PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# Pr**LONSURF**®

trifluridine and tipiracil tablet

15 mg trifluridine/ 6.14 mg tipiracil (as tipiracil hydrochloride)
20 mg trifluridine / 8.19 mg tipiracil (as tipiracil hydrochloride)

Antineoplastic Agent
Thymidine phosphorylase inhibitor/nucleoside metabolic inhibitor

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**RECENT MAJOR LABEL CHANGES**

Not Applicable

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## PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

Lonsurf® (trifluridine and tipiracil [as tipiracil hydrochloride] tablets) is indicated for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents.

Clinical effectiveness of Lonsurf is based on benefit observed in a pivotal study in patients who had been previously treated with all of the above available therapies.

### 1.1 Pediatrics

**Pediatrics** (0 – 18 years): No pediatric data have been made available to Health Canada; therefore, Health Canada has not approved an indication for pediatric use.

### 1.2 Geriatrics

**Geriatrics (≥ *65* years of age):**

The effect of Lonsurf (trifluridine and tipiracil tablets), on overall survival in metastatic colorectal cancer was similar in patients <65 years and ≥65 years of age.

Efficacy and safety data in patients ≥ 75 years old is limited.

## 2 CONTRAINDICATIONS

Lonsurf (trifluridine and tipiracil tablets) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, or component of the container closure. For a complete listing (see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING)**.

## 3 DOSAGE AND ADMINISTRATION

### 3.1 Dosing Considerations

Complete blood cell counts must be obtained prior to initiation of therapy and as needed to monitor blood counts, but at a minimum, prior to each treatment cycle.

Treatment must not be started if the absolute neutrophil count is < 1.5 $\times 10^9$/L, if the platelet counts are < 75$\times$ $10^9$/L, or if the patient has an unresolved Grade 3 or 4 non-hematological clinically relevant toxicity from prior therapies and/or prior Lonsurf cycles.

Lonsurf (trifluridine and tipiracil tablets) is a cytotoxic drug. Follow applicable special handling and disposal procedures (see **WARNINGS AND PRECAUTIONS, NON-CLINICAL**

**TOXICOLOGY, CARCINOGENESIS AND MUTAGENESIS**).

### 3.2 Recommended Dose and Dosage Adjustment

The recommended starting dose of Lonsurf (trifluridine and tipiracil tablets) for adults is 35 mg/m$^2$/dose administered orally with water, twice daily, within 1 hour after completion of morning and evening meals, on Days 1 to 5 and Days 8 to 12 of each 28-day cycle. This treatment cycle is repeated every 4 weeks as long as benefit is observed or until unacceptable toxicity occurs. See Table 1 for dose calculation based on body surface area (BSA). The dosage must not exceed 80 mg/dose based on the trifluridine component.

Lonsurf should not be administered in children less than 18 years of age (See **TOXICOLOGY**)

**Table 1 Lonsurf Starting Dose Calculation According to Body Surface Area (BSA)**

| Lonsurf Dose | BSA (m$^2$) | Dose in mg (2x daily) | Tablets per dose | | Total daily dose (mg) |
|---|---|---|---|---|---|
| | | | 15/6.14 mg | 20/8.19 mg | |
| 35 mg/m$^2$ | < 1.07 | 35 | 1 | 1 | 70 |
| | 1.07 - 1.22 | 40 | 0 | 2 | 80 |
| | 1.23 - 1.37 | 45 | 3 | 0 | 90 |
| | 1.38 - 1.52 | 50 | 2 | 1 | 100 |
| | 1.53 - 1.68 | 55 | 1 | 2 | 110 |
| | 1.69 - 1.83 | 60 | 0 | 3 | 120 |
| | 1.84 - 1.98 | 65 | 3 | 1 | 130 |
| | 1.99 - 2.14 | 70 | 2 | 2 | 140 |
| | 2.15 - 2.29 | 75 | 1 | 3 | 150 |
| | ≥ 2.30 | 80 | 0 | 4 | 160 |

Dosing adjustments may be required based on individual safety and tolerability.

A maximum of 3 dose reductions are permitted to a minimum dose of 20 mg/m$^2$ twice daily. Dose escalation is not permitted after it has been reduced.

In the event of hematological and/or non-hematological toxicities patients should follow the dose interruption, resumption and reduction criteria stated in Table 2, Table 3 and Table 4.

**Table 2 Dose interruption and resumption criteria for hematological toxicities related to myelosuppression**

| Parameter | Interruption Criteria | Resumption Criteria[a] |
|---|---|---|
| Neutrophils | < 0.5 x $10^9$/L | ≥ 1.5 x $10^9$/L |
| Platelets | < 50 x $10^9$/L | ≥ 75 x $10^9$/L |

[a] Resumption criteria applied to the start of the next cycle for all patients regardless of whether or not the interruption criteria were met

**Table 3 Recommended dose modifications for Lonsurf in case of hematological and non-hematological adverse reactions**

| Adverse reaction | Recommended dose modifications |
|---|---|
| • Febrile neutropenia<br>• CTCAE* Grade 4 neutropenia (< 0.5 x $10^9$/L) or thrombocytopenia (< 25 X $10^9$/L) that results in more than 1 week's delay in start of next cycle<br>• CTCAE* non-hematologic Grade 3 or Grade 4 adverse reaction; except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhea responsive to antidiarrheal medicinal products | • Interrupt dosing until toxicity resolves to Grade 1 or baseline.<br>• When resuming dosing, decrease the dose level by 5 mg/m$^2$/dose from the previous dose level (Table 4).<br>• Dose reductions are permitted to a minimum dose of 20 mg/m$^2$/dose twice daily.<br>• Do not increase dose after it has been reduced. |

* Common terminology criteria for adverse events

**Table 4 Lonsurf dose reductions according to body surface area (BSA)**

| Lonsurf dose | BSA ($m^2$) | Dose in mg (2x daily) | Tablets per dose (2x daily) | | Total daily dose (mg) |
|---|---|---|---|---|---|
| | | | 15/6.14 mg | 20/8.19 mg | |
| **Level 1 dose reduction: From 35 mg/$m^2$ to 30 mg/$m^2$** | | | | | |
| **30 mg/$m^2$** | < 1.09 | 30 | 2 | 0 | 60 |
| | 1.09 - 1.24 | 35 | 1 | 1 | 70 |
| | 1.25 - 1.39 | 40 | 0 | 2 | 80 |
| | 1.40 - 1.54 | 45 | 3 | 0 | 90 |
| | 1.55 - 1.69 | 50 | 2 | 1 | 100 |
| | 1.70 - 1.94 | 55 | 1 | 2 | 110 |
| | 1.95 - 2.09 | 60 | 0 | 3 | 120 |
| | 2.10 - 2.28 | 65 | 3 | 1 | 130 |
| | ≥ 2.29 | 70 | 2 | 2 | 140 |
| **Level 2 dose reduction: From 30 mg/$m^2$ to 25 mg/$m^2$** | | | | | |
| **25 mg/$m^2$** | < 1.10 | 25[a] | 2[a] | 1[a] | 50[a] |
| | 1.10 - 1.29 | 30 | 2 | 0 | 60 |
| | 1.30 - 1.49 | 35 | 1 | 1 | 70 |
| | 1.50 - 1.69 | 40 | 0 | 2 | 80 |
| | 1.70 - 1.89 | 45 | 3 | 0 | 90 |
| | 1.90 - 2.09 | 50 | 2 | 1 | 100 |
| | 2.10 - 2.29 | 55 | 1 | 2 | 110 |
| | ≥ 2.30 | 60 | 0 | 3 | 120 |
| **Level 3 dose reduction: From 25 mg/$m^2$ to 20 mg/$m^2$** | | | | | |
| **20 mg/$m^2$** | < 1.14 | 20 | 0 | 1 | 40 |
| | 1.14 – 1.34 | 25[a] | 2[a] | 1[a] | 50[a] |
| | 1.35 – 1.59 | 30 | 2 | 0 | 60 |
| | 1.60 – 1.94 | 35 | 1 | 1 | 70 |
| | 1.95 – 2.09 | 40 | 0 | 2 | 80 |
| | 2.10 – 2.34 | 45 | 3 | 0 | 90 |
| | ≥ 2.35 | 50 | 2 | 1 | 100 |

[a] At a total daily dose of 50 mg, patients should take 1 x 20/8.19 mg tablet in the morning and 2 x 15/6.14 mg tablets in the evening.

**Dose adjustments for special populations**

**Renal impairment**

Mild renal impairment (creatinine clearance 60 to 89 mL/min) or moderate renal impairment (creatinine clearance 30 to 59 mL/min): No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of Lonsurf. No adjustment of the starting dose is recommended in patients with mild or moderate renal impairment. Patients with moderate renal impairment may require dose modification for increased hematological toxicity and should be closely monitored (See **WARNINGS AND PRECAUTIONS, RENAL**).

Severe renal impairment (creatinine clearance below 30 mL/min) or end stage renal disease: Administration of Lonsurf is not recommended in patients with severe renal impairment or end stage renal disease as there are no data available for these patients.

**Hepatic impairment**
Mild hepatic impairment: No adjustment of the starting dose is recommended in patients with mild hepatic impairment.

Moderate or severe hepatic impairment: Administration is not recommended in patients with baseline moderate or severe hepatic impairment (National Cancer Institute [NCI] Criteria Group C and D defined by total bilirubin > 1.5 times the upper limit of normal). A higher incidence of Grade 3 or 4 hyperbilirubinemia has been observed in patients with baseline moderate hepatic impairment, based on limited data.

**Elderly**
No adjustment of the starting dose is required in patients ≥ 65 years old.

**Paediatric population**
Health Canada has not authorized an indication for paediatric use.

**Race**
No adjustment of the starting dose is required on the basis of patient's race. There is limited data on Lonsurf in Black/African American patients but there is no biological rationale to expect any difference between this subgroup and the overall population.

### 3.3 Administration

Lonsurf (trifluridine and tipiracil tablets) is for oral use. Lonsurf must be taken with a glass of water within 1 hour after completion of the morning and evening meals. (See **ACTION AND CLINICAL PHARMACOLOGY, PHARMACOKINETICS, ABSORPTION)**.

### 3.4 Missed Dose

If doses were missed or held, the patient must not make up for missed doses.

## 4 OVERDOSAGE

The highest dose of Lonsurf (trifluridine and tipiracil tablets) administered in clinical trials was 180 mg/$m^2$ per day.

The adverse drug reactions reported in association with overdoses were consistent with the established safety profile.

The primary anticipated complication of an overdose is bone marrow suppression.

There is no known antidote for an overdose of Lonsurf.

Medical management of an overdose should include customary therapeutic and supportive medical intervention aimed at correcting the presenting clinical manifestations and preventing their possible complications.

| For management of a suspected drug overdose, contact your regional poison control centre. |
|---|

## 5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Dosage Forms, Strengths, Composition and Packaging.**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| oral | Tablet 15 mg trifluridine/6.14 mg tipiracil (as tipiracil hydrochloride) | hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, pharmaceutical ink, pregelatinized starch, stearic acid, titanium dioxide |
| oral | Tablet 20 mg trifluridine/8.19 tipiracil mg (as tipiracil hydrochloride) | Ferric oxide, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, pharmaceutical ink, pregelatinized starch, stearic acid, titanium dioxide |

Lonsurf 15 mg/6.14 mg tablets
Each tablet contains 15 mg trifluridine and 6.14 mg tipiracil (as 7.065 mg tipiracil hydrochloride). The tablet is a white, biconvex, round, film-coated tablet, with a diameter of 7.1 mm and a thickness of 2.7 mm, imprinted with ‘15’ on one side, and ‘102’ and ’15 mg’ on the other side, in grey pharmaceutical ink.

Lonsurf 20 mg/8.19 mg tablets
Each tablet contains 20 mg trifluridine and 8.19 mg tipiracil (as 9.420 mg tipiracil hydrochloride). The tablet is a pale red, biconvex, round, film-coated tablet, with a diameter of 7.6 mm and a thickness of 3.2 mm, imprinted with ‘20’ on one side, and ‘102’ and ‘20 mg’ on the other side, in grey pharmaceutical ink.

Both tablets are imprinted with edible ink containing carnauba wax, FD&C Blue No. 2 Aluminum Lake, ferric oxide red, ferric oxide yellow, shellac, talc and titanium dioxide.

Lonsurf is available in aluminium/aluminium blister with laminated desiccant (calcium oxide) trays containing 10 tablets.

Each pack contains 20 tablets.

## 6 WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

- Lonsurf (trifluridine and tipiracil tablets) should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.
- Myelosuppression (See **WARNINGS and PRECAUTIONS, ADVERSE REACTIONS**)
- Gastrointestinal toxicity (See **WARNINGS and PRECAUTIONS, ADVERSE**

**General**
Lonsurf is a cytotoxic drug. Applicable special handling and disposal procedures should be followed.

**Carcinogenesis and Mutagenesis**
Lonsurf should be treated as a potential carcinogen (See **NON-CLINICAL TOXICOLOGY**).

**Driving and Operating Machinery**
It is not known whether Lonsurf affects the patient's ability to drive or use machines. If patients experience symptoms such as fatigue, dizziness and or malaise affecting their ability to concentrate and react during treatment with Lonsurf, it is recommended that they do not drive or use machines until the effect subsides.

**Gastrointestinal**
Lonsurf (trifluridine and tipiracil tablets) 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 early and as clinically indicated. Dose modifications (delay and/or reduction) should be applied as necessary (See **RECOMMENDED DOSE AND DOSAGE ADJUSTMENTS**).

**Lactose intolerance**
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, congenital lactase deficiency or glucose-galactose malabsorption should consult with their physician and discuss whether the benefits outweigh the risks on an individual basis.

**Hematologic**
**Bone Marrow Suppression**: Lonsurf can cause severe and life-threatening myelosuppression. In the pivotal trial in metastatic colorectal cancer (RECOURSE), grades 3 or 4 neutropenia (38%), leukopenia (21%), anemia (18%), thrombocytopenia (5%) and febrile neutropenia (4%) were observed. One patient (0.2%) died due to neutropenic infection.

Complete blood cell counts must be obtained prior to initiation of therapy and as needed to monitor blood counts, but at a minimum, prior to each treatment cycle.

Treatment must not be started if the absolute neutrophil count is $< 1.5 \times 10^9$/L, if the platelet

counts are < 75× $10^9$/L, or if the patient has an unresolved Grade 3 or 4 non-hematological clinically relevant toxicity from prior therapies and/or prior Lonsurf cycles.

Serious infections have been reported following treatment with Lonsurf. Given that the majority of infections in the RECOURSE study 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. In the RECOURSE study, 9.4% of patients in the Lonsurf group received granulocyte-colony stimulating factor mainly for therapeutic use. (See **DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS**)

**Hepatic/Biliary/Pancreatic**
Lonsurf is not recommended for use in patients with moderate or severe hepatic impairment (National Cancer Institute [NCI] Criteria Group C and D defined by total bilirubin > 1.5 X ULN). In a pharmacokinetic trial, Grade 3 or 4 hyperbilirubinemia was observed in 5 of 6 patients with baseline moderate hepatic impairment. (See **DOSAGE AND ADMINISTRATION**)

**Monitoring and Laboratory Tests**
Complete blood cell counts must be obtained prior to initiation of therapy and as needed to monitor blood counts, but at a minimum, prior to each treatment cycle.

Treatment must not be started if the absolute neutrophil count is < 1.5 ×$10^9$/L, if the platelet counts are < 75× $10^9$/L, or if the patient has an unresolved Grade 3 or 4 non-hematological clinically relevant toxicity from prior therapies and/or prior Lonsurf cycles.

Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy.

**Radiotherapy**
There was a slightly higher incidence of overall haematological and myelosuppression-related adverse reactions, including febrile neutropenia, for patients who received prior radiotherapy compared to patients without prior radiotherapy in RECOURSE (54.6% versus 49.2%, respectively).

**Renal**
Lonsurf is not recommended for use in patients with severe renal impairment or end-stage renal disease (creatinine clearance < 30 mL/min or requiring dialysis, respectively), as Lonsurf has not been studied in these patients.

In the RECOURSE study patients with moderate renal impairment (creatinine clearance = 30 to 59 mL/min) had a higher incidence (defined as a difference of at least 5%) of ≥ Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to the patients with normal (creatinine clearance ≥ 90 mL/min) or mild renal impairment (creatinine clearance = 60 to 89 mL/min).

No dose adjustment to the starting dose of Lonsurf is recommended in patients with mild or moderate renal impairment (creatinine clearance of 30 to 89 mL/min). Patients with moderate renal impairment should be monitored for increased hematological toxicities as they may require dose modification. (See **DOSAGE AND ADMINISTRATION)**

**Proteinuria:** Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy.

**Respiratory**
**Interstitial Lung Disease/Pneumonitis**: Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been rarely observed in one clinical trial of Asian patients as well as post marketing.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue Lonsurf in patients diagnosed with treatment-related ILD/pneumonitis (See **ADVERSE REACTIONS**).

### 6.1 Special Populations

#### 6.1.1 Pregnant Women

There are no available data from the use of Lonsurf (trifluridine and tipiracil tablets) in pregnant women. Based on the mechanism of action, trifluridine has a potential to cause congenital malformations when administered during pregnancy. Studies in animals have shown reproductive toxicity. (See **NON-CLINICAL TOXICOLOGY**)

Lonsurf should not be used during pregnancy unless the clinical condition of the woman requires treatment with Lonsurf.

Based on findings in animals, trifluridine may cause fetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking Lonsurf and for up to 6 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking Lonsurf and for 6 months after stopping treatment.

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.

### Females and Males of Reproductive Potential

*Contraception*

Because of the potential for genotoxicity, males with female partners of reproductive potential should be advised to use an adequate form of contraception during treatment with Lonsurf and for up to 6 months after the final dose. (See **NON-CLINICAL TOXICOLOGY)**.

### 6.1.2 Breast-feeding

It is not known whether trifluridine (FTD) or tipiracil hydrochloride are excreted in human milk. Because of the potential for serious adverse reactions in breastfeeding infants, advise nursing women not to breastfeed during treatment with Lonsurf (trifluridine and tipiracil tablets) and for one day following the final dose (See **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics***).*

Studies in animals have shown excretion of trifluridine, tipiracil and/or their metabolites in milk. (See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

### 6.1.3 Pediatrics

Pediatrics (0 to 18 years): Lonsurf (trifluridine and tipiracil tablets) should not be administered in children less than 18 years of age. No data are available to Health Canada; therefore, Health Canada has not approved an indication for pediatric use.

### 6.1.4 Geriatrics

Patients 65 years of age or older who received Lonsurf (trifluridine and tipiracil tablets) had a higher incidence of the following events compared to patients younger than 65 years: Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anemia (26% vs 12%), Grade 3 or 4 leukopenia (26% vs 18%) and Grade 3 or 4 thrombocytopenia (9% vs 2%).

## 7 ADVERSE REACTIONS

### 7.1 Adverse Reaction Overview

A total of 761 colorectal cancer patients were exposed to Lonsurf (trifluridine and tipiracil tablets) at a dose of 35mg/$m^2$ BID. The most serious observed adverse drug reactions in patients receiving Lonsurf (trifluridine/tipiracil) were bone marrow suppression and gastrointestinal toxicity.

In clinical studies, the most frequently observed adverse events in patients receiving Lonsurf were neutropenia 58.3% (444/761), grade ≥ 3 38.7% (295/761); nausea 50% (381/761), grade ≥ 3 2.4% (18/761); fatigue 37.8% (288/761), grade ≥ 3 3.5% (27/761); anemia 32.7% (249/761), grade ≥ 3 13.9% (106/761) and leukopenia 282/761 (37%) grade ≥ 3 114/761 (15%).

In clinical studies 8.9 % (68/761) of Lonsurf patients had adverse events resulting in treatment discontinuation and 56.6% (431/761) (56.6%) of patients had adverse events leading to study treatment interruption, delay or dose reduction.

In clinical studies 2.6% (20/761) of Lonsurf patients reported adverse events with fatal outcomes.

The most common adverse drug reactions in patients receiving Lonsurf that resulted in treatment discontinuation, dose reduction, dose delay, or dose interruption were neutropenia, general deterioration of health, anemia, febrile neutropenia, fatigue, diarrhea and dyspnoea.

## 7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The data described below are from RECOURSE, a randomised (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 frequently observed adverse reactions or laboratory abnormalities (all Grades and ≥10% in incidence) in Lonsurf treated patients at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, fatigue/asthenia, nausea, thrombocytopenia, decreased appetite, diarrhoea, vomiting, pyrexia, and abdominal pain.

Adverse events leading to discontinuation occurred in 55 (10.3%) patients in the Lonsurf group and 36 (13.6%) patients in the placebo group. In the Lonsurf group the most frequent were general physical health deterioration (2.3%), fatigue (1.1%) and dyspnoea (0.6%). In the placebo group, the most frequent adverse events leading to discontinuation were blood bilirubin increased (2.3%), general physical health deterioration (1.9%), ascites (1.9%), decreased appetite (1.5%), hepatic failure (1.1%), abdominal pain (1.1%) and asthenia (1.1%).

At least 1 dose reduction during treatment was reported in 13.7% of patients in the Lonsurf group. Adverse events leading to dose reduction were reported for 72 of these patients. The most frequent adverse events leading to dose reduction in the Lonsurf group were: neutropenia (17, 3.2%), anaemia (11, 2.1%), neutrophil count decreased (10, 1.9%), febrile neutropenia (10, 1.9%), fatigue (8, 1.5%), and diarrhea (7, 1.3%). In the placebo group, 3 (1.1%) patients had a single dose reduction, with 2 reporting adverse events leading to dose reduction (1, anaemia; 1, bronchopneumonia).

**Table 5 Very Common ( ≥ 10 %) and Common ( ≥ 1% and ≤ 10%) Adverse Reactions Reported in Patients with Metastatic Colorectal Cancer in the RECOURSE study**

| | **Lonsurf and BSC N=533 (%)** | | **Placebo and BSC N=255 (%)** | |
|---|---|---|---|---|
| | **Any Grade** | **Grade ≥ 3** | **Any Grade** | **Grade ≥ 3** |
| **Blood and Lymphatic System Disorders** | | | | |
| Anemia | 40 | 16 | 8 | 3 |

| | Lonsurf and BSC N=533 (%) | | Placebo and BSC N=255 (%) | |
|---|---|---|---|---|
| | **Any Grade** | **Grade ≥ 3** | **Any Grade** | **Grade ≥ 3** |
| Neutropenia | 29 | 20 | 0 | 0 |
| Thrombocytopenia | 7 | 2 | 0.4 | 0.4 |
| Leukopenia | 5 | 2 | 0 | 0 |
| Febrile neutropenia | 4 | 4 | 0 | 0 |
| **Gastrointestinal Disorders** | | | | |
| Nausea | 48 | 1.9 | 24 | 1.1 |
| Diarrhea | 32 | 3 | 12 | 0.4 |
| Vomiting | 28 | 2 | 14 | 0.4 |
| Abdominal Pain | 15 | 2 | 14 | 4 |
| Stomatitis | 8 | 0.4 | 6 | 0 |
| Dyspepsia | 3 | 0 | 0.4 | 0 |
| **General Disorders and Administration Site Conditions** | | | | |
| Fatigue | 35 | 4 | 23 | 6 |
| Asthenia | 18 | 3 | 11 | 3 |
| Pyrexia | 18 | 1.1 | 14 | 0.4 |
| Mucosal Inflammation | 6 | 0.4 | 5 | 0 |
| Malaise | 4 | 0 | 2 | 0 |
| Influenza like illness | 1.7 | 0 | 0.4 | 0 |
| Pain | 2 | 0.8 | 1.1 | 0 |
| **Infections and Infestations** | | | | |
| Nasopharyngitis | 4 | 0 | 1.5 | 0 |
| Upper respiratory tract infection | 3 | 0 | 1.5 | 0 |
| Urinary tract infection | 3 | 0.6 | 1.9 | 1.1 |
| Herpes zoster | 1.5 | 0.2 | 0 | 0 |
| **Investigations** | | | | |
| Neutrophil count decreased | 28 | 16 | 0.4 | 0 |
| White blood cell count decreased | 27 | 10 | 0.4 | 0 |
| Platelet count decreased | 15 | 2 | 2 | 0 |
| Lymphocyte count decreased | 4 | 1.9 | 1.9 | 1.1 |
| **Metabolism and Nutrition Disorders** | | | | |
| Decreased appetite | 39 | 4 | 29 | 5 |
| Hypokalemia | 4 | 2 | 1.9 | 0.8 |
| **Nervous System Disorders** | | | | |
| Dysgeusia | 7 | 0 | 2 | 0 |
| **Renal and Urinary Disorders** | | | | |
| Proteinuria | 4 | 0 | 1.9 | 0 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | |
| Pulmonary embolism | 2 | 2 | 0 | 0 |

| | Lonsurf and BSC N=533 (%) | | Placebo and BSC N=255 (%) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥ 3 | Any Grade | Grade ≥ 3 |
| **Skin and Subcutaneous Tissue Disorders** | | | | |
| Alopecia | 7 | 0 | 1 | 0 |
| Rash | 4 | 0 | 2 | 0.4 |

### 7.3 Less Common Clinical Trial Adverse Reactions

Clinically important adverse drug reactions that occur in 0.1 to <1% of Lonsurf (trifluridine and tipiracil tablets) treated patients, and which are reported in 2 or more patients receiving Lonsurf are:

Gastrointestinal Disorders: abdominal tenderness, abnormal faeces, colitis, gastritis, gingival bleeding, ileus

Infections and Infestations: cellulitis, device related infection, ear infection, fungal infection, gastroenteritis, influenza, lower respiratory tract infection, oral candidiasis, paronychia, pneumonia staphylococcal, sepsis, fatal septic shock.

Investigations: bilirubin conjugated increased, blood potassium decreased, haematocrit decreased, protein total decreased

### 7.4 Abnormal Hematologic Laboratory Findings

**Table 6 Shifts from Baseline for Key Hematology Parameters - RECOURSE**

| | Lonsurf + Best Supportive Care | | | Placebo + Best Supportive Care | | |
|---|---|---|---|---|---|---|
| Laboratory Parameter | All Grades (%) | Grade† 3 (%) | Grade† 4 (%) | All Grades (%) | Grade† 3 (%) | Grade† 4 (%) |
| **Blood and lymphatic system disorders** | | | | | | |
| Anemia | 77 | 18 | NA | 33 | 3 | NA |
| Neutropenia | 67 | 27 | 11 | 1 | 0 | 0 |
| Thrombocytopenia | 42 | 5 | 1 | 8 | 0 | <1 |

† Common Terminology Criteria for Adverse Events (CTCAE), v4.03
NA Not applicable
# One Grade 4 anemia adverse reaction based on clinical criteria was reported

The frequency of hematological laboratory abnormalities associated with myelosuppression was much higher in the Lonsurf (trifluridine and tipiracil tablets) group than in the placebo group. Myelosuppression was generally manageable with reductions in dose, delays in cycle initiation and occasional use of granulocyte colony-stimulating factor.

### 7.5 Post-Market Adverse Reactions

Post marketing adverse reactions included interstitial lung disease (reported mainly in Japanese patients). Interstitial lung disease was reported in fifteen (0.2%) patients, three of which were fatal, among approximately 7,000 patients exposed to Lonsurf (trifluridine and tipiracil tablets) in clinical studies and clinical practice settings in Asia.

## 8 DRUG INTERACTIONS

### 8.1 Overview

In vitro studies indicated that trifluridine is a substrate for the nucleoside transporters CNT1, ENT1 and ENT2. Tipiracil was a substrate for OCT2 and MATE1. Therefore, caution is required when using medicinal products that interact with these transporters.

### 8.2 Drug-Drug Interactions

No clinical pharmacokinetic drug-drug interaction studies have been conducted with Lonsurf ((trifluridine and tipiracil tablets).

Trifluridine is a substrate of thymidine phosphorylase, and is not metabolized by cytochrome P450 (CYP) enzyme. Tipiracil is not metabolized in either human liver S9 or hepatocytes.

In vitro studies indicated that trifluridine, tipiracil hydrochloride and its metabolite 5-[trifluoromethyl] uracil did not inhibit the activity of human cytochrome P450 (CYP) isoforms. In vitro evaluation indicated that trifluridine, tipiracil hydrochloride and 5-[trifluoromethyl] uracil had no inductive effect on human CYP isoforms.

In vitro studies indicated that trifluridine is a substrate for the nucleoside transporters CNT1, ENT1 and ENT2. Therefore, caution is required when using medicinal products that interact with these transporters such as zidovudine. Tipiracil was a substrate for OCT2 and MATE1, therefore, the concentration might be increased when Lonsurf (trifluridine/tipiracil) is administered concomitantly with inhibitors of OCT2 or MATE1 such as cimetidine or dolutegravir.

Based on the results from in vitro study in human colon cancer cells, zidovudine (AZT) attenuated the cell growth inhibitory effects of trifluridine, mainly at near clinical concentration of zidovudine. There is a possibility of attenuation of anti-tumor activity of Lonsurf with zidovudine if used concomitantly in clinical practice.

Caution is required when using medicinal products that are human thymidine kinase substrates, e.g., zidovudine. Such medicinal products, if used concomitantly with Lonsurf, may compete with the effector, trifluridine, for activation via thymidine kinases. Therefore, when using antiviral medicinal products that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral medicinal product, and consider switching to an alternative antiviral medicinal product that is not a human thymidine kinase substrate, such as lamivudine, zalcitabine, didanosine and abacavir.

It is unknown whether Lonsurf may reduce the effectiveness of hormonal contraceptives. Therefore, women using a hormonal contraceptive must also use a barrier contraceptive method.

### 8.3 Drug-Food Interactions

It is recommended to take Lonsurf (trifluridine and tipiracil tablets) within 1 hour after completion of the morning and evening meals.

### 8.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 9 ACTION AND CLINICAL PHARMACOLOGY

### 9.1 Mechanism of Action

Trifluridine/tipiracil is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil (as tipiracil hydrochloride)).

Following uptake into cancer cells, trifluridine, is phosphorylated by thymidine kinase, further metabolised in cells to a deoxyribonucleic acid (DNA) substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation. However, trifluridine is rapidly degraded by thymidine phosphorylase and readily metabolised by a first-pass effect following oral administration, hence the inclusion of the thymidine phosphorylase inhibitor, tipiracil (as tipiracil hydrochloride).

In nonclinical studies, trifluridine/tipiracil demonstrated antitumour activity against both 5-fluorouracil sensitive and resistant colorectal cancer cell lines.

The cytotoxic activity of trifluridine/tipiracil against several human tumour xenografts correlated highly with the amount of trifluridine incorporated into DNA, suggesting this as the primary mechanism of action.

### 9.2 Pharmacodynamics

Lonsurf (trifluridine and tipiracil tablets) had no clinically relevant effect on QT/QTc prolongation compared with placebo in an open label study in patients with advanced solid tumours.

A thorough clinical QT study was performed in 30 patients with advanced solid tumours, Lonsurf 35 mg/m$^2$ as single and multiple doses (BID on Days 1 through 5 and Days 8 to 12) had no clinically relevant QT, QTcF, or QTcB prolongation effect compared with placebo. No patient had a QT, QTcF, or QTcB interval >500 msec at any time point. Lonsurf did not appear to be arrhythmogenic as evidenced by the absence of AEs of ventricular tachycardia, ventricular fibrillation, syncope, and seizure.

Studies of cardiovascular parameters in cynomolgus monkeys were found to have no effect at dose levels of up to 108.8 mg/kg of trifluridine, and up to 1000 mg/kg of tipiracil.

In addition, in a HEK293-hERG cell line assay trifluridine concentrations up to 300 mcmol/L and tipiracil at concentrations up to 100 mcmol/L for tipiracil, did not block the hERG potassium channel.

## 9.3 Pharmacokinetics

After twice daily dosing of Lonsurf (trifluridine and tipiracil tablets), systemic exposure (area under the concentration curve, AUC) of trifluridine more than dose-proportionally over the dose range of 15 to 35 mg/m$^2$ on Day 1. However tipiracil was generally dose proportional. After single-dose administration of Lonsurf 35 mg/m$^2$, the mean apparent half-life ($t_{1/2}$) of trifluridine was 1.4 hours and of tipiracil was 1.7 hours based on a 10 hour sampling period. The mean apparent half-life at steady state of trifluridine was 2.0 hours and of tipiracil was 2.4 hours.

Administration of a single dose of Lonsurf containing tipiracil and trifluridine 35 mg/m$^2$ increased the mean $AUC_{0-12}$ of trifluridine by 37-fold and $C_{max}$ by 22-fold with reduced variability compared to trifluridine 35 mg/m$^2$ alone.

**Absorption:**
After oral administration of Lonsurf with [$^{14}$C]-trifluridine, at least 57% of the administered trifluridine was absorbed and only 3% of the dose was excreted into faeces. After oral administration of Lonsurf with [$^{14}$C]-tipiracil, at least 27% of the administered tipiracil was absorbed and 50% of the total radioactivity dose measured into faeces, suggestive of moderate gastrointestinal absorption of tipiracil.

Following a single dose of Lonsurf (35 mg/m$^2$) in patients with advanced solid tumours, the mean times to peak plasma concentrations ($t_{max}$) of trifluridine and tipiracil were around 2 hours and 3 hours, respectively.

In the pharmacokinetic analyses of the multiple dose administration of Lonsurf (35 mg/m$^2$/dose, twice daily for 5 days a week with 2 days rest for 2 weeks followed by a 14-day rest, repeated every 4 weeks), trifluridine area under the concentration-time curve during a dosing interval ($AUC_{0-12}$) was approximately 3-fold higher and maximum concentration ($C_{max}$) was approximately 2-fold higher after multiple dose administration (Day 12 of Cycle 1) of Lonsurf than after single-dose (Day 1 of Cycle 1).

However, there was no accumulation for tipiracil, and no further accumulation of trifluridine with successive cycles (Day 12 of Cycles 2 and 3) of administration of Lonsurf. Following multiple doses of Lonsurf (35 mg/m$^2$/dose twice daily) in patients with advanced solid tumours.

Contribution of tipiracil**:** Single-dose administration of Lonsurf (35 mg/m$^2$/dose) increased the mean $AUC_{0-12}$ of trifluridine by 37-fold and $C_{max}$ by 22-fold with reduced variability compared to trifluridine alone (35 mg/m$^2$/dose).

Linearity/non-linearity
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$^2$. However tipiracil was generally dose proportional.

Effect of food: When Lonsurf at a single dose of 35 mg/m$^2$ was administered to 14 patients with solid tumours after a standardised high-fat, high-calorie meal, trifluridine area under the concentration-time curve (AUC) did not change, but trifluridine $C_{max}$, tipiracil $C_{max}$ and AUC decreased by approximately 40% compared to those in a fasting state. In clinical studies Lonsurf was administered within 1 hour after completion of the morning and evening meals.

**Distribution:**
The protein binding of trifluridine in human plasma is over 96% and trifluridine bound mainly to human serum albumin. Plasma protein binding of tipiracil is below 8%.

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing $^{14}$C-FTD (trifluridine) 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.

**Metabolism:**
Biotransformation
Trifluridine was mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, 5-[trifluoromethyl] uracil. After a single 60mg dose of Lonsurf with [$^{14}$C]-trifluridine, the analytes mostly recovered in urine were 5-[trifluoromethyl] uracil and trifluridine glucuronide isomers. Other minor metabolites, 5-carboxyuracil and 5-carboxy-2'-deoxyuridine, were detected, but those levels in plasma and urine were at low or trace levels.

Tipiracil was not metabolised in human liver S9 or in cryopreserved human hepatocytes. Tipiracil was the major component and 6-hydroxymethyluracil was the major metabolite consistently in human plasma, urine, and faeces.

**Elimination:**
Following the multiple-dose administration of Lonsurf at the recommended dose and regimen, the apparent mean half-lives ($t_{1/2}$) for trifluridine on Day 1 of Cycle 1 and on Day 12 of Cycle 1 were 1.4 hours and 2.0 hours, respectively based on 10 hours of sampling. Due to the 3 to 4 fold accumulation seen in AUC, the true terminal half life of trifluridine may be longer when in presence of tipiracil. The mean $t_{1/2}$ values for tipiracil on Day 1 of Cycle 1 and on Day 12 of Cycle 1 were 1.7 hours and 2.4 hours, respectively. No significant accumulation of tipiracil was seen between Day 1 and Day 12 of cycle 1.

Following twice daily dosing of Lonsurf (35 mg/m$^2$) for 5 days with 2 days rest for 2 weeks in patients with advanced solid tumours, the apparent oral clearance for trifluridine and tipiracil on Day 12 (day 5 of the second week of dosing) were approximately 3 L/hr and 90 L/hr, respectively. After single oral administration of Lonsurf 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) within 24 hours, and the excretion into feces and expired air was less than 3% for both. After single oral administration of Lonsurf with [$^{14}$C]-tipiracil hydrochloride, recovered radioactivity was 77% of the dose, which consisted of 27% urinary excretion and 50% fecal excretion.

**Special Populations and Conditions**

Based on the population pharmacokinetics analysis, there is no clinically relevant effect of age, gender or race on the pharmacokinetics of trifluridine or tipiracil.

**Gastrectomy:** The influence of gastrectomy on pharmacokinetics parameters was not able to be examined in the population pharmacokinetics analysis because there were few patients who had undergone gastrectomy (1% of overall).

**Hepatic Insufficiency:** Based on the population pharmacokinetics analysis, liver function parameters including alkaline phosphatase (ALP, 36-2322 U/L), aspartate aminotransferase (AST, 11-197 U/L), alanine aminotransferase (ALT, 5-182 U/L), and total bilirubin (0.17-3.20 mg/dL) were not significant covariates for pharmacokinetics parameters of either trifluridine or tipiracil. Serum albumin was found to significantly affect trifluridine clearance, with a negative correlation. For low albumin values ranging from 2.2 to 3.5 g/dL, the corresponding clearance values range from 4.2 to 3.1 L/h. No study in severe hepatic impairment (NCI Criteria Group C and D) has been conducted.

In a dedicated study the pharmacokinetics of trifluridine and tipiracil hydrochloride were evaluated in cancer patients with mild or moderate hepatic impairment (National Cancer Institute [NCI] Criteria Group B and C, respectively) and in patients with normal hepatic function. Based upon limited data with a considerable variability, no statistically significant differences were observed in the pharmacokinetics in patients with normal hepatic function versus patients with mild or moderate hepatic impairment. No correlation was seen for trifluridine nor tipiracil hydrochloride between pharmacokinetics parameters and AST or/and total blood bilirubin. Half-life time ($t_{1/2}$) and the accumulation ratio of trifluridine and tipiracil hydrochloride were similar between the moderate, mild and normal hepatic function patients. There is no need for a starting dose adjustment in patients with mild hepatic impairment.

**Renal Insufficiency:** Of the 533 patients in the RECOURSE study who received Lonsurf, 306 (57%) patients had normal renal function (creatinine clearance ≥ 90 mL/min), 178 (33%) patients had mild renal impairment (creatinine clearance 60 to 89 mL/min), and 47 (9%) had moderate renal impairment (creatinine clearance 30 to 59 mL/min), with data missing for 2 patients. Patients with severe renal impairment were not enrolled in the study.

Based on a population pharmacokinetics analysis, the exposure of Lonsurf in patients with mild renal impairment (creatinine clearance = 60 to 89 mL/min) was similar to those in patients with normal renal function (creatinine clearance ≥ 90 mL/min). A higher exposure of Lonsurf was observed in moderate renal impairment (creatinine clearance = 30 to 59 mL/min). Estimated creatinine clearance was a significant covariate for CL/F in both final models of trifluridine and tipiracil. The mean relative ratio of AUC in patients with mild (n=38) and moderate (n=16) renal impairment compared to patients with normal renal function (n=84) were 1.31 and 1.43 for trifluridine, respectively, and 1.34 and 1.65 for tipiracil hydrochloride, respectively. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with severe renal impairment or end-stage renal disease.

## 10 STORAGE, STABILITY AND DISPOSAL

Lonsurf (trifluridine and tipiracil) tablets should be stored at room temperature (15 to 30°C).

Hands should be washed after handling tablets.

Any unused medicinal product or waste material should be disposed according to local requirements.

## PART II: SCIENTIFIC INFORMATION

## 11 PHARMACEUTICAL INFORMATION

### Drug Substance - Trifluridine

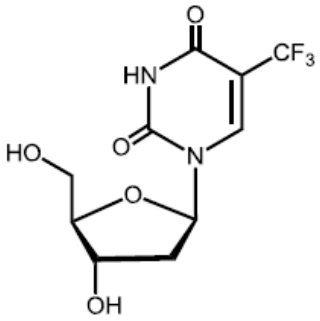
Proper name: Trifluridine

Chemical name: 2′-deoxy-5-(trifluoromethyl) uridine, Trifluorothymidine

Molecular formula: $C_{10}H_{11}F_3N_2O_5$

Molecular mass: 296.20

Structural formula:




Physicochemical properties:

| | |
|---|---|
| Description | White crystalline, non-hygroscopic powder |
| Solubility | Trifluridine is 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. |
| Melting point | 180°C (with decomposition) |
| pH | pH 4.81 (10 mg/mL, water, at 22.4°C) |
| p$K_a$ | 8.08 |

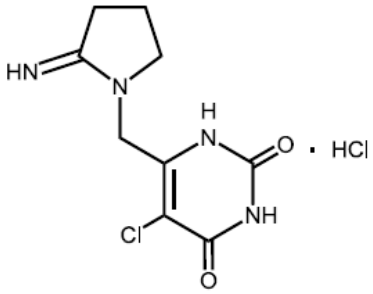
**Drug Substance - Tipiracil (hydrochloride)**

Chemical name: 2,4(*1H,3H*)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (1:1)

Molecular formula: $C_9H_{11}ClN_4O_2$•HCl

Molecular mass tipiracil hydrochloride: 279.12 (tipiracil free base:242.66)

Structural formula:




Physicochemical properties:

| | |
|---|---|
| Description | White crystalline powder |
| Solubility | Tipiracil hydrochloride is very slightly soluble in ethanol, slightly soluble in methanol, practically insoluble in 2-propanol, acetonitrile, acetone, diisopropyl ether and diethyl ether.<br><br>Tipiracil hydrochloride is soluble in 0.01 M hydrochloric acid and in 0.01 M sodium hydroxide solution. |
| Melting point | 240°C (with decomposition) |
| pH | pH 3.74 (10 mg/mL, water) |
| p$K_a$ | 5.95 |

## 12 CLINICAL TRIALS

### 12.1 Trial Design and Study Demographics

**Table 7 Summary of patient demographics for clinical trials in Metastatic Colorectal Cancer**

| Study # | Trial design | Dosage, route of administration and duration | Study subjects (N = number) | Mean age (Range) | Gender |
|---|---|---|---|---|---|
| TPU-TAS-102-301 (RECOURSE) | Multinational, double-blind, two-arm, parallel-group, randomised, Phase 3 study | Lonsurf, starting dose of 35 mg/m$^2$/dose<br>or<br>Placebo bid, x 5 days/week x 2 weeks, followed by a 14-day rest (one 28 day treatment cycle).<br>Treatment continued until disease progression or unacceptable toxicity. | N = 800<br>Lonsurf: 534<br>Placebo: 266 | 63.0 years<br>44.0% ≥65 years | 61.4% Males<br>38.6% Females |

**Study TPU-TAS-102-301 (RECOURSE) – Metastatic colorectal cancer**

The clinical efficacy and safety of Lonsurf (trifluridine and tipiracil tablets) were evaluated in an international, randomised, double-blind, placebo-controlled Phase III study (RECOURSE) in patients with previously treated metastatic colorectal cancer. The primary efficacy endpoint was overall survival, and secondary efficacy endpoints included progression-free survival, and overall response rate and disease control rate.

In total, 800 patients were randomised 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. United States, Europe and Australia). Key eligibility criteria included prior treatment with at least 2 lines of standard chemotherapy for metastatic CRC and being refractory to or intolerant of those therapies, ECOG PS 0-1, absence of brain metastasis, and absence of ascites requiring drainage in the past four weeks.

Lonsurf dosing was based on BSA with a starting dose of 35 mg/m$^2$/dose. Study treatment was administered orally twice daily after morning and evening meals for 5 days a week with 2 days rest for 2 weeks, followed by 14 days rest, repeated every 4 weeks. Patients continued therapy until disease progression or unacceptable toxicity.

Of the 800 randomised patients, the median age was 63 years, 61% were male, 58% were Caucasian/White, 35% were Asian/Oriental, and 1% were Black/African American, and all patients had baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

of 0 or 1. The primary site of disease was colon (62%) or rectum (38%). KRAS status was wild (49%) or mutant (51%) at study entry. The median number of prior lines of therapy for metastatic disease was 3. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but 1 patient received bevacizumab, and all but 2 patients with KRAS wild type tumours received panitumumab or cetuximab. The 2 treatment groups were comparable with respect to demographic and baseline disease characteristics.

## 12.2 Study Results

Study TPU-TAS-102-301 (RECOURSE) – Metastatic colorectal cancer

An overall survival analysis of the study, carried out as planned at 72% (N = 574) of events, demonstrated a statistically significant survival benefit of Lonsurf (trifluridine and tipiracil tablets) plus best supportive care compared to placebo plus best supportive care. PFS was significantly improved in patients receiving Lonsurf plus best supportive care (See Table , Figure 1 and Figure 2).

**Table 8 Efficacy Results of RECOURSE Study**

| **Primary Endpoints** | **Lonsurf + BSC (N=534)** | **Placebo + BSC (N=266)** |
|---|---|---|
| **Overall Survival (OS)** | | |
| Number of deaths, N (%) | 364 (68.2) | 210 (78.9) |
| 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] | < 0.0001 (1-sided and 2-sided) | |
| **Progression-Free Survival (PFS)[d]** | | |
| Number of Progression or Death, N (%) | 472 (88.4) | 251 (94.4) |
| Median PFS (months)[a] [95% CI][b] | 2.0 [1.9, 2.1] | 1.7 [1.7, 1.8] |
| Hazard ratio [95% CI] | 0.48 [0.41, 0.57] | |
| P-value[c] | <0.0001 (1-sided and 2-sided) | |

[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)
[d] Investigator assessed

**Figure 1 Kaplan-Meier curves of overall survival**

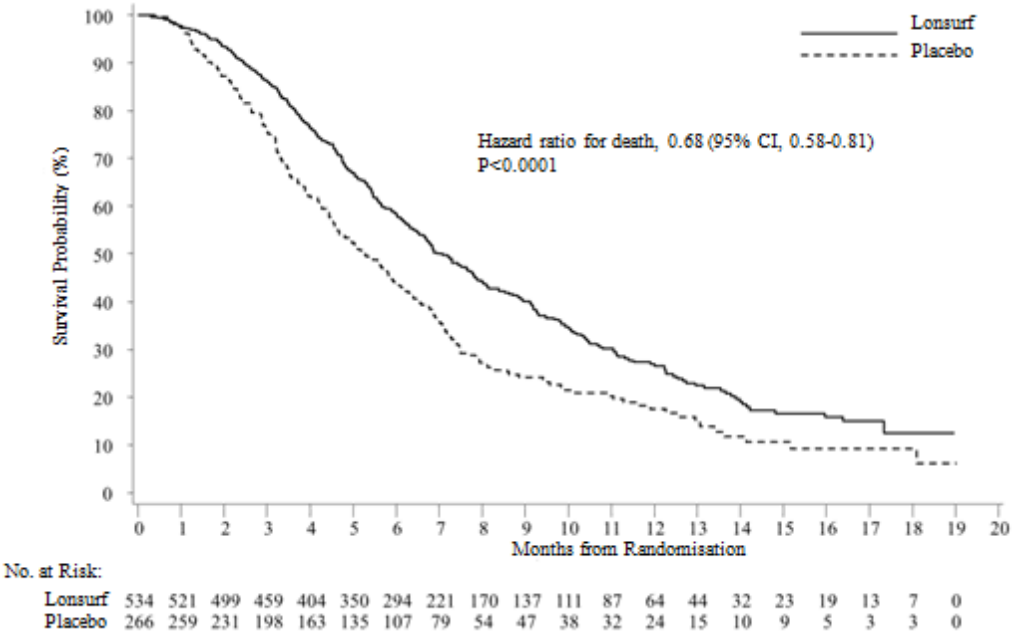
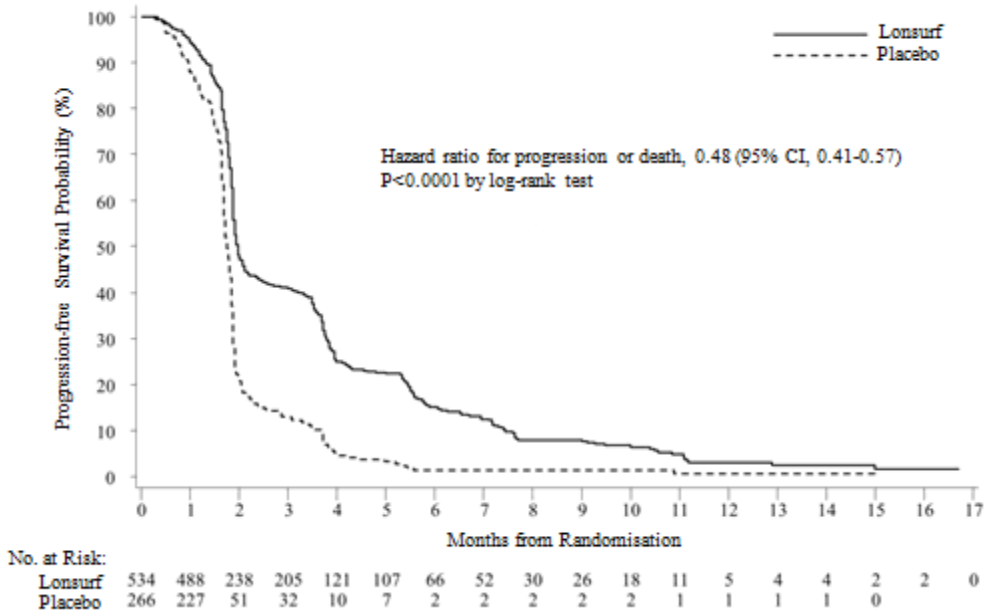



**Figure 2 Kaplan-Meier curves of progression-free survival**



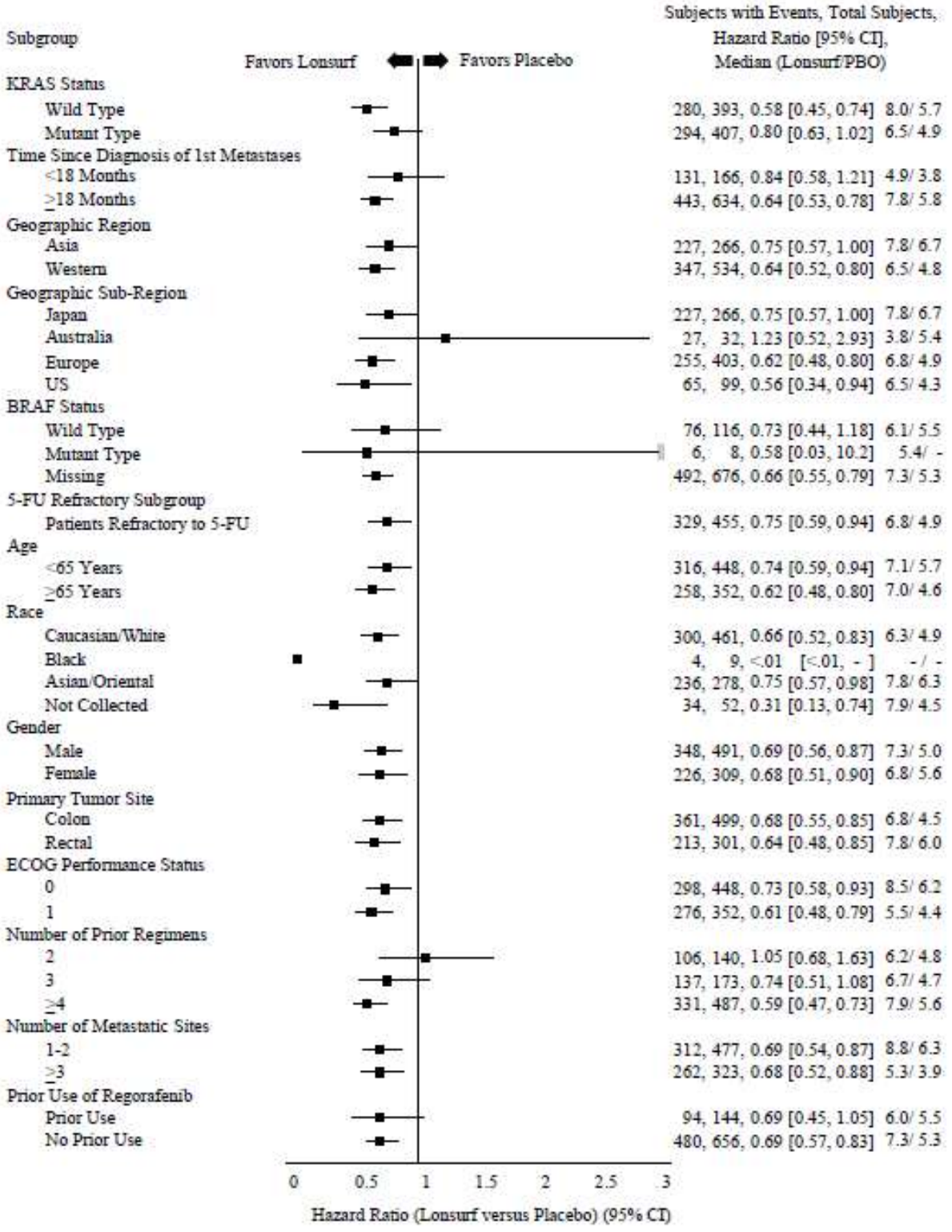

An updated overall survival analysis, carried out at 89% (N = 712) of events, confirmed the clinically meaningful and statistically significant survival benefit of Lonsurf plus best supportive care compared to placebo plus best supportive care (hazard ratio: 0.69; 95% with a confidence interval of 0.59 to 0.81; p < 0.0001) and a median overall survival of 7.2 months vs 5.2 months; with 1-year survival rates of 27.1% and 16.6%, respectively.

The overall survival benefit was observed consistently in all pre-specified subgroups.

Sixty one percent (61%, N = 485) of all randomised patients received a fluoropyrimidine as part of their last treatment regimen prior to randomisation, of which 455 (94%) were refractory to the fluoropyrimidine at that time. Among these patients, the overall survival benefit with Lonsurf was maintained.

Eighteen percent (18%, N = 144) of all randomised patients received regorafenib prior to randomisation. Among these patients, the overall survival benefit with Lonsurf was maintained. The effect was also maintained in regorafenib-naive patients.

**Figure 3 Forest Plot of Hazard Ratios for Treatment Effect on Overall Survival by Selected Subgroups**



The overall response rate (complete response or partial response) was 1.6% in patients treated with Lonsurf and 0.4% in patients treated with placebo.

## 13 NON-CLINICAL TOXICOLOGY

**Repeat-dose toxicity**
Toxicology assessment of trifluridine/tipiracil hydrochloride was performed in rats, dogs and monkeys. The target organs identified were the lymphatic and hematopoietic systems and the gastrointestinal tract. All changes, i.e., leucopenia, anaemia, bone marrow hypoplasia, atrophic changes in the lymphatic and hematopoietic tissues and the gastrointestinal tract, were reversible within 9 weeks of drug withdrawal. Whitening, breakage, and malocclusion were observed in teeth of rats treated with trifluridine/tipiracil hydrochloride, which are considered rodent specific and not relevant for human.

**Carcinogenesis and mutagenesis**
No long term studies evaluating the carcinogenic potential of trifluridine/tipiracil hydrochloride in animals have been performed. Trifluridine was shown to be genotoxic in a reverse mutation test in bacteria, a chromosomal aberration test in mammal-cultured cells, and a micronucleus test in mice. Therefore, Lonsurf should be treated as a potential carcinogen.

**Reproductive toxicity**
Animal studies did not indicate an effect of trifluridine and tipiracil hydrochloride on male fertility in rats. Dose related increases in the corpus luteum count and implanting embryo count observed in female rats but female fertility was not affected. Trifluridine/tipiracil hydrochloride has been shown to cause embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given at dose levels lower than the clinical exposure. No peri/post-natal developmental toxicity studies have been performed.

**Juvenile Animals**
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 twice daily).

## READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

## PATIENT MEDICATION INFORMATION

### LONSURF®
### trifluridine and tipiracil tablets

Read this carefully before you start taking **Lonsurf** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Lonsurf**.

**Serious Warnings and Precautions**

**Lonsurf should only be prescribed by a doctor with experience in the use of anti-cancer drugs.**

**The following serious side effects have been seen in people taking Lonsurf:**

- **Bone Marrow Suppression (Myelosuppression)**: signs and symptoms of infections (including fever, chills, sore throat, mouth ulcers), fatigue, easy bruising, bleeding of the nose, gums or mouth, tiny red spots on the skin, rash, shortness of breath, pale skin lips and nail beds.

- **Stomach Problems (Gastrointestinal Toxicity)**: nausea, vomiting and diarrhea that can cause you to become dehydrated.

**What is Lonsurf used for?**
Lonsurf is used to treat adults with colon cancer or rectal cancer - sometimes called 'colorectal' cancer.

- It is used when the cancer has spread to other parts of the body.
- It is used when other treatments have not worked or when other treatments are not suitable for you.

**How does Lonsurf work?**
Lonsurf is a combination therapy containing 2 drugs: trifluridine and tipiracil. Trifluridine interferes with DNA in cancer cells to stop them from making new cancer cells. Tipiracil stops trifluridine from being broken down by enzymes before it can act.

**What are the ingredients in Lonsurf?**
Medicinal ingredients: trifluridine and tipiracil (as tipiracil hydrochloride)

Non-medicinal ingredients: carnauba wax, FD&C Blue No. 2 Aluminum Lake, ferric oxide red, ferric oxide yellow, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, pregelatinized starch, shellac, stearic acid, talc and titanium dioxide.

**Lonsurf comes in the following dosage forms:**
Tablets: 15 mg/6.14 mg and 20 mg/8.19 mg

**Do not use Lonsurf if you:**
- are allergic to trifluridine or tipiracil or any of the other ingredients of this medicine.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Lonsurf. Talk about any health conditions or problems you may have, including if you:**
- have or have a history of kidney disease
- have or have a history of liver disease
- have had radiation treatment for your cancer
- are pregnant or you or your partner are planning on becoming pregnant
- are breastfeeding or planning to breastfeed. You should not breastfeed while taking Lonsurf and for one day after your last dose.
- have an intolerance to galactose or the Lapp lactase deficiency or glucose-galactose malabsorption. Lonsurf contains lactose.
- are 65 years of age or older as you may be at higher risk of side effects related to low blood cell levels.

**Other warnings you should know about:**
**Pregnancy and Contraception**
Lonsurf can harm your unborn baby. You should not become pregnant or father a child while you are taking Lonsurf. If you are a female who could become pregnant or if you are a male taking Lonsurf and your female partner could become pregnant, you must use a very effective birth control while taking Lonsurf, and for 6 months after your last dose. It is not known if Lonsurf reduces the effectiveness of hormonal birth control (such as "the pills"), therefore women using hormonal birth control should also use a barrier birth control such as condoms. If you think you, or your female partner, have become pregnant contact your healthcare professional immediately.

**Serious Side Effects**
Tell your healthcare professional immediately if you experience any of the following as they could be signs of very serious side effects:
- signs of infection such as sore throat, mouth ulcers or a fever - these may be signs of low white blood cells
- feeling short of breath, tired or having pale skin - these may be signs of low red blood cells (anemia)
- unusual bruising or bleeding - these may be signs of low blood cells platelets
- stomach problems such as feeling sick (nausea) or being sick (vomiting) or having diarrhea - you may be at risk of dehydration

Regular blood and urine tests are important while taking Lonsurf. This includes before you start treatment with Lonsurf and before each new treatment cycle. Your healthcare professional will decide when to perform blood and urine tests and will interpret the results.

**Driving and Operating Machinery**
If you experience symptoms such as fatigue, dizziness or generally feeling unwell, which affects your ability to concentrate and react, while taking Lonsurf you should not drive or use machines.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**How to take Lonsurf:**

- Take Lonsurf twice daily. In the morning within 1 hour of eating your morning meal and in the evening within 1 hour of eating your evening meal.
- Lonsurf must be taken with a glass of water. Take Lonsurf on Days 1 to 5 and again on Days 8 to 12 of a 28-day treatment cycle. Each treatment cycle is repeated every 4 weeks.
- Lonsurf must be handled with caution. Always wash your hands after handling Lonsurf tablets.

**Usual adult dose:**
Lonsurf is given based on body surface area, calculated from your height and weight. Your healthcare professional will tell you how many tablets to take.

**Overdose:**

| |
|---|
| If you think you have taken too much Lonsurf, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms. |

**Missed Dose:**
Do not take additional doses of Lonsurf to make up for missed or held doses.

**What are the possible side effects from using Lonsurf?**
These are not all the possible side effects you may feel when taking Lonsurf. If you experience any side effects not listed here, contact your healthcare professional.

**Side effects may include:**

- Weakness
- Feeling tired
- Decreased appetite
- Abdominal pain
- Indigestion
- Common cold
- Hair loss
- Swelling of the gums, tongue, lips and/or mouth
- Rash
- Bleeding gums
- Change in taste

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| **VERY COMMON** | | | |
| **Stomach problems (Gastrointestinal toxicity):** nausea, vomiting and diarrhea which may lead to dehydration | | √ | |
| **RARE** | | | |
| **Bone marrow suppression (Myelosuppression):** unusual bruising or bleeding, feeling short of breath, tired or having pale skin or signs of infection (fever, chills, sore throat, mouth ulcers) | | √ | |
| **Pulmonary embolism:** shortness of breath, severe chest pain, coughing up blood | | | √ |
| **Lung problems (interstitial lung disease, pneumonitis):** fatal and serious or with suddenly worsening of shortness of breath, wheezing, tiredness, possibly with a cough or fever, painful breathing have been reported in Asian (especially Japanese) patients. | | | √ |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**
Lonsurf should be stored at room temperature (15ºC to 30ºC).

Hands should be washed after handling Lonsurf tablets.

Keep out of reach and sight of children.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

**If you want more information about Lonsurf:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); www.taihopharma.ca., or by calling 1-844-648-2446.

This leaflet was prepared by Taiho Pharma Canada, Inc.
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