

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LONSURF safely and effectively. See full prescribing information for LONSURF.

LONSURF (trifluridine and tipiracil) tablets, for oral use  
Initial U.S. Approval: 2015

### INDICATIONS AND USAGE

LONSURF is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of 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)

### DOSAGE AND ADMINISTRATION

- Recommended dose: 35 mg/m<sup>2</sup>/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

Tablets:

- 15 mg trifluridine/6.14 mg tipiracil (3)
- 20 mg trifluridine/8.19 mg tipiracil (3)

### CONTRAINDICATIONS

None. (4)

### WARNINGS AND PRECAUTIONS

- Severe Myelosuppression: Obtain complete blood counts prior to and on Day 15 of each cycle. Reduce dose and/or hold LONSURF as clinically indicated. (5.1)
- Embryo-Fetal Toxicity: Fetal harm can occur. Advise women of potential risk to a fetus. (5.2)

### ADVERSE REACTIONS

The most common adverse reactions (≥10%) are anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Taiho Oncology, Inc. at 1-844-878-2446 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

- Lactation: Do not breastfeed. (8.2)
- Geriatric Use: Grade 3 or 4 neutropenia and thrombocytopenia and Grade 3 anemia occurred more commonly in patients 65 years old or older who received LONSURF. (8.5)
- Hepatic Impairment: Do not initiate LONSURF in patients with baseline moderate or severe hepatic impairment. (8.6)
- Renal Impairment: Patients with moderate renal impairment may require dose modifications for increased toxicity. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 3/2017

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

LONSURF is indicated for the treatment of 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.

### **2 DOSAGE AND ADMINISTRATION**

#### **2.1 Recommended Dose**

The recommended starting dose of LONSURF is 35 mg/m<sup>2</sup> 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.

Do not take additional doses to make up for missed or held doses.

LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures.<sup>1</sup>

#### **2.2 Dose Modifications**

Obtain complete blood cell counts prior to and on Day 15 of each cycle.

Do not initiate the cycle of LONSURF until:

- Absolute neutrophil count (ANC) is greater than or equal to 1,500/mm<sup>3</sup> or febrile neutropenia is resolved
- Platelets are greater than or equal to 75,000/mm<sup>3</sup>
- 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<sup>3</sup> or febrile neutropenia
- Platelets less than 50,000/mm<sup>3</sup>
- Grade 3 or 4 non-hematological adverse reactions

After recovery, resume LONSURF after reducing the dose by 5 mg/m<sup>2</sup>/dose from the previous dose level, if the following occur:

- Febrile neutropenia
- Uncomplicated Grade 4 neutropenia (which has recovered to greater than or equal to 1,500/mm<sup>3</sup>) or thrombocytopenia (which has recovered to greater than or equal to 75,000/mm<sup>3</sup>) 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 to a minimum dose of 20 mg/m<sup>2</sup> twice daily. Do not escalate LONSURF dose after it has been reduced.

### **3 DOSAGE FORMS AND STRENGTHS**

LONSURF (15 mg trifluridine/6.14 mg tipiracil) 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 (20 mg trifluridine/8.19 mg tipiracil) 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 Study 1, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated 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 febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm<sup>3</sup>. Upon recovery resume LONSURF at a reduced dose. [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 dose levels resulting in exposures lower than those achieved at the recommended dose of 35 mg/m<sup>2</sup> twice daily.

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. [see *Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)*]

### **6 ADVERSE REACTIONS**

The following serious adverse reactions are discussed in detail in other sections of the labeling:

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

## **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 described below are from Study 1, 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<sup>2</sup>/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 drug 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 Study 1, 3.6% of patients discontinued LONSURF for an adverse event and 13.7% of patients required a dose reduction. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

**Table 1 Per Patient Incidence of Adverse Drug Reactions ( $\geq 5\%$ ) in Study 1 Occurring More Commonly ( $>2\%$ ) than in Patients Receiving Placebo.**

Adverse Reactions	LONSURF (N=533)		Placebo (N=265)	
	All Grades	Grades 3-4*	All Grades	Grades 3-4*
<b>Gastrointestinal disorders</b>				
Nausea	48%	2%	24%	1%
Diarrhea	32%	3%	12%	<1%
Vomiting	28%	2%	14%	<1%
Abdominal pain	21%	2%	18%	4%
Stomatitis	8%	<1%	6%	0%
<b>General disorders and administration site conditions</b>				
Asthenia/fatigue	52%	7%	35%	9%
Pyrexia	19%	1%	14%	<1%
<b>Metabolism and nutrition disorders</b>				
Decreased appetite	39%	4%	29%	5%
<b>Nervous system disorders</b>				
Dysgeusia	7%	0%	2%	0%
<b>Skin and subcutaneous tissue disorders</b>				
Alopecia	7%	0%	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.

**Table 2 Laboratory Test Abnormalities**

Laboratory Parameter	LONSURF (N=533*)			Placebo (N=265*)		
	Grade†			Grade†		
	All %	3 %	4 %	All %	3 %	4 %
<b>Blood and lymphatic system disorders</b>						
Anemia‡	77	18	N/A#	33	3	N/A
Neutropenia	67	27	11	1	0	0
Thrombocytopenia	42	5	1	8	<1	<1

\* % based on number of patients with post-baseline samples, which may be less than 533 (LONSURF) or 265 (placebo)

† Common Terminology Criteria for Adverse Events (CTCAE), v4.03

‡ Anemia: No Grade 4 definition for these laboratory parameters in CTCAE, v4.03

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

In Study 1, infections occurred more frequently in LONSURF-treated patients (27%) compared to those receiving placebo (15%). The most commonly reported infections which occurred more frequently in LONSURF-treated patients were nasopharyngitis (4% versus 2%), and urinary tract infections (4% versus 2%).

In Study 1, pulmonary emboli occurred more frequently in LONSURF-treated patients (2%) compared to no patients on placebo.

#### *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.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### *Risk Summary*

Based on animal data and its mechanism of action, 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 exposures at the recommended dose in humans. [see *Data*] There are no available data on LONSURF exposure in pregnant women. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

### 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 exposure at the clinical dose of 35 mg/m<sup>2</sup> 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<sup>2</sup> twice daily) embryoletality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies) were observed.

## **8.2 Lactation**

### Risk Summary

It is not known whether LONSURF or its metabolites are present in human milk. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk. There are no data to assess the effects of LONSURF or its metabolites on the breastfed infant or the effects on milk production. Because of the potential for serious adverse reactions in breastfeeding infants, 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 <sup>14</sup>C-FTD or <sup>14</sup>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.

## **8.3 Females and Males of Reproductive Potential**

### Contraception

#### Females

LONSURF can cause fetal harm when administered to a pregnant woman. [see *Use in Specific Populations (8.1)*]

Advise females of reproductive potential to use effective contraception during treatment.

#### Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose. [see *Nonclinical Toxicology (13.1)*]

#### **8.4 Pediatric Use**

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

##### **Animal 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<sup>2</sup> twice daily).

#### **8.5 Geriatric Use**

In Study 1, 533 patients received LONSURF; 44% were 65 years of age or over, while 7% were 75 and over. No overall differences in effectiveness were observed in patients 65 or older versus younger patients, and no adjustment is recommended for the starting dose of LONSURF based on age.

Patients 65 years of age or older who received LONSURF had a higher incidence of the following compared to patients younger than 65 years: Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anemia (26% vs 12%, and Grade 3 or 4 thrombocytopenia (9% vs 2%).

#### **8.6 Hepatic Impairment**

In a pharmacokinetic trial comparing 10 patients with mild hepatic impairment (total bilirubin less than or equal to the upper limit of normal (ULN) and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST) and 6 patients with moderate hepatic impairment (total bilirubin greater than 1.5 to 3 times ULN and any AST) to 8 patients with normal hepatic function, no clinically important differences in the mean exposures of trifluridine and tipiracil were observed. Five of 6 patients with moderate hepatic impairment experienced Grade 3 or 4 increased bilirubin levels. Patients with severe hepatic impairment (total bilirubin greater than 3 times ULN and any AST) were not studied. No adjustment to the starting dose of LONSURF is recommended for patients with mild hepatic impairment. 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 (12.3)*]

#### **8.7 Renal Impairment**

No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of LONSURF.

In Study 1, patients with moderate renal impairment (CL<sub>cr</sub> = 30 to 59 mL/min, n= 47) had a higher incidence (difference of at least 5%) of ≥ Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to patients with normal renal function (CL<sub>cr</sub> ≥ 90 mL/min, n= 306) or patients with mild renal impairment (CL<sub>cr</sub> = 60 to 89 mL/min, n= 178).

No adjustment to the starting dose of LONSURF is recommended in patients with mild or moderate renal impairment (CL<sub>cr</sub> of 30 to 89 mL/min); however patients with moderate renal impairment may require dose modification for increased toxicity. Patients with severe renal impairment (CL<sub>cr</sub> < 30 mL/min) were not studied. [see *Clinical Pharmacology (12.3)*]



## 8.8 Ethnicity

There were no clinically meaningful differences in Study 1 between Western and Asian subgroups with respect to overall incidence of adverse events or  $\geq$  Grade 3 adverse events in either the LONSURF or placebo groups.

## 10 OVERDOSAGE

The highest dose of LONSURF administered in clinical studies was 180 mg/m<sup>2</sup> per day.

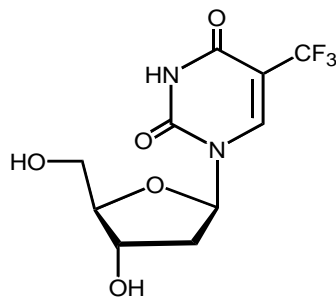
There is no known antidote for LONSURF overdose.

## 11 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:

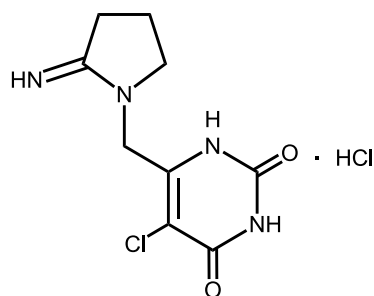


Trifluridine has a molecular formula C<sub>10</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> and a molecular weight of 296.20.

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  $C_9H_{11}ClN_4O_2 \cdot HCl$  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 Tablet (15 mg trifluridine/6.14 mg tipiracil)

Each film-coated tablet of LONSURF, 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 tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, and magnesium stearate.

LONSURF Tablet (20 mg trifluridine/8.19 mg tipiracil)

Each film-coated tablet of LONSURF, 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 tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, ferric oxide, and magnesium stearate.

Both film-coated tablets (LONSURF 15 mg/6.14 mg and 20 mg/8.19 mg) are imprinted with ink containing shellac, ferric oxide red, ferric oxide yellow, titanium dioxide, FD&C Blue No. 2 Aluminum Lake, carnauba wax, and talc.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

LONSURF consists of a thymidine-based nucleoside analog, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil, 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.

## 12.2 Pharmacodynamics

### *Cardiac Electrophysiology*

LONSURF administered to 42 patients with advanced solid tumors at the recommended dosage regimen had no large effect (i.e. > 20 ms) 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 1 of 42 patients (2.4%) had a QTc increase from baseline greater than 60 msec.

## 12.3 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 to 35 mg/m<sup>2</sup>. After administration of LONSURF 35 mg/m<sup>2</sup> twice daily, the mean elimination half-life (t<sub>1/2</sub>) 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.

The accumulation of trifluridine was 3-fold for AUC<sub>0-last</sub> and 2-fold for peak plasma concentration (C<sub>max</sub>) at steady state while no accumulation was observed for tipiracil.

Administration of a single dose of LONSURF containing tipiracil and trifluridine 35 mg/m<sup>2</sup> increased the mean AUC<sub>0-last</sub> of trifluridine by 37-fold and C<sub>max</sub> by 22-fold with reduced variability compared to trifluridine 35 mg/m<sup>2</sup> alone.

### *Absorption*

Following a single oral administration of LONSURF at 35 mg/m<sup>2</sup> in patients with cancer, the mean time to peak plasma concentration (T<sub>max</sub>) of trifluridine was around 2 hours.

A standardized high-fat, high-calorie meal decreased trifluridine C<sub>max</sub>, tipiracil C<sub>max</sub> 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<sup>2</sup>. 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<sub>max</sub> 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*

#### **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 [<sup>14</sup>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 [<sup>14</sup>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-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 Study 1, the estimated mean AUC of trifluridine at steady state was 31% higher in patients with mild renal impairment (CL<sub>cr</sub> = 60 to 89 mL/min, n= 38) and 43% higher in patients with moderate renal impairment (CL<sub>cr</sub> = 30 to 59 mL/min, n= 16) than that in patient with normal renal function (CL<sub>cr</sub> ≥ 90 mL/min, n= 84) based on the population pharmacokinetic analysis. The estimated mean AUC of tipiracil was 34% higher in patients with mild renal impairment and 65% higher in patients with moderate renal impairment than that in patients with normal renal function. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with severe renal impairment (CL<sub>cr</sub> < 30 mL/min) or end-stage renal disease. [see *Use in Specific Populations (8.7)*]

### **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 less 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). Five of 6 patients with moderate hepatic impairment experienced Grade 3 or 4 increased bilirubin levels and patients with severe hepatic impairment were not studied. [see *Dose Modifications (2.2)*, *Use in Specific Populations (8.6)*]

### ***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.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 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.

## 14 CLINICAL STUDIES

### 14.1 Colorectal Cancer

#### Study 1

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, ECOG 0-1, absence of brain metastasis, and absence of ascites requiring drainage in the past four weeks. Patients received 35 mg/m<sup>2</sup> 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 Performance Status (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. [see *Dosage and Administration (2.1)*, *Clinical Pharmacology (12.3)*]

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 3](#) and [Figure 1](#)).

**Table 3 Efficacy Results**

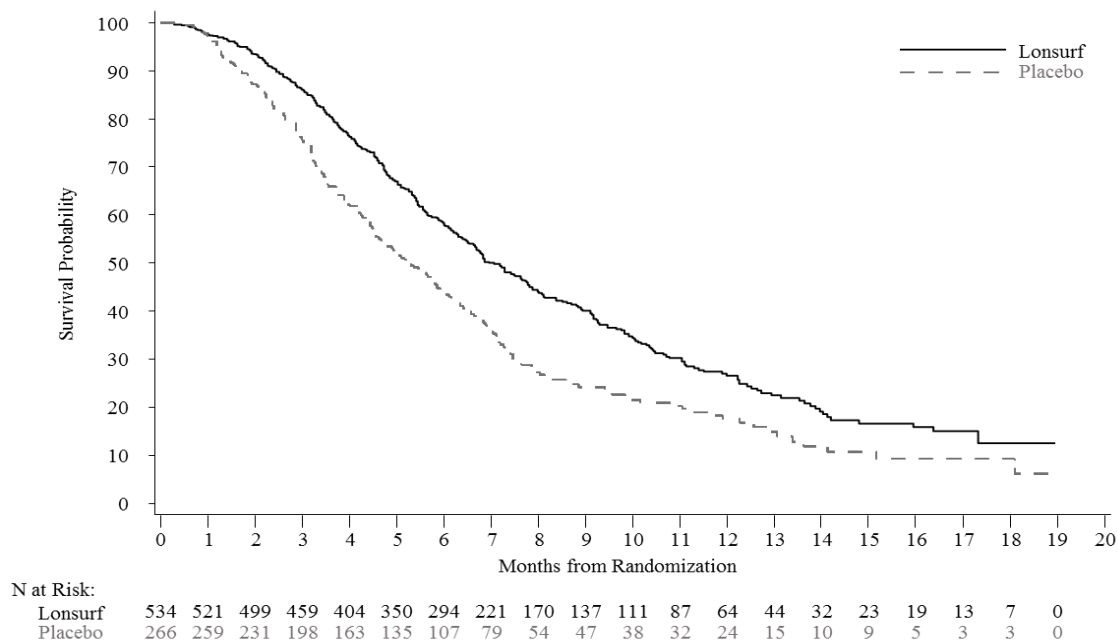
	<b>LONSURF (N=534)</b>	<b>Placebo (N=266)</b>
<b>Overall Survival</b>		
Number of deaths, N (%)	364 (68)	210 (79)
Median OS (months) <sup>a</sup> [95% CI] <sup>b</sup>	7.1 [6.5, 7.8]	5.3 [4.6, 6.0]
Hazard ratio [95% CI]	0.68 [0.58, 0.81]	
P-value <sup>c</sup>	<0.001	
<b>Progression-Free Survival</b>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

<sup>a</sup> Kaplan-Meier estimates

<sup>b</sup> Methodology of Brookmeyer and Crowley

<sup>c</sup> Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region)

**Figure 1 Kaplan-Meier Curves of Overall Survival**



## 15 REFERENCES

1. “OSHA Hazardous Drugs”. OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

LONSURF 15 mg/6.14 mg tablets are supplied as 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 packaged in HDPE bottles with child resistant closures in the following presentations:

- 20 count: NDC 64842-1025-1
- 40 count: NDC 64842-1025-2
- 60 count: NDC 64842-1025-3

LONSURF 20 mg/8.19 mg tablets are supplied as 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 packaged in HDPE bottles with child resistant closures in the following presentations:

- 20 count: NDC 64842-1020-1
- 40 count: NDC 64842-1020-2
- 60 count: NDC 64842-1020-3

## 16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures.<sup>1</sup>

If stored outside of original bottle, discard after 30 days.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling ([Patient Information](#)).

### Severe Myelosuppression:

Advise the patient 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 *Adverse Reactions (6.1)*]

### Administration Instructions:

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

Advise the patient to take LONSURF within 1 hour after eating their morning and evening meals. [see *Dosage and Administration (2.1)*]

Advise the patient that anyone else who handles their medication should wear gloves. [see *References (15)*]

### Embryo-Fetal Toxicity:

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. [see *Warnings and Precautions (5.2)* and *Use in Specific Populations (8.3)*]

### Lactation:

Advise women not to breastfeed during treatment with LONSURF and for one day following the final dose. [see *Use in Specific Populations (8.2)*]