LONSURF® (trifluridine and tipiracil) tablets are 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.

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 13 and full Prescribing Information in pocket.
Introduction

You and your loved one with refractory metastatic colon or rectal cancer (mCRC) have been through a lot. You have seen rounds of treatments, side effects, and a whole new way of living. What is “normal” keeps changing, and priorities change, too. It is important to recognize this shift. It is also important to support the way your loved one chooses to manage the next part of his or her journey.

This brochure is meant to help you understand:
• Your loved one’s treatment with LONSURF® (trifluridine and tipiracil) tablets
• How to help your loved one with his or her treatment plan
• That it is important for you to take care of yourself, too

On the following pages, you will find information about:
• Colon or rectal cancer
• The role of the caregiver
• Treatment with LONSURF (who it is for and how it works)
• How LONSURF is taken
• Side effects and how to help manage them

You will also find answers to some frequently asked questions about LONSURF, Important Safety Information, and places to find additional support.
Fast facts about colon and rectal cancer

• It is the third most common cancer in men and women

• Approximately 1 in 20 Americans will be diagnosed with colon or rectal cancer in his or her lifetime

• In 2017, the estimated number of people diagnosed with colon or rectal cancer in the United States was projected to be about:
  – 71,400 men
  – 64,000 women

• Colon and rectal cancer in both men and women combined is the second leading cause of cancer-related death in the United States. However, death rates have been dropping, especially in the last 10 years. The declines are thought to be due in part to:
  – Increased screening
  – Improved treatment

What is refractory 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.
The role of the caregiver

A caregiver provides more than just care for a patient. A caregiver is many things:
- An advocate
- A friend
- An extra set of hands
- A trusted comfort and guide along the treatment journey

Here are some things you may already do but are good to keep in mind about the caregiver role:
- Educate yourself and stay informed about your loved one’s treatment plan and schedule
- Organize an emergency contact list and a folder for important health resources
- Know your loved one’s limits
- Ensure quality time with your loved one
- Go to check-ups with your loved one. He or she may not make sense of what the healthcare provider says. Listen closely so you can explain later
- Be honest and clear

Listening to your loved one is just as important as talking to him or her. Take what he or she says to heart. You do not need to have all the answers. Simply being an active listener can help your loved one find answers and feel heard.

Please see Important Safety Information on page 13 and full Prescribing Information in pocket.
Caring for yourself

You play a key part in your loved one’s treatment journey. But you are not alone. There are family members, doctors, nurses, an extended care team, and other resources to help you and your loved one through this.

Being a caregiver is not easy. Cancer makes a big impact not only on the patient, but also on those around him or her. It can take an emotional and physical toll.

Sometimes, it is easy to forget about yourself. Your well-being has a direct effect on how well you care for your loved one.

It is important to maintain balance in your life. Find a little part of your day to relax and take care of yourself. Take some time to participate in things you enjoy.

Plan time for:

- **Mental health**: Have coffee with a friend or dinner with your wife, husband, or partner; watch a movie, read a book, or listen to music
- **Physical health**: Get regular exercise, go for a walk, stretch, do yoga, continue with any sports or clubs you are part of. Remember that a few minutes every day can still make a difference
- **Emotional/spiritual health**: Consider meditation, stay in touch with your religious community, and try to appreciate the good things and people in your life

Getting the support you need

You don’t have to take on the entire task of providing care. Don’t be afraid to ask for help. Create a support network. This could be close family or friends.

Plan a schedule for the week and share it with family and friends so they can help. The doctor, nurses, or office staff may help you find a counselor, support group, or other means of support.

You can also find caregiver support online at the websites listed on page 14.
Treatment with LONSURF

LONSURF® (trifluridine and tipiracil) tablets, a prescription medicine, are 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

Help your loved one understand that LONSURF has been proven to help some patients with refractory mCRC live longer.

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

LONSURF is an oral chemotherapy that is 2 medicines in 1:

2→1

• 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

How LONSURF is taken

LONSURF is an oral tablet and comes in 2 strengths: 15-mg and 20-mg tablets.* The healthcare provider may prescribe both strengths for your loved one’s prescribed dose.

Help make sure your loved one is taking LONSURF:
• Twice a day
• After 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 your loved one more prone to infection
  – The type of food does not matter

*Tablet strength of LONSURF is based on 1 active part of the medicine.
LONSURF 28-day dosing schedule

<table>
<thead>
<tr>
<th>Morning dose</th>
<th>Evening dose</th>
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<tr>
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<td>Day 28: Rest</td>
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</tbody>
</table>

The dosing schedule is 5 days a week with 2 days rest for 2 weeks, then no treatment for 2 weeks (14 days). The cycle may be repeated. Always follow the healthcare provider’s directions carefully.

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 medications. 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
- Anyone who handles LONSURF should wash his or her hands afterward. Even though it is a pill, it is still chemotherapy
- You should wear gloves when handling LONSURF
- Note that there is a packet inside the bottle that helps absorb moisture. This material should not be swallowed
- Keep LONSURF out of the reach of children

Contact your loved one’s healthcare provider:

- If your loved one misses a dose of LONSURF. He or she should not take the missed dose. Instead, check with a healthcare provider about how to proceed
- If for some reason your loved one has leftover tablets. You should speak with a healthcare provider or pharmacist about how to dispose of them properly

If your loved one has a LONSURF Starter Kit, use the Treatment Calendar to help keep track of his or her treatment. The nurse may provide a Dosing Schedule as well.
Side effects

A healthcare provider should check your loved one’s blood cell counts before he or she receives LONSURF® (trifluridine and tipiracil) tablets, 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 white blood cells, red blood cells, and platelets. Low white blood cells can make your loved one more likely to get serious infections that could lead to death. A healthcare provider may lower the dose of LONSURF or stop LONSURF if your loved one has low white blood cell or low platelet counts.

- Tell a healthcare provider right away if your loved one develops any signs of infection such as fever, chills, or body aches.

Fever is often the first sign of infection in people with cancer.

You can use the thermometer provided in the Starter Kit to check your loved one’s temperature each day.

Keep an eye out for other signs of infection, like:

- Chills or sweats
- Sore throat
- Cough or shortness of breath
- Burning or pain when urinating

Things to do to help avoid infection:

- Wash hands frequently
- Maintain a balanced diet
- Stay hydrated
- Clean cuts and scrapes in the skin
- Clean the anus with moist towelettes or baby wipes after bowel movements
- Get plenty of sleep

Please see Important Safety Information on page 13 and full Prescribing Information in pocket.
The most common side effects
Almost all patients treated with LONSURF experience side effects at some time. Some patients in a clinical trial had 1 or more of these:

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

Talk to your loved one’s healthcare provider if he or she has nausea, vomiting, or diarrhea that is severe or that does not go away. These are not all of the possible side effects of LONSURF.

You can also 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.
Tips for managing side effects

Your loved one’s healthcare provider may have ways to help manage some of the side effects of LONSURF® (trifluridine and tipiracil) tablets. This could include adjusting your loved one’s treatment plan by changing the dosage or stopping treatment. The following information may also be helpful to you or your loved one in managing some of the side effects of LONSURF while under a healthcare provider’s care; however, these tips may not always work.

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

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Tips for managing</th>
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<tbody>
<tr>
<td>Tiredness</td>
<td>Help your loved one:</td>
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<td></td>
<td>- Set reasonable goals each day and don’t let them overdo it</td>
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<td>- Prioritize important tasks over less important ones</td>
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<td>- Plan time to rest or nap (less than 1 hour). Keeping naps short will help with better sleep at night</td>
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<td></td>
<td>- Stay active. Talk with a healthcare provider about exercise that can help, like going for a 15-minute walk, doing yoga, or riding an exercise bike</td>
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<td>- Get at least 8 hours of sleep each night</td>
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<td>- Establish a bedtime routine. Bathing or listening to relaxing music before bed may help</td>
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<tr>
<td>Nausea and vomiting</td>
<td>Remind your loved one to:</td>
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<td></td>
<td>- Make 5 or 6 small meals a day, instead of 3 big ones (this does not change the dosing schedule)</td>
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<td></td>
<td>- Have food and drinks that are warm or cool instead of hot or cold</td>
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<td></td>
<td>- Choose foods that are easy on the stomach, like saltine crackers or angel food cake</td>
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<td></td>
<td>- Avoid certain foods. Don’t eat greasy, fried, sweet, or spicy foods if you feel sick after eating them</td>
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<td></td>
<td>- Take any medicine a healthcare provider prescribes to help with nausea</td>
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<tr>
<td>Decreased appetite</td>
<td>Remind your loved one to:</td>
</tr>
<tr>
<td></td>
<td>- Make 5 or 6 small meals a day, instead of 3 big ones (this does not change the dosing schedule)</td>
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<tr>
<td></td>
<td>- Have milkshakes, smoothies, juice, or soup instead of solid food</td>
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<td></td>
<td>- Choose foods that are high in calories and/or protein</td>
</tr>
<tr>
<td></td>
<td>- Stay active. Talk with a healthcare provider about exercises that can help, like going for a 15-minute walk</td>
</tr>
<tr>
<td></td>
<td>- Plan some meals with friends and loved ones</td>
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<tr>
<td></td>
<td>- Ask a healthcare provider about seasonings that may help some foods taste better</td>
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<td></td>
<td>- Take note of how much he or she is eating and drinking each day</td>
</tr>
</tbody>
</table>

Please see Important Safety Information on page 13 and full Prescribing Information in pocket.
For diarrhea, encourage your loved one to:
- Make 5 or 6 small meals a day, instead of 3 big ones (this does not change the 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
- Use warm water and a towelette if the rectal area becomes sore, and keep the area dry. Also, ask a healthcare provider about creams that can help
- Take any medicine that a healthcare provider prescribes to help with diarrhea

For abdominal pain, remind your loved one to:
- Eat plenty of foods that are high in fiber such as fruits and vegetables
- Avoid foods that produce gas
- Exercise regularly

Remind your loved one to:
- Drink plenty of liquids, like water, juice, and broth
- Get rest
- Keep cool with light clothing and by sleeping with only a sheet
- Call a healthcare provider immediately if he or she has a fever or other signs of infection such as chills or body aches. Your loved one can use the thermometer provided in the Starter Kit to check his or her temperature each day

Tell your loved one’s healthcare provider if he or she has nausea, vomiting, or diarrhea that is severe or that does not go away.

You or your loved one can also use the LONSURF Treatment Calendar provided in the Starter Kit to track any side effects or other issues. Make sure to bring it to appointments for discussion with a healthcare provider.
Frequently asked questions

How do LONSURF® (trifluridine and tipiracil) tablets work against colon or rectal cancer?
LONSURF is an oral chemotherapy that is 2 medicines in 1.
It 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

What if my loved one or I have a question about LONSURF and the healthcare provider’s office is not available?
Contact our 24-hour call center, where you can get answers to your questions about LONSURF, at 1-844-TAIHO-4U (1-844-824-4648).
Or visit LONSURF.com/caregivers

Where can I get help understanding what costs will be associated with LONSURF treatment and find out about financial assistance?
Taiho Oncology Patient Assistance provides:
• Help with understanding your loved one’s insurance coverage and what payments he or she will be responsible for
• Co-pay assistance
• Financial assistance for uninsured or underinsured patients who qualify

For more information about Taiho Oncology Patient Assistance:
• See the Patient Assistance Brochure
• Call 1-844-TAIHO-4U (1-844-824-4648)
• Go to TaihoPatientSupport.com
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, at day 15 during treatment with 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 or liver 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.
Stay informed and get support

One way you can help your loved one is to stay informed about colon or rectal cancer and the treatments for it. The following organizations can provide you with updated information about colon or rectal cancer as well as resources, advocacy, community, and support.

- **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 fightcolorectalcancer.org  
  or call 1-877-427-2111

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

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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) tablets.

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/caregivers

Please see Important Safety Information on page 13 and full Prescribing Information in pocket.

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Selected Important Safety Information

Low blood counts.

LONSURF can decrease the number of your blood cells. This can sometimes be severe and life-threatening.

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LONSURF is a registered trademark of Taiho Pharmaceutical Co., Ltd., used under license by Taiho Oncology, Inc.
Taiho Oncology Patient Support

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Learn more at LONSURF.com/caregivers

Please see Important Safety Information on page 13 and full Prescribing Information in pocket.
**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

LONSURF (trifluridine and tipiracil) tablets, for oral use

Initial U.S. Approval: 2015

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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)

**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.
- **Administer:** LONSURF within 1 hour after completion of morning and evening meals. (2.1)

**DOSAGE FORMS AND STRENGTHS**

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

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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)

**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)
- **Hepatic Impairment:** Do not initiate LONSURF in patients with baseline moderate or severe hepatic impairment. (8.6)
- **Renal Impairment:** Patients with moderate renal impairment may require dose modifications for increased toxicity. (8.7)

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

Revised: 3/2017

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**FULL PRESCRIBING INFORMATION: CONTENTS**

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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/m\(^2\) up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily within one hour of completion of morning and evening meals on Days 1 through 5 and Days 8 through 12 of each 28-day cycle until disease progression or unacceptable toxicity. Round dose to the nearest 5 mg increment.

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.\(^1\)

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

Do not initiate the cycle of LONSURF until:

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

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

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

After recovery, resume LONSURF after reducing the dose by 5 mg/m\(^2\)/dose from the previous dose level, if the following occur:

- Febrile neutropenia
- Uncomplicated Grade 4 neutropenia (which has recovered to greater than or equal to 1,500/mm\(^3\)) or thrombocytopenia (which has recovered to greater than or equal to 75,000/mm\(^3\)) that results in more than 1 week delay in start of next cycle
- Non-hematologic Grade 3 or Grade 4 adverse reaction except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication
A maximum of 3 dose reductions are permitted 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 %</td>
<td>3 %</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia ‡</td>
<td>77</td>
<td>18</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>67</td>
<td>27</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>42</td>
<td>5</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-treated patients (2%) compared to no patients on placebo.

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

8  USE IN SPECIFIC POPULATIONS

8.1  Pregnancy

Risk Summary
Based on animal data and its mechanism of action, LONSURF can cause fetal harm. LONSURF caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to exposures at the recommended dose in humans. [see Data] There are no available data on LONSURF exposure in pregnant women. Advise pregnant women of the potential risk to a fetus.
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

**Data**

**Animal Data**

Trifluridine/tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50, and 150 mg/kg [trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/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) embryolethality 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

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

8.7 Renal Impairment

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

In Study 1, patients with moderate renal impairment (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 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. Patients with severe renal impairment (CLcr < 30 mL/min) were not studied. [see Clinical Pharmacology (12.3)]
8.8 Ethnicity

There were no clinically meaningful differences in Study 1 between Western and Asian subgroups with respect to overall incidence of adverse events or ≥ 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 C$_9$H$_{11}$ClN$_4$O$_2$•HCl and a molecular weight of 279.12. Tipiracil hydrochloride is a white crystalline powder, soluble in water, 0.01 mol/L hydrochloric acid, and 0.01 mol/L sodium hydroxide; slightly soluble in methanol; very slightly soluble in ethanol; and practically insoluble in acetonitrile, 2-propanol, acetone, diisopropyl ether, and diethyl ether.

**LONSURF 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 AUC₀₋ₐₙₙ₆ₜ and 2-fold for peak plasma concentration (Cₘₐₓ) 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 AUC₀₋ₐₙ₆ₜ of trifluridine by 37-fold and Cₘₐₓ 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 (Tₘₐₓ) of trifluridine was around 2 hours.

A standardized high-fat, high-calorie meal decreased trifluridine Cₘₐₓ, tipiracil Cₘₐₓ 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 Cₘₐₓ of trifluridine and the decrease in neutrophil counts.

Distribution

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

Elimination

Metabolism

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

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

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

Specific Populations

Age, Sex, and Race

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

Renal Impairment

In Study 1, the estimated mean AUC of trifluridine at steady state was 31% higher in patients with mild renal impairment (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 a pharmacokinetic trial of patients with hepatic impairment, no clinically important differences in the mean exposures of trifluridine and tipiracil were observed between patients with mild hepatic impairment (total bilirubin less than or equal to the ULN and AST greater than ULN or total bilirubin less than 1 to 1.5 times ULN and any AST) to moderate hepatic impairment (total bilirubin greater than 1.5 to 3 times ULN and any AST) and patients with normal hepatic function (total bilirubin and AST less than or equal to the ULN). Five of 6 patients with moderate hepatic impairment experienced Grade 3 or 4 increased bilirubin levels and patients with severe hepatic impairment were not studied. [see Dose Modifications (2.2), Use in Specific Populations (8.6)]

Drug Interaction Studies

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

In vitro studies indicated that trifluridine, tipiracil, and FTY did not inhibit the CYP enzymes and had no inductive effect on CYP1A2, CYP2B6, or CYP3A4/5.
In vitro studies indicated that trifluridine was not an inhibitor of or substrate for human uptake and efflux transporters.

13  NONCLINICAL TOXICOLOGY

13.1  Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

14  CLINICAL STUDIES

14.1  Colorectal Cancer

Study 1

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

A total of 800 patients were randomized 2:1 to receive LONSURF (N=534) plus best supportive care (BSC) or matching placebo (N=266) plus BSC. Randomization was stratified by KRAS status (wild-type vs. mutant), time since diagnosis of first metastasis (<18 months vs. ≥ 18 months), and region (Japan vs. US, Europe and Australia). Key eligibility criteria included prior treatment with at least 2 lines of standard chemotherapy for metastatic CRC, ECOG 0-1, absence of brain metastasis, and absence of ascites requiring drainage in the past four weeks. Patients received 35 mg/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>Table 3</th>
<th>Efficacy Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LONSURF (N=534)</td>
</tr>
<tr>
<td>Overall Survival</td>
<td></td>
</tr>
<tr>
<td>Number of deaths, N (%)</td>
<td>364 (68)</td>
</tr>
<tr>
<td>Median OS (months)(^a) [95% CI](^b)</td>
<td>7.1 [6.5, 7.8]</td>
</tr>
<tr>
<td>Hazard ratio [95% CI]</td>
<td>0.68 [0.58, 0.81]</td>
</tr>
<tr>
<td>P-value(^c)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression-Free Survival</td>
<td></td>
</tr>
<tr>
<td>Number of Progression or Death, N (%)</td>
<td>472 (88)</td>
</tr>
<tr>
<td>Hazard ratio [95% CI]</td>
<td>0.47 (0.40, 0.55)</td>
</tr>
<tr>
<td>P-value(^c)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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