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 pages 18 and 19 and full Prescribing Information in pocket.
# Table of Contents

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## About LONSURF® (trifluridine and tipiracil) tablets

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Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
You have been through a lot since your colon or rectal cancer diagnosis. You have had a number of treatments, experienced certain side effects, and dealt with a whole range of emotions. Hearing the news that a treatment has stopped working is never easy—but LONSURF® (trifluridine and tipiracil) tablets offer you another treatment option.

**LONSURF is for those**

- 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

It may give you the chance to journey longer alongside your family, friends, and loved ones.

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

This booklet can help you and your caregiver(s) make the most of your new treatment plan with LONSURF. In the following pages, you will find information about helpful resources and places to go for treatment, financial, and emotional support services. Note that **bold purple words** are defined in the glossary, which begins on page 48. The glossary also includes other terms that you may hear while on treatment.

The information in this booklet is not a substitute for your healthcare provider’s advice. Always ask your healthcare provider any questions you may have about LONSURF and colon or rectal cancer.

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### Fast facts

**You have likely read a lot about colon or rectal cancer since you were diagnosed.**

As you may have already discovered, colon and rectal cancers combined are the third most common cancers in men and women.

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

In 2017, about 71,400 men and 64,000 women in the United States were projected to be diagnosed with colon or rectal cancer.

**What is refractory metastatic colon or rectal cancer (mCRC)?**

**Refractory** means that the cancer has continued to grow despite treatment. The cancer may be resistant in the beginning of treatment or it may become resistant during treatment.

**Metastatic** means that the cancer has spread to other parts of the body.
You can learn more about colon or rectal cancer through these organizations:

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

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

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

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

Trademarks, registered or otherwise, are the property of their respective owners.

For more information about these organizations, please see pages 37 and 38 of this booklet.

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
LONSURF® (trifluridine and tipiracil) tablets are a prescription medicine for refractory mCRC.

LONSURF is an oral tablet, which means it is taken by mouth. It is a prescription chemotherapy tablet that is made up of 2 parts. (These parts are explained on page 10.)

LONSURF offers you a chance to continue treating your cancer. It may help you live longer and slow or stop the growth of your cancer for a period of time.

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

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

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

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

LONSURF is used to treat those with colon or rectal cancer that has spread to other parts of the body and who have been previously treated with or cannot take certain chemotherapy medicines.

Those previous medicines may include
- **Fluoropyrimidine**: Such as 5-fluorouracil, also known as 5-FU
- **Oxaliplatin-based treatment**: Such as FOLFOX (5-FU, leucovorin, and oxaliplatin); CAPOX (capecitabine and oxaliplatin); or Eloxatin® (oxaliplatin)
- **Irinotecan-based treatment**: Such as FOLFIRI (5-FU, leucovorin, and irinotecan); CAPIRI (capecitabine and irinotecan); or Camptosar® (irinotecan)
- **Anti-VEGF biological therapy, or VEGF inhibitors**: Such as Avastin® (bevacizumab) or Zaltrap® (ziv-afibercept)
- **Anti-EGFR therapy, or EGFR inhibitors** (if you have the **KRAS wild type gene**): Such as Erbitux® (cetuximab); or Vectibix® (panitumumab)

If you aren’t sure what treatments you’ve had in the past, ask your healthcare provider.

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Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
LONSURF® (trifluridine and tipiracil) tablets work in a different way than other treatments for colon or rectal cancer. That is why it may still help people for whom other treatments have stopped working.

LONSURF is the first FDA-approved combination tablet for refractory mCRC. It is an oral chemotherapy that is 2 medicines in 1. With the 2 medicines working together, LONSURF may help stop cancer cell growth (see diagram below).

- One part (A) helps the other part (B) stay active and work properly
  - Without A, B would break down
- The second part (B) stops cells from making copies of themselves. This may help stop tumors from growing

### How it works

**B alone**

- B breaks down

**A + B**

- A prevents breakdown of B
- B inhibits cancer cell growth

### What to expect

**How can LONSURF help me?**

LONSURF has been proven to

- Allow some patients with refractory mCRC to live longer
- Slow or stop the growth of cancer for a period of time

Like all medicines approved by the FDA, LONSURF was studied in clinical trials. The clinical trial in which LONSURF was studied included 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

Some people in the trial lived longer than others. It is difficult to say exactly how much LONSURF may help extend a particular person’s life, because everyone is different.

FDA=Food and Drug Administration.

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
What to expect (continued)

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

Your healthcare provider should check your blood cell counts before you receive LONSURF® (trifluridine and tipiracil) tablets, at day 15 of each treatment cycle, 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. Remember, 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.

For information about managing side effects, please see pages 20 to 30.

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
How to take it

LONSURF® (trifluridine and tipiracil) tablets are taken
  • Twice a day
  • After you eat breakfast and dinner (immediately after or up to 1 hour after)
    – The type of food does not matter

Your LONSURF dose is calculated based on your body surface area, or BSA. This is based on your height and weight. The higher your BSA, the higher your LONSURF dose will be. If you have any questions about your BSA or LONSURF dose, ask your healthcare provider.

LONSURF comes in 2 strengths: 15-mg and 20-mg tablets.* Your healthcare provider may prescribe both strengths for your prescribed dose based on your BSA. It is important you take your medication exactly as prescribed.

15-mg tablet 20-mg tablet

Why is it important to take LONSURF after morning and evening meals?

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 you eat does not affect LONSURF. Just be sure to take your dose immediately after or up to 1 hour after meals.

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.

LONSURF 28-day dosing schedule

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). That is 1 cycle.

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

Use the Treatment Calendar provided in the LONSURF Starter Kit or the Online Treatment Calendar to keep track of your treatment. Then bring it with you to your appointments to discuss any side effects you may have experienced.
How to take it (continued)

Other things to keep in mind about taking LONSURF

• Store LONSURF® (trifluridine and tipiracil) tablets 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
• Wash your hands after handling LONSURF. Even though it is a tablet, 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
• You have nausea, vomiting, or diarrhea that is severe or that does not go away
• You develop any signs of infection such as fever, chills, or body aches

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
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.

Important Safety Information

LONSURF® (trifluridine and tipiracil) tablets 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

Please see full Prescribing Information in pocket.
Managing side effects

Your healthcare provider may have ways to help manage some of the side effects of LONSURF® (trifluridine and tipiracil) tablets. 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.

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.

Tiredness

52% of patients taking LONSURF in the clinical trial reported tiredness compared with 35% of patients not taking LONSURF.

Many people describe tiredness as feeling weak, worn out, heavy, or slow.

Use the Treatment Calendar provided in the LONSURF Starter Kit or the Online Treatment Calendar to keep track of how often you have tiredness. Then bring it with you to your appointments.

SOME TIPS TO HELP MANAGE TIREDNESS

- Do the things that are most important first each day. Don’t overdo it
- Take time to rest
- Take naps that are less than 1 hour. Keeping naps short will help you sleep at night
- Try to be active each day. Talk with your healthcare provider about exercise that can help, like going for a 15-minute walk, doing yoga, or riding an exercise bike
- Make a bedtime routine. Bathing, reading, listening to music, or meditating before you go to bed may help you relax
- Try to sleep at least 8 hours each night
- Ask family members and friends for help with chores, driving to your appointments, shopping, and cooking
- Talk with your healthcare provider. He or she may prescribe medication that can help decrease tiredness

SOME TIPS FOR EATING WHEN YOU HAVE TIREDNESS

- Eat a healthy diet. Consider eating 5 or 6 small meals a day instead of 3 big ones (this does not change your dosing schedule)
- Keep foods on hand that are easy to prepare, such as
  - Canned soups
  - Frozen meals
  - Yogurt
  - Cottage cheese
- Drink plenty of fluids each day—about 8 cups

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
Managing side effects  (continued)

**Nausea and vomiting**

48% of patients taking LONSURF® (trifluridine and tipiracil) tablets in the clinical trial reported nausea (feeling sick or queasy) compared with 24% of patients not taking LONSURF. In addition, 28% of patients taking LONSURF in the clinical trial reported vomiting compared with 14% of patients not taking LONSURF.

**SOME TIPS TO HELP MANAGE NAUSEA AND/OR VOMITING**

- A good way to prevent vomiting is to first prevent nausea. It may help to avoid certain foods. Don’t eat greasy, fried, sweet, or spicy foods if you feel sick after eating them.
- Choose foods that are easy on the stomach, like saltine crackers or angel food cake. See the table on the next page for some ideas.
- Eat 5 or 6 small meals a day instead of 3 big ones (this does not change your dosing schedule).
- Do not drink a lot before or during meals.
- Do not lie down right after you eat.
- Have foods and drinks that are warm instead of hot and cool instead of cold.
- Stay away from foods and drinks with strong smells.
- Try small bites of popsicles or fruit ices. You can see if sucking on ice cubes helps (stop if the cold temperature bothers you).
- Try sugar-free mints or tart candies.
- If you feel like vomiting, breathe deeply and slowly. Try to get fresh air.
- Talk with your healthcare provider, who may prescribe something to help. You can also ask your healthcare provider about acupuncture.

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**SOME FOODS AND DRINKS THAT ARE EASY ON THE STOMACH**

**Drinks**
- Clear carbonated beverages that have lost their fizz
- Cranberry or grape juice
- Fruit punch
- Tea
- Fruit-flavored drinks
- Sports drinks
- Water

**Sweets**
- Canned fruit like applesauce, peaches, and pears
- Angel food cake
- Popsicles
- Yogurt (plain or vanilla)
- Gelatin
- Sherbet or sorbet

**Staples**
- Chicken (broiled or baked without skin)
- Cream of rice
- Noodles
- Pretzels
- White rice
- Instant oatmeal
- Potatoes (boiled without skins)
- Saltine crackers
- White toast

**Soups**
- Clear chicken, beef, or vegetable broth

Use the Treatment Calendar provided in the LONSURF Starter Kit or the Online Treatment Calendar to keep track of how often you vomit or experience nausea. Then bring it with you to your appointments.

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

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
Managing side effects (continued)

Decreased appetite

39% of patients taking LONSURF® (trifluridine and tipiracil) tablets in the clinical trial reported a decrease in appetite compared with 29% of patients not taking LONSURF.

It is important to keep eating a healthy diet even when you have no appetite. That means eating and drinking plenty of protein, vitamins, and calories. This will help your body fight infection and repair tissues. Not eating well can lead to weight loss, weakness, and tiredness.

SOME TIPS TO HELP MANAGE DECREASED APPETITE

• Eat 5 or 6 small meals each day instead of 3 big ones (this does not change your dosing schedule)
• Choose foods or drinks high in calories and/or protein. See the table on the next page for some suggestions
• Set a daily schedule for eating meals and snacks. Eat when it’s time, not only when you feel hungry
• Being active may help you feel hungrier. Talk with your healthcare provider about exercises that can help, like going for a 15-minute walk
• Be careful not to drink too much liquid before or during meals
• Try to make meals more fun. Eat in a different room than usual. Plan to eat with a friend or family member. Listen to music or watch TV while you eat. Try new foods, drinks, and recipes
• Talk with your healthcare provider, who may suggest that you take extra vitamins or supplements

Use the Treatment Calendar provided in the LONSURF Starter Kit or the Online Treatment Calendar to keep track of how often and when you experience decreased appetite. Then bring it with you to your appointments.

SOME HIGH-CALORIE/HIGH-PROTEIN FOODS AND DRINKS

<table>
<thead>
<tr>
<th>Drinks</th>
<th>Staples</th>
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</thead>
<tbody>
<tr>
<td>• Instant breakfast drinks</td>
<td>• Beef</td>
</tr>
<tr>
<td>• Smoothies</td>
<td>• Butter, margarine, or oil added to your food</td>
</tr>
<tr>
<td>• Milkshakes</td>
<td>• Deviled ham</td>
</tr>
<tr>
<td>• Whole milk</td>
<td>• Eggs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Soups</th>
<th>Fish</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cream soups</td>
<td>• Cottage cheese</td>
</tr>
<tr>
<td>• Soups with lentils, peas, or beans</td>
<td>• Cream cheese</td>
</tr>
<tr>
<td>• Cream soups</td>
<td>• Croissants</td>
</tr>
<tr>
<td>• Soups with lentils, peas, or beans</td>
<td>• Nuts, seeds, and wheat germ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sweets</th>
<th>Cheese</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Custards</td>
<td>• Chicken</td>
</tr>
<tr>
<td>• Ice cream</td>
<td>• Cooked peas and beans</td>
</tr>
<tr>
<td>• Pudding</td>
<td>• Peanut butter</td>
</tr>
<tr>
<td>• Frozen yogurt</td>
<td>• Sour cream</td>
</tr>
<tr>
<td>• Muffins</td>
<td></td>
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<tr>
<td>• Yogurt (plain or vanilla)</td>
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<table>
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<tr>
<th>Replacements and supplements</th>
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</thead>
<tbody>
<tr>
<td>• Liquid meal replacements</td>
<td></td>
</tr>
<tr>
<td>• Powdered milk added to foods like pudding, milkshakes, and scrambled eggs</td>
<td></td>
</tr>
</tbody>
</table>

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
Managing side effects (continued)

Diarrhea

32% of patients taking LONSURF® (trifluridine and tipiracil) tablets in the clinical trial reported experiencing diarrhea compared with 12% of patients not taking LONSURF.

As you may know, diarrhea means frequent bowel movements that may be soft, loose, or watery.

SOME TIPS TO HELP MANAGE DIARRHEA

• Eat 5 or 6 small meals each day instead of 3 big ones (this does not change your dosing schedule)
• Ask your healthcare provider about foods high in sodium and potassium. Because your body can lose these minerals when you have diarrhea, it is important to replace them. Foods that are high in sodium and potassium include bananas, oranges, peach and apricot nectar, and boiled or mashed potatoes
• Eat low-fiber foods. See the table on the next page for some suggestions. High-fiber foods can make diarrhea worse
• Drink 8 to 12 cups of clear liquids each day
• Drink liquids at room temperature slowly
• Talk with your healthcare provider, who may prescribe medicine to help. Do not take any medicine without discussing it beforehand

Use the Treatment Calendar provided in the LONSURF Starter Kit or the Online Treatment Calendar to keep track of how often you experience diarrhea. Then bring it with you to your appointments.

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

SOME RECOMMENDED FOODS WHEN YOU HAVE DIARRHEA

LOW-FIBER FOODS

Staples
• Skinless chicken or turkey
• Potatoes (baked or mashed without the skin)
• Cottage cheese
• Fish
• White bread
• Eggs
• Noodles
• White rice
• Cooked, refined cereals

Fruits and vegetables
• Canned fruit like applesauce, peaches, and pears
• Asparagus
• Bananas
• Clear fruit juice
• Vegetable juice

Snacks
• Angel food cake
• Sherbet or sorbet
• Saltine crackers
• Yogurt (plain or vanilla)

CLEAR LIQUIDS

Drinks
• Clear apple juice
• Clear carbonated beverages
• Fruit-flavored drinks
• Fruit juice, including cranberry or grape
• Fruit punch
• Sports drinks
• Tea with no caffeine
• Water

Soups
• Bouillon
• Clear, fat-free broth
• Consommé

Sweets
• Fruit ices made without fruit pieces or milk
• Honey
• Popsicles
• Jelly
• Gelatin

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
Managing side effects (continued)

Fever

19% of patients taking LONSURF® (trifluridine and tipiracil) tablets in the clinical trial reported having a fever compared with 14% of patients not taking LONSURF. Call a healthcare provider immediately if you have a fever or other signs of infection such as chills or body aches.

**SOME TIPS TO HELP MANAGE FEVER**

- Do not take aspirin, acetaminophen, ibuprofen products, or any other drugs that reduce fever without first talking with your healthcare provider.
- Keep cool when experiencing a fever by dressing in light clothing and sleeping with only a sheet.
- Rest.
- Drink plenty of liquids, like water, juice, and broth because a fever can cause fluid loss and dehydration.

Use the Treatment Calendar provided in the LONSURF Starter Kit or the Online Treatment Calendar to keep track of how often and when you experience a fever. Then bring it with you to your appointments.

Call a healthcare provider right away 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.

Abdominal pain

21% of patients taking LONSURF in the clinical trial reported abdominal pain compared with 18% of patients not taking LONSURF. This is also called stomach pain.

**SOME TIPS TO HELP MANAGE ABDOMINAL PAIN**

- Exercise regularly.
- Try deep breathing, yoga, or other ways to relax. This can help with muscle tension, anxiety, and pain.
- Eat plenty of foods that are high in fiber such as fruits and vegetables.
- Avoid foods that produce gas.
- Let your caregiver know about your pain so he or she can try and help.
- Take any medicine your healthcare provider prescribes for pain.

Talk to your healthcare provider about your pain. Be specific. Think of answers to these questions to help him or her understand your pain:

- Is it a sharp or dull pain?
- Is it constant or throbbing?
- How strong is it on a scale of 1 to 10?
- How long does it last?
- Does it change over time?

Use the Treatment Calendar provided in the LONSURF Starter Kit or the Online Treatment Calendar to keep track of how often you experience abdominal pain. Then bring it with you to your appointments.
27% of patients taking LONSURF® (trifluridine and tipiracil) tablets in the clinical trial reported having an infection compared with 15% of patients not taking LONSURF.

Your healthcare provider should check your blood cell counts before you receive LONSURF, at day 15 of each treatment cycle, 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.

**SOME GENERAL INFECTION TIPS**

Your healthcare provider may offer general health tips regarding infection that may apply to some patients. These tips may include:

• Wash your hands often with soap and water. Be sure to wash your hands before cooking and eating, and after using the bathroom, blowing your nose, coughing, sneezing, or touching animals.

• Use sanitizing wipes to clean surfaces that you need to touch. This is especially true in public places for things like ATMs, doorknobs, and subway and bus handles.

• Be careful not to cut yourself. Use an electric razor. Be extra careful with knives and scissors.

• Clean cuts right away with warm water, soap, and an antiseptic.

Call a healthcare provider right away if you develop any signs of infection such as fever, chills, or body aches.

**Potential treatment changes**

During your treatment with LONSURF, your healthcare provider may need to change your treatment plan. These changes are often made to help address certain side effects.

**Why would my healthcare provider change my LONSURF treatment plan?**

Your healthcare provider may change your LONSURF treatment plan if you have a decrease in your white blood cells, red blood cells, or platelets, or if you experience certain other serious side effects.

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.

Keep track of any side effects you may experience in the Treatment Calendar included in your LONSURF Starter Kit and bring it with you to your appointments.

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

**How could my healthcare provider change my LONSURF treatment plan?**

There are 3 ways your healthcare provider may change your treatment plan. In each case, your healthcare provider may first stop your treatment.

Stopping your treatment is an important step your healthcare provider may take before deciding whether to:

1. **Restart your LONSURF treatment at the same dose.**

2. **Restart your LONSURF treatment at a lower dose.**

3. **Stop your LONSURF treatment permanently.**

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
Potential treatment changes (continued)

How common is it to experience a change in my treatment plan?

The rates below represent how common each type of treatment change was in the clinical trial in which LONSURF® (trifluridine and tipiracil) tablets were studied. Treatment changes were used to help address certain side effects.

- 53% of patients had their treatment stopped and then restarted at the same dose.
- 14% of patients had their treatment stopped and then restarted at a lower dose.
- 4% of patients had their treatment stopped permanently.

Although experiencing a change in your treatment plan may feel overwhelming, remember that it is not uncommon. If you receive a change in your treatment plan and would like to know more, don’t hesitate to ask your healthcare provider about it. Always follow their instructions carefully.

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
The LONSURF Starter Kit is meant to help you get the most out of your treatment. The materials provided are not meant to replace your healthcare provider’s advice. Always speak with your healthcare provider about any questions or concerns you have. Together, you and your healthcare provider can develop a personalized treatment plan based on your needs.

The LONSURF Starter Kit includes the following items:

- **LONSURF Treatment Companion:** Contains helpful information you and your caregiver should know about mCRC and LONSURF, including how to obtain treatment and financial support and ways to help manage common side effects while taking LONSURF
- **Treatment Calendar (pen included):** Provides a place to record how you are feeling each day. You can take it to your appointments to help you remember what you want to discuss
- **LONSURF Offerings Flashcard:** Describes just a few of the helpful online resources available to you and your caregiver during your treatment journey with LONSURF
- **LONSURF Pillboxes:** Are designed to help you organize your medicine. One pillbox is for the first week of every treatment cycle (days 1 to 7), and the other is for the second week of every treatment cycle (days 8 to 14)
- **Carrying Case:** Can help you keep your LONSURF materials in 1 place—whether you’re at home, at your appointments, or anywhere else
- **Thermometer:** To check your temperature regularly

You can learn more about all the services offered by Taiho Oncology at TaihoPatientSupport.com/assistance.

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Taiho Oncology Patient Support

At Taiho Oncology Inc., we understand that you are going through a lot living with refractory mCRC. Taiho Oncology is committed to partnering with your healthcare provider to help you

- With any financial challenges you are facing in getting your medicine
- Take your medicine exactly as instructed by your healthcare provider

Taiho Oncology Patient Support is tailored to your needs

- User-friendly
- Informative
- Flexible

This program offers

- Financial support services
  - Help with understanding your insurance coverage and what payments you will be responsible for
  - Help with applying for alternative coverage and reimbursement
  - Co-pay assistance for patients who qualify
  - Financial assistance for uninsured or underinsured patients who qualify
- Treatment support services
  - 24-hour hotline for any questions you have about LONSURF® (trifluridine and tipiracil) tablets, including side effects, what to expect on treatment, and your treatment schedule

For questions about support program enrollment, call 1-844-TAIHO-4U (1-844-824-4648) or visit TaihoPatientSupport.com.

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
Online resources

LONSURF Video

This video discusses the importance of taking LONSURF® (trifluridine and tipiracil) tablets exactly the way your healthcare provider prescribed it and tips for taking it correctly.

Tips for Taking Your Medicine as Prescribed

You can watch the video at LONSURF.com/video

Online Treatment Calendar

This tool is a simple way to generate a personalized treatment calendar.

On the website, input your treatment start date. Then the calendar will fill in and show which days you should and should not take LONSURF. Your healthcare provider will advise you of any changes to this schedule. You can print out the calendar and keep it on your refrigerator or another place where you will see it each day. You can also view it on your computer or mobile device.

Create your Treatment Calendar now at LONSURF.com/calendar

Advocacy groups

Patient advocacy groups can
• Help you find support groups in your area
• Assist you in finding financial support resources
• Keep you up to date about colon or rectal cancer and its treatments
• Provide patients with a voice in cancer research and policy

Here are groups you may find helpful

CancerCare®
CancerCare is a national organization providing free, professional support services and information to help people manage the emotional, practical, and financial challenges of cancer. Comprehensive services include counseling and support groups over the phone, online, and in-person, educational workshops, publications, and financial and co-payment assistance. All services are provided by oncology social workers and world-leading cancer experts, free of charge.

Learn more at cancercare.org or by calling 1-800-813-HOPE (4673).

Fight Colorectal Cancer
Fight Colorectal Cancer envisions victory over colon and rectal cancers. We raise our voice to empower and activate a community of patients, fighters, and champions to push for better policies and to support research, education, and awareness for all those touched by this disease.

Learn more at fightcolorectalcancer.org or by calling 1-877-427-2111.
Advocacy groups (continued)

Cancer Support Community (CSC)
CSC is an international nonprofit dedicated to providing support, education, and hope to people affected by cancer. Likely the largest employer of psychosocial oncology mental health professionals in the United States, CSC offers a menu of personalized services and education for all people affected by cancer. Its global network brings the highest quality cancer support to the millions of people touched by cancer. These support services are available through a network of professionally led community-based centers, hospitals, community oncology practices, and online, so that no one has to face cancer alone.

Learn more at cancersupportcommunity.org or by calling 1-888-793-9355.

Colon Cancer Alliance
The Colon Cancer Alliance, Inc., is the largest and oldest national nonprofit patient advocacy organization dedicated to increasing screening rates and survivorship. The mission is to knock colon cancer out of the top 3 cancer killers by championing prevention, funding cutting-edge research, and providing the highest quality patient support services, including grants to help pay for treatment-related costs.

Learn more at ccalliance.org or by calling 1-877-422-2030.
Coping with advanced colon or rectal cancer

SOME HELPFUL WAYS TO COPE

Recognize that you have been through a lot
You have had to face the diagnosis of advanced colon or rectal cancer, learning that the cancer has spread to other parts of your body despite going through a number of treatments and likely suffering from side effects.

There’s no right or wrong way to feel
Having advanced cancer can bring anxiety and uncertainty to your life, and you may be grieving that your life has gone a different way than you had hoped. It’s natural to have ups and downs and all kinds of emotions, but remember that your family and friends can provide a strong support system for you.

You are not alone
Talk about your feelings with someone you trust. Choose someone who can focus on you, such as a close friend, family member, chaplain, nurse, or social worker.

You may also find it helpful to talk with someone else who is getting chemotherapy or join a support group where you can meet others going through the same experiences.

Reminders for staying positive
• You are still in control of your choices
• You can still have hope and joy in your life
• You can strive for comfort, peace, and acceptance of yourself as you are
• It is impossible to predict exactly how long someone will live. Some people live much longer than expected. Others live a shorter time. The best anyone can do is to try and live fully each day

Tips from others with advanced cancer
• Strive to keep doing things you enjoy
• Find small things in life to appreciate
• Set dates and events to look forward to
• Hear other people’s stories online and in support groups

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
Tips for your appointments

HOW TO COME PREPARED

Write down questions for your healthcare provider and bring them with you.
Write down your questions when you think of them. You can use your Treatment Calendar provided in the LONSURF® (trifluridine and tipiracil) tablets Starter Kit, the online Treatment Calendar, the journal in the back of this booklet, or another diary or piece of paper. Bring your notes with you to your appointments. That way, you have a reminder of your questions.

Keep a record of any side effects.
Note when they occur. You can use the Treatment Calendar provided in your LONSURF Starter Kit and bring it with you to your appointments so your healthcare provider can help manage certain side effects.

Bring any health insurance information or other disease or treatment information.
You can use the zipper pocket in the back of this booklet, your LONSURF Carrying Case, or a folder to keep these all in one place.

HOW TO GET THE MOST OUT OF YOUR APPOINTMENTS

Don’t feel like you have to go to your appointments alone.
Bring your caregiver, a family member, or a trusted friend with you to your appointments. He or she can help you remember what your healthcare provider says and can be there to serve as your support system.

Take notes at your appointments.
You can do this or your caregiver, family member, or friend can do it for you. You can use the journal in the back of this booklet.

Get your healthcare provider’s contact information.
Be sure you have phone numbers or e-mail addresses for follow-up questions. You can write them at the end of this booklet in the journal provided.

Plan ahead for an emergency.
Ask your healthcare provider what to do in an emergency, including:
• Who to contact during office hours and off-hours
• How to reach them
• Where to go

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
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 source of comfort and guidance 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. You can use the space provided in the back of this booklet
• Keep a folder for important health resources. You can use the pocket in the back of this booklet
• Go to appointments with your loved one, who may not understand what his or her healthcare provider says. Listen closely so you can explain later
• Know your loved one’s limits
• Ensure quality time with your loved one
• 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. By simply being an active listener, you can help your loved one find answers and feel heard.

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
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. There are family members, healthcare providers, an extended care team, and other resources to help you and your loved one through this.

Plan a schedule for the week and share it with family and friends so they can help.

Ask your loved one’s healthcare provider to help you find a counselor, support group, or other means of support.

You can also find caregiver support online at the following websites.

- **CancerCare**:
  Go to [cancercare.org/tagged/caregiving](http://cancercare.org/tagged/caregiving) or call 1-800-813-HOPE (4673)

- **Cancer Support Community (CSC)**:
  Go to [cancersupportcommunity.org/MainMenu/Family-Friends](http://cancersupportcommunity.org/MainMenu/Family-Friends) or call 1-888-793-9355

- **Colon Cancer Alliance**:
  Go to [ccalliance.org/friends](http://ccalliance.org/friends) or call 1-877-422-2030

Read the rest of this booklet to learn more about your loved one’s treatment with LONSURF® (trifluridine and tipiracil) tablets. The “Managing side effects” section on pages 20 to 30 can help you address some of the common side effects your loved one may experience. **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.

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You can find more information and support at LONSURF.com/caregivers.

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Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
Colony-stimulating factor (KAH-luh-nee-STIM-yoo-LAY-ting FAK-ter)
A substance that stimulates the production of blood cells. Colony-stimulating factors include granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), and promegapoietin.

Comorbidity (koh-mor-BIH-dih-tee)
The condition of having 2 or more diseases at the same time.

Control group (kun-TROLE groop)
In a clinical trial, the group that does not receive the new treatment being studied. This group is compared with the group that receives the new treatment in order to see if the new treatment works.

Cycle (SY-kul)
In medicine, a course of treatment is repeated on a regular schedule with periods of rest in between. For example, treatment given for 2 weeks followed by 2 weeks of rest is 1 cycle of LONSURF. Also called treatment cycle.

Diarrhea (dy-uh-REE-uh)
Frequent and watery bowel movements.

Disease progression (dih-ZEEZ pruh-GREH-shun)
When cancer continues to grow or spread.

Dose (dose)
The amount of medicine taken at 1 time.

EGFR (EE-jee-eff-are)
EGFR is a protein found on the surface of some normal cells and is involved in cell growth. It may also be found at high levels on some types of cancer cells and helps these cells to grow and divide. Blocking EGFR may help stop cancer cells from growing. Some EGFR inhibitors (also known as anti-EGFR therapies) are used to treat cancer.

Febrile neutropenia (FEH-brile noo-troh-PEE-nee-uh)
A condition marked by fever and a lower-than-normal number of neutrophils in the blood. A neutrophil is a type of white blood cell that helps fight infection. Not having enough neutrophils increases the risk of infection.

Fluoropyrimidine (FLOOR-oh-py-RIH-mih-deen)
One of a group of substances used to treat cancer. Examples are capecitabine, floxuridine, and 5-fluorouracil (5-FU).
**Glossary (continued)**

**Gene** (jeen)  
The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA. Most genes contain the information for making a specific protein.

**Hand-foot syndrome** (hand foot SIN-drome)  
A condition marked by pain, swelling, numbness, tingling, or redness of the hands or feet. It sometimes occurs as a side effect of certain anticancer drugs. Also called palmar-plantar erythrodysesthesia.

**Inhibitor** (in-HIH-bih-ter)  
A substance that blocks the activity of a protein, such as EGFR or VEGF.

**Irinotecan** (I-rih-noh-TEE-kan)  
The active ingredient in a drug used alone or with other drugs to treat colon or rectal cancer that has spread to other parts of the body or has come back after treatment with S-fluorouracil. It is also being studied in the treatment of other types of cancer. Irinotecan blocks certain molecules needed for cell division and DNA repair, and it may kill cancer cells.

**KRAS gene** (K-ras jeen)  
A gene that may cause cancer when it is mutated (changed). The KRAS gene makes the KRAS protein, which is involved in cell-signaling pathways, cell growth, and cell death. Agents that block the activity of the mutated KRAS gene or its protein may stop the growth of cancer.

**KRAS wild type gene** (K-ras WY-uld type jeen)  
A KRAS gene that has not been mutated (changed). People who have the KRAS wild type gene are more likely to respond to treatment with an anti-EGFR therapy, or EGFR inhibitor.

**Median overall survival** (MEE-dee-un oh-ver-AWL ser-VY-vul)  
The length of time, starting from either the date of diagnosis or the start of treatment for a disease, during which half of the patients in a group of patients diagnosed with the disease are still alive. In a clinical trial, measuring the median overall survival is 1 way to see how well a new treatment works. Also called median survival.

**Oxaliplatin** (ok-SA-lih-pla-tin)  
A drug used with other drugs to treat colon or rectal cancer that is advanced or has come back. It is also being studied in the treatment of other types of cancer. Oxaliplatin attaches to DNA in cells and may kill cancer cells. Also called Eloxatin® (oxaliplatin).

**Palliative care** (PA-lee-uh-tiv kayr)  
Care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal of palliative care is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment. Also called comfort care, supportive care, and symptom management.

**Performance status** (per-FOR-munts STA-tus)  
A measure of how well a patient is able to perform ordinary tasks and carry out daily activities.

**Platelet** (PLAY-let)  
A tiny piece of blood cell that is made by breaking off of a large cell in the bone marrow. Platelets are found in the blood and spleen. They help form blood clots to slow or stop bleeding and to help wounds heal. Also called thrombocyte.

**Progression-free survival** (pruh-GREH-shun free ser-VY-vul)  
The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works. Also called PFS.

**Protein** (PROH-teen)  
A molecule made up of amino acids. Proteins are needed for the body to function properly. They are the basis of body structures, such as skin and hair, and of other substances.

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
**Glossary (continued)**

**Red blood cell** (red blud sel)
A type of blood cell that is made in the bone marrow and found in the blood. Red blood cells contain a protein called hemoglobin, which carries oxygen from the lungs to all parts of the body. Checking the number of red blood cells in the blood is usually part of a complete blood cell test. It may be used to look for conditions such as anemia, dehydration, malnutrition, and leukemia.

**Stable disease** (STAY-bul dih-ZEEZ)
Cancer that is neither decreasing nor increasing in size or severity.

**Stomatitis** (STOH-muh-TY-tis)
Inflammation or irritation of the mucous membranes in the mouth, including the inside of the cheeks, gums, tongue, lips, and palate.

**Thrombocytopenia** (THROM-boh-sy-toh-PEE-nee-uh)
A condition in which there is a lower-than-normal number of platelets in the blood. It may result in easy bruising and excessive bleeding from wounds or bleeding in mucous membranes and other tissues.

**Tumor** (TOO-mer)
An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancer) or malignant (cancer). Also called neoplasm.

**VEGF** (vej-eff)
A molecule made by cells that stimulates new blood vessel formation. VEGF stands for vascular endothelial growth factor. Drugs that block VEGF may prevent the formation of blood vessels, which may help slow or stop the growth of tumor cells. These drugs are known as anti-VEGF therapies or biologics.

**White blood cell** (white blud sel)
A type of blood cell that is made in the bone marrow and found in the blood and lymph tissue. White blood cells are part of the body’s immune system. They help the body fight infection and other diseases. Types of white blood cells include granulocytes (neutrophils, eosinophils, and basophils), monocytes, and lymphocytes (T cells and B cells). Checking the number of white blood cells in the blood is usually part of a complete blood cell test. It may be used to look for conditions such as infection, inflammation, allergies, and leukemia. Also called leukocyte and WBC.

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
Journal

You can use these pages to write down questions for your healthcare provider, take notes during your appointments, or make note of anything else you would like to remember. You may want to include the date next to each entry.
Journal (continued)

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.
Important contact information

Office or clinic contact information
Name: ________________________________________________________________
Address: __________________________________________________________________________
Phone: ___________________________ E-mail: _______________________________________

1. Healthcare provider contact information
Name: _________________________________________________________________________
Address: _________________________________________________________________________
Phone: ___________________________ E-mail: _______________________________________

2. Healthcare provider contact information
Name: _________________________________________________________________________
Address: _________________________________________________________________________
Phone: ___________________________ E-mail: _______________________________________

3. Healthcare provider contact information
Name: _________________________________________________________________________
Address: _________________________________________________________________________
Phone: ___________________________ E-mail: _______________________________________

Financial consultant contact information
Name: ________________________________________________________________
Address: __________________________________________________________________________
Phone: ___________________________ E-mail: _______________________________________

Pharmacy contact information
Name: _________________________________________________________________________
Address: _________________________________________________________________________
Phone: ___________________________ E-mail: _______________________________________

Emergency contact information
Name: _________________________________________________________________________
Address: _________________________________________________________________________
Phone: ___________________________ E-mail: _______________________________________
Taiho Oncology Patient Support

For questions about financial support or treatment with LONSURF® (trifluridine and tipiracil) tablets,

Call 1-844-TAIHO-4U (1-844-824-4648)

Or visit TaihoPatientSupport.com

You can also learn more about our patient support program at LONSURF.com/assistance

Please see Important Safety Information on pages 18 and 19 and full Prescribing Information in pocket.

LONSURF is a registered trademark of Taiho Pharmaceutical Co., Ltd., used under license by Taiho Oncology, Inc.
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LONSURF safely and effectively. See full prescribing information for LONSURF.

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

INDICATIONS AND USAGE
LONSURF is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. (1)

DOSAGE AND ADMINISTRATION
• Recommended dose: 35 mg/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)

DOSAGE FORMS AND STRENGTHS
Tablets:
• 15 mg trifluridine/6.14 mg tipiracil (3)
• 20 mg trifluridine/8.19 mg tipiracil (3)

CONTRAINDICATIONS
None. (4)

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

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

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

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

FULL PRESCRIBING INFORMATION: CONTENTS*
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2 DOSAGE AND ADMINISTRATION
  2.1 Recommended Dose
  2.2 Dose Modifications
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
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  5.1 Severe Myelosuppression
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
LONSURF is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose
The recommended starting dose of LONSURF is 35 mg/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.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/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><strong>Gastrointestinal disorders</strong></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><strong>General disorders and administration site conditions</strong></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><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>39%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></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>
</tbody>
</table>

Blood and lymphatic system disorders

<table>
<thead>
<tr>
<th></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>
</tbody>
</table>

Blood and lymphatic system disorders

<table>
<thead>
<tr>
<th></th>
<th>77</th>
<th>18</th>
<th>N/A</th>
<th>33</th>
<th>3</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia‡</td>
<td>77</td>
<td>18</td>
<td>N/A</td>
<td>33</td>
<td>3</td>
<td>N/A</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>67</td>
<td>27</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>42</td>
<td>5</td>
<td>1</td>
<td>8</td>
<td>&lt;1</td>
<td>&lt;1</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 C_{10}H_{11}F_{3}N_{2}O_{5} and a molecular weight of 296.20. Trifluridine is a white crystalline powder, soluble in water, ethanol, 0.01 mol/L hydrochloric acid, 0.01 mol/L sodium hydroxide solution; freely soluble in methanol, acetone; sparingly soluble in 2-propanol, acetonitrile; slightly soluble in diethyl ether; and very slightly soluble in isopropyl ether.

Tipiracil hydrochloride

Tipiracil hydrochloride, a thymidine phosphorylase inhibitor, is described chemically as 5-chloro-6-[(2-imino-pyrrolidin-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_9H_{11}ClN_4O_2•HCl and a molecular weight of 279.12. Tipiracil hydrochloride is a white crystalline powder, soluble in water, 0.01 mol/L hydrochloric acid, and 0.01 mol/L sodium hydroxide; slightly soluble in methanol; very slightly soluble in ethanol; and practically insoluble in acetonitrile, 2-propanol, acetone, diisopropyl ether, and diethyl ether.

**LONSURF 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 (t₁/₂) of trifluridine was 1.4 hours and of tipiracil was 2.1 hours after a single dose. The mean elimination half-life at steady state of trifluridine was 2.1 hours and of tipiracil was 2.4 hours.

The accumulation of trifluridine was 3-fold for AUC₀₉₉₉ 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 AUC₀₉₉₉ 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 patients 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 3  Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>LONSURF (N=534)</th>
<th>Placebo (N=266)</th>
</tr>
</thead>
<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)$^a$ [95% CI]$^b$</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$^c$</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>P-value$^c$</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

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$^a$ Kaplan-Meier estimates  
$^b$ Methodology of Brookmeyer and Crowley  
$^c$ Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region)
Figure 1  Kaplan-Meier Curves of Overall Survival

REFERENCES

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)]