LONSURF® (trifluridine and tipiracil) is a prescription medicine used to treat people with colon or rectal cancer that has spread to other parts of the body and who have previously been treated with or cannot receive certain chemotherapy medicines. It is not known if LONSURF is safe and effective in children.

In a clinical trial, half of the patients treated with LONSURF were still alive at 7.1 months and half of the patients who received placebo were still alive at 5.3 months. Worsening of the disease or death occurred in 88% of patients treated with LONSURF and 94% of patients who received placebo.

Selected Important Safety Information
Low blood counts: LONSURF can decrease the number of your blood cells. This can sometimes be severe and life-threatening.

Please see Important Safety Information on page 10 and full Prescribing Information in pocket.
Introduction
LONSURF® (trifluridine and tipiracil), a prescription medicine, is for people:
• Whose colon or rectal cancer has spread to other parts of the body
• Who have been previously treated with or cannot receive certain chemotherapy medicines
• Who now may need another option
LONSURF was studied in a clinical trial of 800 patients.
• Half of the patients treated with LONSURF were still alive at 7.1 months and half of the patients who received placebo were still alive at 5.3 months
• Worsening of the disease or death occurred in 88% of patients treated with LONSURF and 94% of patients who received placebo

About this brochure
Whether you have been prescribed LONSURF or just want to know more about it, this brochure is for you.
• If you have been prescribed LONSURF, this brochure can help you with your treatment plan
• If you are considering LONSURF, it may help you and your healthcare provider decide if LONSURF is right for you
This booklet is not a substitute for your healthcare provider’s advice. Always ask your healthcare provider your questions about LONSURF and colon or rectal cancer.
You can always learn more at LONSURF.com/patients

Who it’s for
What is refractory metastatic colon or rectal cancer (mCRC)?
Refractory means that the cancer may continue to grow despite treatment. The cancer may be resistant at the beginning of treatment or it may become resistant during treatment.
Metastatic means that the cancer has spread to other parts of the body.

Who should take LONSURF?
LONSURF may be an option for patients who have previously been treated with or cannot receive the following treatments:
• Fluoropyrimidine: Such as 5-fluorouracil, also known as 5-FU, and Xeloda® (capecitabine)
• Oxaliplatin-based treatment: Such as FOLFOX (5-FU, leucovorin, and oxaliplatin) and Eloxatin® (oxaliplatin)
• Irinotecan-based treatment: Such as FOLFIRI (5-FU, leucovorin, and irinotecan) and Camptosar® (irinotecan)
• Anti-VEGF biological therapy: Such as Avastin® (bevacizumab) and Zaltrap® (ziv-aflibercept)
• Anti-EGFR therapy: Such as Erbitux® (cetuximab) and Vectibix® (panitumumab)
If you aren’t sure what treatments you’ve had in the past, ask your healthcare provider.

Living with colon or rectal cancer can be difficult, but you are not alone. You are facing it with your family, friends, and loved ones. LONSURF may give you the chance to continue the journey longer alongside them.
How it works

LONSURF is the first FDA-approved combination tablet for refractory mCRC. It is an oral chemotherapy that is 2 medicines in 1. LONSURF interferes with cell replication in the life cycle of cells.

• One part helps the other part stay active and work properly
• The other part stops cells from making copies of themselves. This may help stop tumors from growing

FDA=Food and Drug Administration.

What is the most important information I should know about LONSURF?

Your healthcare provider should check your blood cell counts before you receive LONSURF, at day 15 during treatment, and as needed.

• Low blood counts are common with LONSURF and can sometimes be severe and life-threatening. LONSURF can cause a decrease in your white blood cells, red blood cells, and platelets. Low white blood cells can make you more likely to get serious infections that could lead to death. Your healthcare provider may lower your dose or stop LONSURF if you have low white blood cell or low platelet counts
• Tell your healthcare provider right away if you develop any signs of infection such as fever, chills, or body aches

What are the most common side effects caused by LONSURF?

Almost all patients treated with LONSURF experience side effects at some time. Some common side effects you may experience include:

• Tiredness
• Nausea
• Vomiting
• Decreased appetite
• Diarrhea
• Abdominal pain
• Fever

Tell your healthcare provider if you have nausea, vomiting, or diarrhea that is severe or that does not go away. These are not all of the possible side effects of LONSURF.

If you have a LONSURF Starter Kit, you can use the thermometer to check your temperature. You can record it in the Treatment Calendar along with any side effects you have. Then bring the Calendar with you to your doctor’s appointments.

How can LONSURF help me?

With proven results to help patients live longer, LONSURF® (trifluridine and tipiracil) is a treatment that may allow you to continue your journey with refractory mCRC.

LONSURF has been proven to
• Allow patients to live longer
• Slow or stop the growth of cancer for a period of time

LONSURF was studied in a clinical trial of 800 patients with colon or rectal cancer that had spread to other parts of the body and had been previously treated with certain chemotherapy medicines.

• Half of the patients treated with LONSURF were still alive at 7.1 months and half of the patients who received placebo were still alive at 5.3 months
• Worsening of the disease or death occurred in 88% of patients treated with LONSURF and 94% of patients who received placebo

Please see Important Safety Information on page 10 and full Prescribing Information in pocket.
How to manage side effects

Your healthcare provider may have ways to help manage some of the side effects of LONSURF® (trifluridine and tipiracil). This could include adjusting your treatment plan by changing your dosage or stopping treatment.

The following information may also be helpful to you in managing some of the side effects of LONSURF while under your healthcare provider’s care; however, these tips may not always work.

This information is not meant to replace your healthcare provider’s advice. Always discuss any side effects with your healthcare provider.

### Tips for managing

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Tips for managing</th>
</tr>
</thead>
</table>
| **Tiredness**                     | - Plan time to rest or to take a short nap (less than 1 hour). Keeping naps short will help you sleep better at night.  
- Talk with your healthcare provider about exercise that can help, like going for a 15-minute walk, doing yoga, or riding an exercise bike.  
- Don’t overdo it.  
- Try to sleep at least 8 hours each night.  
- Make a bedtime routine. Bathing or listening to music before you go to bed may help you relax. |
| **Nausea and vomiting**           | - Eat 5 or 6 small meals a day, instead of 3 big ones (this does not change your dosing schedule).  
- Have food and drinks that are warm or cool instead of hot or cold.  
- Choose foods that are easy on the stomach, like saltine crackers or angel food cake.  
- Avoid certain foods. Don’t eat greasy, fried, sweet, or spicy foods if you feel sick after eating them.  
- Remember to take any medicine that your healthcare provider has prescribed to you to help with nausea. |
| **Decreased appetite**            | - Eat 5 or 6 small meals a day, instead of 3 big ones (this does not change your dosing schedule).  
- Drink milkshakes, smoothies, juice, or soup if you do not feel like eating solid foods.  
- Choose foods that are high in calories and/or protein.  
- Being active may help you feel hungrier. Talk with your healthcare provider about exercises that can help, like going for a 15-minute walk. |
| **Diarrhea/ abdominal pain**      | For diarrhea:  
- Eat 5 or 6 small meals a day, instead of 3 big ones (this does not change your dosing schedule).  
- Eat low-fiber foods. Foods that are high in fiber can make diarrhea worse. Low-fiber foods include bananas, white rice, white toast, and plain or vanilla yogurt.  
- Have food and drinks that are warm or cool instead of hot or cold.  
- Eat bland foods instead of greasy, fried, salty, sweet, or spicy foods.  
- Avoid dairy products, such as milk, cheese, and sour cream.  
- Avoid alcohol and caffeine.  
- Drink plenty of liquids to replace the fluids being lost.  
- If the rectal area becomes sore, use warm water and a towelette. Keep the area dry. Ask your healthcare provider about creams that can help. |
| **Fever**                         | - Drink plenty of liquids, like water, juice, and broth.  
- Rest.  
- Keep cool by dressing in light clothing and sleeping with only a sheet.  
- Call a healthcare provider immediately if you have a fever or other signs of infection such as chills or body aches. You can use the thermometer in the Starter Kit to check your temperature each day. |

Tell your healthcare provider if you have nausea, vomiting, or diarrhea that is severe or that does not go away.

You can call the Taiho Oncology 24/7 hotline with questions about side effects with LONSURF at 1-844-US-TAIHO (1-844-878-2446). You may report side effects to the FDA at 1-800-FDA-1088.

Please see Important Safety Information on page 10 and full Prescribing Information in pocket.
How to take LONSURF

LONSURF® (trifluridine and tipiracil) is a tablet you swallow:
- Twice a day
- After you eat breakfast and dinner (immediately after or up to 1 hour after)
  - LONSURF may cause a decrease in white blood cells. Taking LONSURF
    after morning and evening meals may help lessen this effect. This is
    important because a low white blood cell count can make you more
    prone to infection
  - The type of food does not matter

LONSURF comes in 2 strengths: 15-mg and 20-mg tablets.*
Your healthcare provider may prescribe both strengths for your prescribed dose.

15-mg tablet  20-mg tablet  Tablets shown are not actual size.

LONSURF 28-day dosing schedule

<table>
<thead>
<tr>
<th>Morning dose</th>
<th>Evening dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1:</td>
<td>Day 2:</td>
</tr>
<tr>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Day 3:</td>
<td>Day 4:</td>
</tr>
<tr>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Day 5:</td>
<td>Day 6: REST</td>
</tr>
<tr>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Day 7: REST</td>
<td></td>
</tr>
</tbody>
</table>


You will take LONSURF after morning and evening meals for 5 days a week, and then rest for 2 days. This goes on for 2 weeks.

Then you will not take LONSURF for 2 weeks (14 days).

This is repeated for as long as your healthcare provider says. Always follow all of your healthcare provider’s directions carefully.

*Tablet strength of LONSURF is based on 1 active part of the medicine.

Other things to keep in mind about taking LONSURF

- Store LONSURF at room temperature between 68°F and 77°F (20°C to 25°C)
- Don’t store LONSURF with other medicines. Keep LONSURF in its own container
- If you store your tablets outside of the original container, any unused LONSURF tablets should be disposed of after 30 days
- Wash your hands after handling LONSURF. Even though it is a pill, it is still chemotherapy
- Make sure your caregiver wears gloves when handling LONSURF
- Note that there is a packet inside the bottle that helps absorb moisture. Do not swallow this material
- Keep LONSURF out of the reach of children

Contact your healthcare provider if:
- You miss a dose. Do not take additional doses to make up for the missed dose. Call your healthcare provider for instructions about what to do for a missed dose
- You have leftover tablets. Your healthcare provider or pharmacist will tell you how to dispose of them properly

If you have a LONSURF Starter Kit, use the Calendar to help you keep track of your treatment. Your nurse may provide you with a Dosing Schedule as well.

Please see Important Safety Information on page 10 and full Prescribing Information in pocket.
LONSURF® (trifluridine and tipiracil) is a prescription medicine used to treat people with colon or rectal cancer that has spread to other parts of the body and who have been previously treated with or cannot receive certain chemotherapy medicines. It is not known if LONSURF is safe and effective in children.

**Important Safety Information**

**LONSURF may cause serious side effects, including:**

- **Low blood counts.** Low blood counts are common with LONSURF and can sometimes be severe and life-threatening. LONSURF can cause a decrease in your white blood cells, red blood cells, and platelets. Low white blood cells can make you more likely to get serious infections that could lead to death. Your healthcare provider should do blood tests before you receive LONSURF and as needed to check your blood cell counts. Your healthcare provider may lower your dose of LONSURF or stop LONSURF if you have low white blood cell or platelet counts.

Tell your healthcare provider right away if you get any of the following signs and symptoms of infection during treatment with LONSURF: fever, chills, or body aches.

**Before taking LONSURF, tell your healthcare provider about all of your medical conditions, including if you:**

- Have kidney problems
- Are pregnant or plan to become pregnant. LONSURF can harm your unborn baby
  - **Females** who can become pregnant should use effective birth control during treatment with LONSURF. Tell your healthcare provider immediately if you become pregnant
  - **Males**, while on treatment and for 3 months after your last dose of LONSURF, you should use a condom during sex with female partners who are able to become pregnant. Tell your healthcare provider right away if your partner becomes pregnant while you are taking LONSURF.
- Are breast-feeding or plan to breast-feed. It is not known if LONSURF passes into your breast milk. Do not breast-feed during treatment with LONSURF and for 1 day after your last dose of LONSURF.

Tell your healthcare provider about all the prescription and over-the-counter medicines, vitamins, and herbal supplements you take.

The **most common side effects** with LONSURF include tiredness, nausea, decreased appetite, diarrhea, vomiting, abdominal pain, and fever.

Tell your doctor if you have nausea, vomiting, or diarrhea that is severe or that does not go away.

These are not all of the possible side effects of LONSURF. For more information, ask your healthcare provider. Call your doctor for medical advice about side effects.

**Get the support you need**

Meeting and learning from other people with colon or rectal cancer can be helpful. Connect with others online or in a local support group.

You can find colon or rectal cancer information, support, and community at:

- **CancerCare®:**
  Go to cancercare.org
  or call 1-800-813-HOPE (4673)

- **Cancer Support Community (CSC):**
  Go to cancersupportcommunity.org
  or call 1-888-793-9355

- **Fight Colorectal Cancer:**
  Go to FightCRC.org
  or call 1-877-427-2111

- **Colon Cancer Alliance:**
  Go to ccalliance.org
  or call 1-877-422-2030

- **Chris4Life:**
  Go to chris4life.org
  or call 1-855-610-1733

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Taiho Oncology Patient Support

Taiho Oncology is committed to providing ongoing services that include treatment support, referral to financial assistance resources to help you pay for your medicine, informational e-mails, and 24-hour access to our call center, where you can get answers to your questions about LONSURF® (trifluridine and tipiracil).

For more information about LONSURF financial support:
• See the Patient Assistance Brochure
• Call 1-844-TAIHO-4U (1-844-824-4648)
• Go to TaihoPatientSupport.com

Learn more at LONSURF.com/patients

Sources:

Please see Important Safety Information on page 10 and full Prescribing Information in pocket.
LONSURF (trifluridine and tipiracil) tablets, for oral use
Initial U.S. Approval: 2015

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**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)

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**DOSAGE AND ADMINISTRATION**

- Recommended dose: 35 mg/m²/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)

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**DOSAGE FORMS AND STRENGTHS**

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

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**CONTRAINDICATIONS**

None. (4)

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**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)

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**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.

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**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)
- 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: 09/2015

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2 DOSAGE AND ADMINISTRATION
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5.1 Severe Myelosuppression
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*Sections or subsections omitted from the full prescribing information are not listed.*
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/m² 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.

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/mm³ or febrile neutropenia is resolved
- Platelets are greater than or equal to 75,000/mm³
- 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/mm³ or febrile neutropenia
- Platelets less than 50,000/mm³
- Grade 3 or 4 non-hematological adverse reactions

After recovery, resume LONSURF after reducing the dose by 5 mg/m²/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/mm³) or thrombocytopenia (which has recovered to greater than or equal to 75,000/mm³) 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/m² 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/mm³. 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/m² 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/m²/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 (≥5%) in Study 1 Occurring More Commonly (>2%) than in Patients Receiving Placebo.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LONSURF (N=533)</th>
<th>Placebo (N=265)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades 3-4*</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>48%</td>
<td>2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32%</td>
<td>3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28%</td>
<td>2%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>21%</td>
<td>2%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
<td>52%</td>
<td>7%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19%</td>
<td>1%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>39%</td>
<td>4%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>7%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>LONSURF (N=533*)</th>
<th>Placebo (N=265*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade†</td>
<td>Grade†</td>
</tr>
<tr>
<td></td>
<td>All % 3 % 4 %</td>
<td>All % 3 % 4 %</td>
</tr>
</tbody>
</table>

Blood and lymphatic system disorders

<table>
<thead>
<tr>
<th></th>
<th>LONSURF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia‡</td>
<td>77</td>
<td>33</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>67</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>42</td>
<td>8</td>
</tr>
</tbody>
</table>

* % 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-treatment 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.

7  DRUG INTERACTIONS

No pharmacokinetic drug-drug interaction studies have been conducted with LONSURF.

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/m² twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m² twice daily) embryo lethality 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 14C-FTD or 14C-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/m² 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
No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of LONSURF. No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin (TB) 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). Patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment were not enrolled in Study 1. [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 (CLcr = 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 (CLcr ≥ 90 mL/min, n= 306) or patients with mild renal impairment (CLcr = 60 to 89 mL/min, n= 178).

No dose adjustment to the starting dose of LONSURF is recommended in patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min); however patients with moderate renal impairment may require dose modification for increased toxicity. No patients with severe renal impairment (CLcr < 30 mL/min) were enrolled in Study 1. [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 ≥ 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/m² per day. There is no known antidote for LONSURF overdosage.

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 C₁₀H₁₁F₃N₂O₅ 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-(1H,3H)-dione monohydrochloride or 2,4(1H,3H)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (1:1), and has the following structural formula:
Tipiracil hydrochloride has a molecular formula C₉H₁₁ClN₄O₂•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/m². After administration of LONSURF 35 mg/m² twice daily, the mean elimination half-life (t½) 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 \(\text{AUC}_{0-\text{last}}\) and 2-fold for peak plasma concentration (\(C_{\text{max}}\)) at steady state while no accumulation was observed for tipiracil.

Administration of a single dose of LONSURF containing tipiracil and trifluridine 35 mg/m² increased the mean \(\text{AUC}_{0-\text{last}}\) of trifluridine by 37-fold and \(C_{\text{max}}\) by 22-fold with reduced variability compared to trifluridine 35 mg/m² alone.

Absorption

Following a single oral administration of LONSURF at 35 mg/m² in patients with cancer, the mean time to peak plasma concentration (\(T_{\text{max}}\)) of trifluridine was around 2 hours.

A standardized high-fat, high-calorie meal decreased trifluridine \(C_{\text{max}}\), tipiracil \(C_{\text{max}}\) and AUC by approximately 40%, but did not change trifluridine AUC compared to those in a fasting state in patients with cancer following administration of a single dose of LONSURF 35 mg/m². 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 \(C_{\text{max}}\) of trifluridine and the decrease in neutrophil counts.

Distribution

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

Elimination

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

Following a single dose of LONSURF at 60 mg, the mean 48-hour cumulative urinary excretion was 1.5% for unchanged trifluridine, 19.2% for FTY, and 29.3% for unchanged tipiracil.

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 (CLcr = 60 to 89 mL/min, n= 38) and 43% higher in patients with moderate renal impairment (CLcr = 30 to 59 mL/min, n= 16) than that in patient with normal renal function (CLcr ≥ 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 (CLcr < 30 mL/min) or end-stage renal disease. [see Use in Specific Populations (8.7)]

**Hepatic Impairment**

In Study 1, with data from patients with normal liver function (TB and AST less than or equal to the ULN, n=96) and patients with mild hepatic impairment (TB less than or equal to the ULN and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST, n= 42), there is no clinically relevant effect of mild hepatic impairment on the exposure of either trifluridine or tipiracil based on the population pharmacokinetic analysis. Patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment were not enrolled in Study 1. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with moderate to severe hepatic impairment. [see 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/m² 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>
<thead>
<tr>
<th></th>
<th>LONSURF (N=534)</th>
<th>Placebo (N=266)</th>
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<tbody>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths, N (%)</td>
<td>364 (68)</td>
<td>210 (79)</td>
</tr>
<tr>
<td>Median OS (months)&lt;sup&gt;a&lt;/sup&gt; [95% CI]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.1 [6.5, 7.8]</td>
<td>5.3 [4.6, 6.0]</td>
</tr>
<tr>
<td>Hazard ratio [95% CI]</td>
<td>0.68 [0.58, 0.81]</td>
<td></td>
</tr>
<tr>
<td>P-value&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Progression-Free Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Progression or Death, N (%)</td>
<td>472 (88)</td>
<td>251 (94)</td>
</tr>
<tr>
<td>Hazard ratio [95% CI]</td>
<td>0.47 (0.40, 0.55)</td>
<td></td>
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<tr>
<td>P-value&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td></td>
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</tbody>
</table>

<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)
15 REFERENCES


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.¹

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)]