimens for advanced CRC; all patients received prior fluoropyrimidine; 99.8% of patients received prior irinotecan; 98% of patients received prior oxaliplatin. Among all 492 treated patients, 76% received prior anti-VEGF treatment, and 72% received an anti-VEGF monoclonal antibody. Among the 142 patients with RAS wild-type mCRC, 94% received prior anti-EGFR monoclonal antibody.

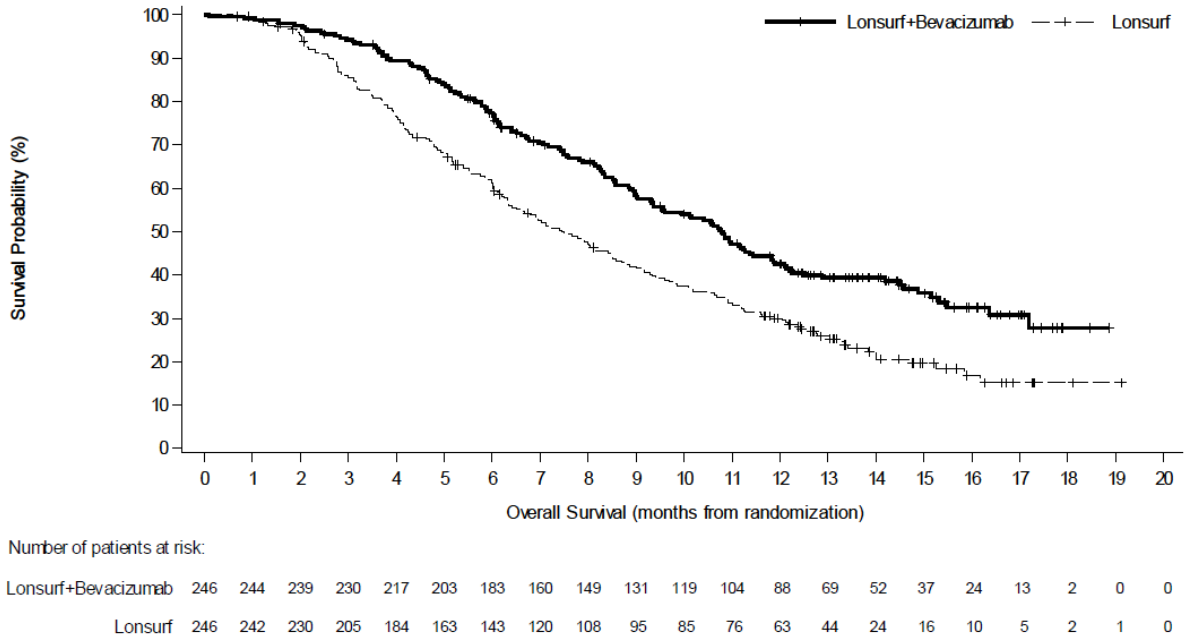
Efficacy results are summarized in Table 10 and Figure 2

Table 10: Efficacy Results from SUNLIGHT

	Lonsurf® plus Bevacizumab (N=246)	**Lonsurf® (N=246)**
Overall survival		
Number of deaths, N (%)	148 (60)	183 (74)
Median OS (months)[a] (95% CI)[b]	10.8 (9.4, 11.8)	7.5 (6.3, 8.6)
Hazard ratio (95% CI)[c]	0.61 (0.49, 0.77)	
p-value[d]	<0.001	
Progression-free survival (per investigator)		
Number of events N (%)	206 (84)	236 (96)
Median PFS (months)[a] (95% CI)[b]	5.6 (4.5, 5.9)	2.4 (2.1, 3.2)
Hazard ratio (95% CI)[d]	0.44 (0.36, 0.54)	
p-value[d]	<0.001	

a Kaplan-Meier estimates
b Methodology of Brookmeyer and Crowley
c Stratified proportional hazards model (strata: region, time since first metastasis diagnosis, RAS status)
d Stratified log-rank test (strata: region, time since first metastasis diagnosis, RAS status), 1-sided p-value

Figure 2: Kaplan-Meier Curves of Overall Survival in SUNLIGHT



12.2 Metastatic Gastric Cancer

TAGS Study

The clinical efficacy and safety of Lonsurf® were evaluated in an international, randomized, double-blind, placebo-controlled study conducted in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma previously treated with at least 2 prior regimens for advanced disease.

A total of 507 patients were randomized 2:1 to receive Lonsurf® (N = 337) plus BSC or matching placebo (N = 170) plus BSC. Randomization was stratified by ECOG PS at baseline (0 vs. 1), prior ramucirumab (yes vs. no), and geographic region (Japan vs. rest of world). Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Other key eligibility criteria included ECOG PS 0 or 1. Patients received 35 mg/m^2 Lonsurf® or matching placebo orally twice daily after meals on Days 1 – 5 and 8 – 12 of each 28-day cycle until disease progression or unacceptable toxicity. The major efficacy outcome measure was OS and an additional efficacy outcome measure was PFS. The median age was 63 years, 73% were male, 70% and 16% were White and Asian respectively, and 38% had a baseline ECOG PS of 0. Seventy-one percent of patients had gastric tumors, 29% had GEJ tumors, and two patients had gastric/GEJ tumors. All patients received platinum-based chemotherapy, 99% received fluoropyrimidine-based therapy, 91% received a taxane, 55% received irinotecan, and 33% received ramucirumab. The HER2 status was negative in 62%, positive in 19%, and unknown in 20% of patients. Among the 94 patients with HER2 positive tumors, 89% received prior anti-HER2 therapy.

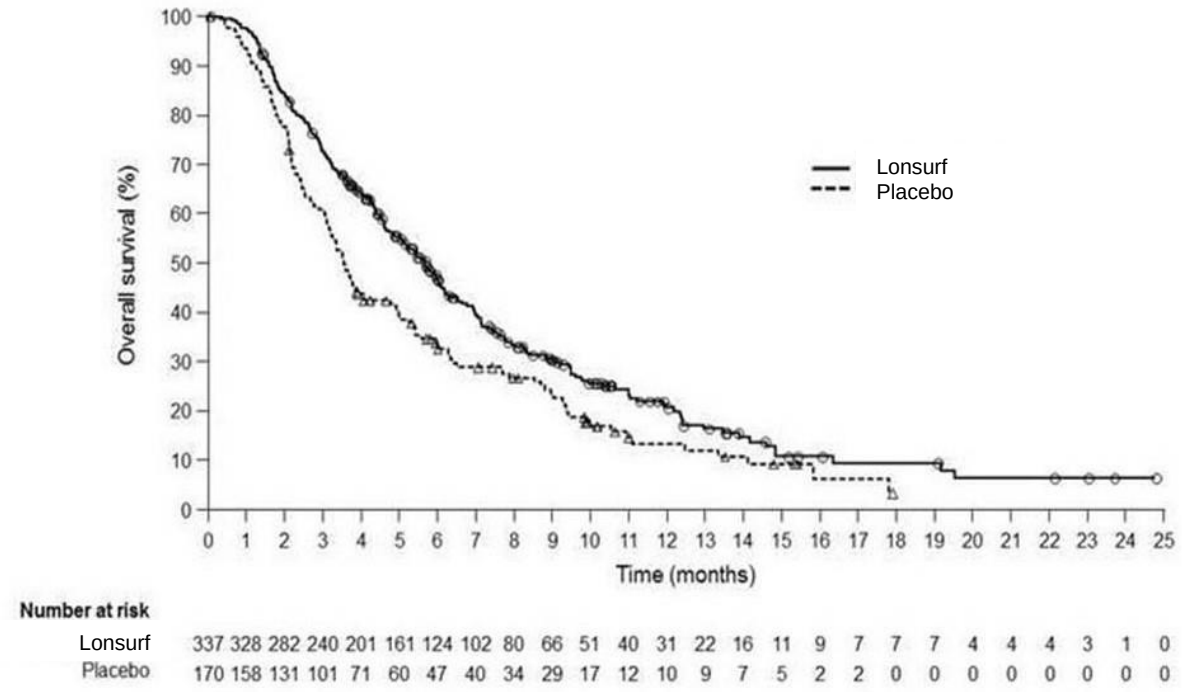
A statistically significant improvement in overall survival and progression-free survival were demonstrated in patients in the Lonsurf® plus BSC arm compared to those who received placebo plus BSC *(*see *Table 11 and Figure 3)*.

Table 11: Efficacy Results from TAGS study

	Lonsurf® (N=337)	**Placebo (N=170)**
Overall Survival		
Number of deaths, N (%)	244 (72)	140 (82)
Median OS (months)[a] [95% CI][b]	5.7 [4.8, 6.2]	3.6 [3.1, 4.1]
Hazard ratio [95% CI]	0.69 [0.56, 0.85]	
P-value[c]	0.0006	
Progression-Free Survival		
Number of Progression or Death, N (%)	287 (85)	156 (92)
Hazard ratio [95% CI]	0.56 [0.46, 0.68]	
P-value[c]	< 0.0001	

[a] Kaplan-Meier estimates
[b] Methodology of Brookmeyer and Crowley
[c] Stratified log-rank test (strata: ECOG PS, prior ramucirumab treatment, region), 2-sided

Figure 3: Kaplan-Meier Curves of Overall Survival in TAGS study



13 HOW SUPPLIED/STORAGE AND HANDLING

13.1 How Supplied

Lonsurf® Film-coated Tablet 15 mg/6.14 mg is a white, biconvex, round, film-coated tablet, imprinted with '15' on one side, and '102' and '15 mg' on the other side, in gray ink. The tablets are packed in blisters in an aluminium foil pouch with a desiccant. It comes in a pack size of 20 film-coated tablets (10 tablets × 2 blisters).

Lonsurf® Film-coated Tablet 20 mg/8.19 mg is a pale red, biconvex, round, film-coated tablet, imprinted with '20' on one side, and '102' and '20 mg' on the other side, in gray ink. The tablets are packed in blisters in an aluminium foil pouch with a desiccant. It comes in a pack size of 20 film-coated tablets (10 tablets × 2 blisters).

13.2 Storage and Handling

Store at or below 30°C. Store in the original package in order to protect from moisture.

Lonsurf® is a cytotoxic drug. Follow applicable special handling and disposal procedures.

14 PATIENT COUNSELING INFORMATION

Severe Myelosuppression:

Advise patients to immediately contact their healthcare provider if they experience signs or symptoms of infection and advise patients to keep all appointments for blood tests. *[*see *Warnings and Precautions (5.1)]*

Gastrointestinal Toxicity:

Advise patients to contact their healthcare provider for severe or persistent nausea, vomiting, diarrhea, or abdominal pain. *[*see *Warnings and Precautions (5.3)]*

Administration Instructions:

Advise patients that Lonsurf® is available in two strengths and they may receive both strength tablets to provide the prescribed dosage. Advise patients of the importance of reading prescription labels carefully and taking the appropriate number of tablets.

Advise patients to take Lonsurf® within 1 hour after eating their morning and evening meals. *[*see *Dosage and Administration (2.1)]*

Advise patients that anyone else who handles their medication should wear gloves.

Embryo-Fetal Toxicity:

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy. *[*see *Warnings and Precautions (5.2), Use in Specific Populations (7.3)]*

Advise female patients of reproductive potential to use effective contraception during treatment with Lonsurf® and for at least 6 months after the final dose. *[*see *Warnings and Precautions (5.2), Use in Specific Populations (7.3)]*

Advise males with female partners of reproductive potential to use condoms during treatment with Lonsurf® and for up to 6 months after the final dose. *[*see *Use in Specific Populations (7.3), Nonclinical Toxicology (11.1)]*

Lactation:

Advise women not to breastfeed during treatment with Lonsurf® and for one day following the final dose. *[*see *Use in Specific Populations (7.2)]*

15 MANUFACTURER

Taiho Pharmaceutical Co., Ltd. Kitajima Plant
1-1, Iuchi, Takabo, Kitajima-cho,
Itano-gun, Tokushima 771-0206, Japan

16 DATE OF REVISION OF THE TEXT

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