BECAUSE MY TOMORROW IS STILL UNWRITTEN

My story continues with LONSURF® (trifluridine/tipiracil) [LON-serf] tablets

LONSURF is a prescription medicine used to treat adults with
• colorectal cancer that has spread to other parts of the body and who have been previously treated or cannot receive certain chemotherapy medicines.
• a kind of stomach cancer called gastric cancer including cancer of the gastroesophageal junction that has spread to other parts of the body and who have been previously treated or cannot receive certain chemotherapy medications.

It is not known if LONSURF is safe and effective in children

Please see Important Safety Information on pages 22-23 and full Prescribing Information in pocket.
What is metastatic colon or rectal cancer?

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.

Metastatic means that the cancer has spread to other parts of the body.

About this guide

You have been through a lot since your 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/tipiracil) tablets offer you another treatment option. Whether you have been prescribed LONSURF or just want to know more about it, this brochure is for you.

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.

You can always learn more at LONSURF.com/tomorrow

What is LONSURF?

LONSURF tablets are a prescription medicine for colon or rectal cancer.

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

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

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

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

Please see Important Safety Information on pages 22-23 and full Prescribing Information in pocket.
Who should take LONSURF?

LONSURF® (trifluridine/tipiracil) tablets are for those:

- Living with colon or rectal cancer that 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

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 Eluxatin® (oxaliplatin)
- Irinotecan-based treatment: Such as FOLFIRI (5-FU, leucovorin, and irinotecan); CAPIRI (capecitabine and irinotecan); or Camptosar® (irinotecan)
- Anti-VEGF biological therapy: Such as Avastin® (bevacizumab); or Zaltrap® (ziv-aflibercept)
- Anti-EGFR therapy: Such as Erbitux® (cetuximab); or Vectibix® (panitumumab)

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

Do not use LONSURF if you are allergic to any of the ingredients in LONSURF. Talk to your healthcare provider if you are not sure whether you are allergic to any of the ingredients in LONSURF.

Selected Important Safety Information

- 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

Selected Important Safety Information

- 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

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About this guide

You have been through a lot since your 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/tipiracil) tablets offer you another treatment option.

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 stomach cancer.

You can always learn more at LONSURF.com/tomorrow.

What is metastatic stomach cancer?

You have likely read a lot about stomach cancer since you were diagnosed. As you may have already discovered, stomach cancer is not as common as some other cancers in men and women.

Metastatic means that the cancer has spread to other parts of the body.

Stomach cancer is sometimes called gastric cancer.

• Your healthcare provider may have told you that you have gastroesophageal junction cancer, which is a type of stomach cancer located in the lower part of the esophagus that connects to the stomach.

About this guide

You have been through a lot since your 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/tipiracil) tablets offer you another treatment option.

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 stomach cancer.

You can always learn more at LONSURF.com/tomorrow.

What is LONSURF?

LONSURF tablets are a prescription medicine for stomach cancer.

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

LONSURF was studied in a clinical trial of 507 patients with stomach cancer that had spread to other parts of the body and had been previously treated with certain chemotherapy medicines.

• Half of the patients treated with LONSURF were still alive at 5.7 months and half of the patients who received placebo were still alive at 3.6 months.

• Worsening of the disease or death occurred in 85% of patients treated with LONSURF and 92% of patients who received placebo.

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

Please see Important Safety Information on pages 22-23 and full Prescribing Information in pocket.
Who should take LONSURF?

LONSURF® (trifluridine/tipiracil) tablets are for those:
• Living with stomach cancer that 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

Those previous medicines may include:
• Fluoropyrimidine: Such as 5-fluorouracil, also known as 5-FU, and Xeloda® (capecitabine)
• Platinum
• Taxane and/or irinotecan-based treatment: Such as FOLFIRI (5-FU, leucovorin, and irinotecan) and Camptosar® (irinotecan)
• HER-2 inhibitor

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

Do not use LONSURF if you are allergic to any of the ingredients in LONSURF. Talk to your healthcare provider if you are not sure whether you are allergic to any of the ingredients in LONSURF.

You can learn more about stomach cancer through these organizations
You can find information about stomach cancer, support, and community at:

CancerCare®
Visit cancercare.org or call 1-800-813-HOPE (4673)

Cancer Support Community®
Visit cancersupportcommunity.org or call 1-888-793-9355

Debbie’s Dream Foundation
Visit debbiesdream.org or call 1-855-475-1200

Gastric Cancer Foundation
Visit gastriccancer.org

Hope for Stomach Cancer
Visit stocan.org or call 1-424-239-9943

No Stomach For Cancer®
Visit nostomachforcancer.org or call 1-608-692-5141

The Raymond Foundation
Visit TheRaymondFoundation.org or call 1-646-598-2001

Selected Important Safety Information
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.

Please see additional Important Safety Information on pages 22-23 and full Prescribing Information in pocket.
How can LONSURF help me?

With proven results to help patients live longer, LONSURF® (trifluridine/tipiracil) tablets may allow you to continue your journey with cancer.

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

How it works

LONSURF is a prescription medicine used to treat people with colon/rectal or stomach cancer that has spread to other parts of the body and who have been previously treated with or cannot receive certain chemotherapy medicines. LONSURF consists of two medicines in one:

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

What is the most important information I need to know about LONSURF?

It’s important to know what to expect so you can recognize side effects right away and talk to your healthcare provider. There are things you can do to help manage them while the treatment team is monitoring your symptoms.

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

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

Selected Important Safety Information

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.

Please see additional Important Safety Information on pages 22-23 and full Prescribing Information in pocket.
How to take LONSURF

LONSURF® (trifluridine/tipiracil) tablets are swallowed:
• Twice a day with food
• The type of food does not matter

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

15-mg tablet 20-mg tablet

*Tablet strength of LONSURF is based on 1 active part of the medicine. Actual tablet size is 7 mm for 15-mg dose and 8 mm for 20-mg dose.

Tips for the 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).

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

Use the digital calendar at LONSURF.com/mycalendar to help you keep track of your treatment. Your healthcare provider may give you a treatment calendar as well.

Please see Important Safety Information on pages 22-23 and full Prescribing Information in pocket.
Other things to keep in mind about taking LONSURF

• Store LONSURF® (trifluridine/tipiracil) tablets at room temperature between 68°F and 77°F (20°C to 25°C)

• Don’t store LONSURF with other medicines. Keep LONSURF in its own container

• If you store your tablets outside of the original container, any unused LONSURF tablets should be disposed of after 30 days

• Wash your hands after handling LONSURF. Even though it is a pill, it is still chemotherapy

• Make sure your caregiver wears gloves when handling LONSURF

• Note that there is a packet inside the bottle that helps absorb moisture. Do not swallow this material

• Keep LONSURF out of the reach of children

Contact your healthcare provider if:

• You miss a dose. Do not take additional doses to make up for the missed dose. Call your healthcare provider for instructions about what to do for a missed dose

• You have leftover tablets. Your healthcare provider or pharmacist will tell you how to dispose of them properly

Selected Important Safety Information

• **Females** who can become pregnant: Your healthcare provider will verify your pregnancy status before you start treatment with Lonsurf. You should use effective birth control during and 6 months after the last dose of 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 additional Important Safety Information on pages 22-23 and full Prescribing Information in pocket.
Safety

How to manage side effects

Your healthcare provider may have ways to help manage some of the side effects of LONSURF 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.

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

**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 to 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 to your healthcare provider. He or she may prescribe medication that can help decrease tiredness**

**Tiredness (fatigue/weakness)**

• 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 to 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 to your healthcare provider. He or she may prescribe medication that can help decrease tiredness

What are the most common side effects caused by LONSURF?

Almost all patients treated with LONSURF® (trifluridine/tipiracil) tablets experience side effects at some time. Some common side effects you may experience include:

• Tiredness (fatigue/weakness)
• Nausea
• Vomiting
• Decreased appetite
• Diarrhea
• Abdominal pain
• Fever

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

If you have a LONSURF Starter Kit, you can use the thermometer to check your temperature. Record your temperature, along with any side effects you have, then bring this information with you to discuss with your healthcare provider at your next appointment.

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.

Please see Important Safety Information on pages 22-23 and full Prescribing Information in pocket.
### Diarrhea/abdominal pain

#### For 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

#### For abdominal pain:
- Exercise regularly
- Eat plenty of foods that are high in fiber such as fruits and vegetables

### Nausea and vomiting

#### How to manage side effects (cont’d)

- 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
- Eat 5 or 6 small meals a day, instead of 3 big ones (this does not change your dosing schedule)
- Have food and drinks that are warm or cool instead of hot or cold
- Try small bites of popsicles or fruit ices. You can see if sucking on ice cubes helps (stop if the cold temperature bothers you)
- Talk to your healthcare provider, who may prescribe something to help. You can also ask your healthcare provider about acupuncture

#### Decreased appetite

- Patients with stomach cancer should talk to their healthcare provider for special dietary needs that may be impacted by their condition
- Eat 5 or 6 small meals a day, instead of 3 big ones (this does not change your dosing schedule)
- Drink milkshakes, smoothies, juice, or soup if you do not feel like eating solid foods
- Choose foods that are high in calories and/or protein
- Being active may help you feel hungrier. Talk to your healthcare provider about exercises that can help, like going for a 15-minute walk, stretching, swimming, or riding a bike
- Talk to your healthcare provider, who may suggest that you take extra vitamins or supplements
- 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
- Try deep breathing, yoga, or other ways to relax. This can help with muscle tension, anxiety, and pain
- Avoid foods that produce gas
- Let your caregiver know about your pain so he or she can try and help

Please see Important Safety Information on pages 22-23 and full Prescribing Information in pocket.
How to manage side effects (cont’d)

**Fever**

- Drink plenty of liquids, like water, juice, and broth because a fever can cause fluid loss and dehydration
- Rest
- Keep cool by dressing in light clothing and sleeping with only a sheet
- **Call your healthcare provider immediately** if you have a fever or other signs of infection. You can use the thermometer in the Starter Kit to check your temperature each day

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Selected Important Safety Information

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 (fatigue, weakness), 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.

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Trademarks, registered or otherwise, are the property of their respective owners.
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: Your healthcare provider will verify your pregnancy status before you start treatment with Lonsurf. You should use effective birth control during and 6 months after the last dose of 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.

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

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This Patient Information has been approved by the U.S. Food and Drug Administration.

Issued: 02/2019

Please see full Prescribing Information in pocket.
**Appointment Tips**

**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 the journal in this guide, the LONSURF Treatment Calendar (LONSURF.com/mycalendar), 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 journal provided in this guide 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 pocket on the back of this booklet or a folder to keep these all in one place.

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**How to make 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:

- Whom to contact during office hours and off-hours
- How to reach them
- Where to go

Please see Important Safety Information on pages 22-23 and full Prescribing Information in pocket.
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.
My story continues with LONSURF® (trifluridine/tipiracil) tablets

BECAUSE MY TOMORROW IS STILL UNWRITTEN

Please see Important Safety Information on pages 22-23 and full Prescribing Information in pocket.

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 access to our call center, where you can get answers to your questions about LONSURF® (trifluridine/tipiracil) tablets.

For more support with LONSURF:
• Call 1-844-TAIHO-4U (1-844-824-4648) Monday-Friday, 8 AM to 8 PM ET
• Go to TaihoPatientSupport.com
• See the Patient Access Brochure available at LONSURF.com/resources

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

LONSURF is a prescription medicine used to treat adults with:
• colorectal cancer that has spread to other parts of the body and who have been previously treated or cannot receive certain chemotherapy medicines.
• a kind of stomach cancer called gastric cancer including cancer of the gastroesophageal junction that has spread to other parts of the body and who have been previously treated or cannot receive certain chemotherapy medications.

It is not known if LONSURF is safe and effective in children.

About this guide

You have been through a lot since your 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/tipiracil) tablets offer you another treatment option. Whether you have been prescribed LONSURF or just want to know more about it, this brochure is for you.

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You can always learn more at LONSURF.com/tomorrow

What is metastatic colon or rectal cancer?

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.

Metastatic means that the cancer has spread to other parts of the body.
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 access to our call center, where you can get answers to your questions about LONSURF® (trifluridine/tipiracil) tablets.

For more support with LONSURF:

- Call 1-844-TAIHO-4U (1-844-824-4648) Monday-Friday, 8 AM to 8 PM ET
- Go to TaihoPatientSupport.com
- See the Patient Access Brochure available at LONSURF.com/resources

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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

RECENT MAJOR CHANGES
Indications and Usage (1.2)       2/2019
Recommended Dosage (2.1)       2/2019
Warnings and Precaution (5.1)       2/ 2019

INDICATIONS AND USAGE
LONSURF is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of adult 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. (1.1)
• metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy. (1.2)

DOSE AND ADMINISTRATION
• Recommended Dosage: 35 mg/m²/dose orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. (2.1)

DOSE 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. Withhold and resume at next lower LONSURF dosage as recommended. (2.1, 5.1)
• Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.2, 8.1, 8.3)

ADVERSE REACTIONS
The most common adverse reactions or laboratory abnormalities (≥10%) are anemia, neutropenia, fatigue/asthenia, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, 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: Advise not to breastfeed. (8.2)
• Geriatric Use: Grade 3 or 4 neutropenia and thrombocytopenia and Grade 3 anemia occurred more commonly in patients 65 years or older. (8.5)
• Hepatic Impairment: Do not initiate LONSURF in patients with baseline moderate or severe hepatic impairment. (8.7)
• Renal Impairment: Reduce LONSURF dose in patients with severe renal impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling
Revised: 12/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer
LONSURF is indicated for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

1.2 Metastatic Gastric Cancer
LONSURF is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage
The recommended dosage of LONSURF is 35 mg/m² up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily with food 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.

Instruct patients to swallow LONSURF tablets whole.

Instruct patients not to retake doses of LONSURF that are vomited or missed and to continue with the next scheduled dose.

LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Table 1 shows the calculated initial daily dose based on body surface area (BSA).
Table 1  Recommended Dosage According to Body Surface Area (BSA)

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>Total daily dose (mg)</th>
<th>Dose (mg) administered twice daily</th>
<th>Tablets per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.07</td>
<td>70</td>
<td>35</td>
<td>15mg 0</td>
</tr>
<tr>
<td>1.07 - 1.22</td>
<td>80</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>1.23 - 1.37</td>
<td>90</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>1.38 - 1.52</td>
<td>100</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>1.53 - 1.68</td>
<td>110</td>
<td>55</td>
<td>1</td>
</tr>
<tr>
<td>1.69 - 1.83</td>
<td>120</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>1.84 - 1.98</td>
<td>130</td>
<td>65</td>
<td>3</td>
</tr>
<tr>
<td>1.99 - 2.14</td>
<td>140</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>2.15 - 2.29</td>
<td>150</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td>≥2.30</td>
<td>160</td>
<td>80</td>
<td>0</td>
</tr>
</tbody>
</table>

2.2   Dosage Modifications for Adverse Reactions

Obtain complete blood cell counts prior to and on Day 15 of each cycle [see Warnings and Precautions (5.1)].

Do not initiate the cycle of LONSURF until:

- Absolute neutrophil count (ANC) greater than or equal to 1,500/mm³ or febrile neutropenia is resolved
- Platelets 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-hematologic adverse reaction

After recovery, resume LONSURF after reducing the dose by 5 mg/m²/dose from the previous dose, 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. Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 20 mg/m² orally twice daily. Do not escalate LONSURF dosage after it has been reduced.
2.3 Recommended Dosage for Renal Impairment

Severe Renal Impairment

In patients with severe renal impairment [creatinine clearance (CLcr) of 15 to 29 mL/min as determined by the Cockcroft-Gault formula], the recommended dosage is 20 mg/m² (based on the trifluridine component) orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle (Table 2) [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]. Reduce dose to 15 mg/m² twice daily in patients with severe renal impairment who are unable to tolerate a dose of 20 mg/m² twice daily (Table 2). Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 15 mg/m² twice daily.

Table 2 Recommended Dosage for Severe Renal Impairment According to BSA

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>Total daily dose (mg)</th>
<th>Dose (mg) administered twice daily</th>
<th>Tablets per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>15mg</td>
</tr>
<tr>
<td>For a dose of 20 mg/m² twice daily:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1.14</td>
<td>40</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>1.14 – 1.34</td>
<td>50</td>
<td>25*</td>
<td>2 in the evening*</td>
</tr>
<tr>
<td>1.35 – 1.59</td>
<td>60</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>1.60 – 1.94</td>
<td>70</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>1.95 – 2.09</td>
<td>80</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>2.10 – 2.34</td>
<td>90</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>≥ 2.35</td>
<td>100</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>For a dose of 15 mg/m² twice daily:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1.15</td>
<td>30</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>1.15 – 1.49</td>
<td>40</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>1.50 – 1.84</td>
<td>50</td>
<td>25*</td>
<td>2 in the evening*</td>
</tr>
<tr>
<td>1.85 – 2.09</td>
<td>60</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>2.10 – 2.34</td>
<td>70</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>≥ 2.35</td>
<td>80</td>
<td>40</td>
<td>0</td>
</tr>
</tbody>
</table>

* For a total daily dose of 50 mg, instruct patients to take 1 x 20-mg tablet in the morning and 2 x 15-mg tablets in the evening.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 15 mg trifluridine/6.14 mg tipiracil: white, biconvex, round, film-coated, imprinted with ‘15’ on one side, and ‘102’ and ‘15 mg’ on the other side, in gray ink.
- 20 mg trifluridine/8.19 mg tipiracil: pale red, biconvex, round, film-coated, 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 the 868 patients who received LONSURF in RECOURSE and TAGS, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3%). Two patients (0.2%) died due to neutropenic infection/sepsis and four other patients (0.5%) died due to septic shock. A total of 12% 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 severe myelosuppression and resume at the next lower dosage [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 dosage levels resulting in exposures lower than those achieved at the recommended dosage of 35 mg/m² twice daily. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with LONSURF and for at least 6 months after the final dose [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in 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 in the WARNINGS AND PRECAUTIONS section and below reflect exposure to LONSURF at the recommended dose in 533 patients with metastatic colorectal cancer in RECOURSE and 335 patients with metastatic gastric cancer in TAGS. Among the 868 patients who received LONSURF, 11% were exposed for 6 months or longer and 1% were exposed for 12 months or longer. The most common adverse reactions or laboratory abnormalities (≥10%) are anemia, neutropenia, fatigue/asthenia, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, and pyrexia.

Metastatic Colorectal Cancer
The safety of LONSURF was evaluated in RECOURSE, a randomized (2:1), double-blind, placebo-controlled trial in patients with previously treated metastatic colorectal cancer [see Clinical Studies (14.1)]. Patients received LONSURF 35 mg/m²/dose (n=533) or placebo (n=265) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. In RECOURSE, 12% of patients received LONSURF for more than 6 months and 1% of patients received LONSURF for more than 1 year.

The study population characteristics were: median age 63 years; 61% male; 57% White, 35% Asian, and 1% Black.

The most common adverse reactions or laboratory abnormalities (≥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 RECOURSE, 3.6% of patients discontinued LONSURF for an adverse reaction and 14% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

Tables 3 and 4 list the adverse reactions and laboratory abnormalities (graded using CTCAE v4.03), respectively, observed in RECOURSE.
Table 3  Adverse Reactions (≥5%) in Patients Receiving LONSURF and at a Higher Incidence (>2%) than in Patients Receiving Placebo in RECOURSE

<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>General</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>Gastrointestinal</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>Metabolism and nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>39</td>
<td>4</td>
</tr>
<tr>
<td><strong>Infections†</strong></td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</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
†Incidence reflects 64 preferred terms in the Infections and Infestations system organ class.
In RECOURSE, pulmonary emboli occurred more frequently in LONSURF-treated patients (2%) compared to no patients on placebo.

**Metastatic Gastric Cancer**

The safety of LONSURF was evaluated in TAGS, an international, randomized (2:1), double-blind, placebo-controlled trial in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma who were previously treated with at least 2 prior chemotherapy regimens for advanced disease [see Clinical Studies (14.2)]. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Patients received LONSURF 35 mg/m²/dose (n=335) or placebo (n=168) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle with best supportive care. In TAGS, 10% of patients received LONSURF for more than 6 months and 0.9% of patients received LONSURF for more than 1 year.

The study population characteristics were: median age 63 years (24 to 89 years); 73% male; 70% White, 16% Asian, and 1% Black.

The most common adverse reactions or laboratory abnormalities (≥10% in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were neutropenia, anemia, nausea, decreased appetite, thrombocytopenia, vomiting, and diarrhea. In TAGS, 13% of patients discontinued LONSURF for an adverse reaction and 11% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, and diarrhea.

Tables 5 and 6 list the adverse reactions and laboratory abnormalities (graded using CTCAE v4.03), respectively, observed in TAGS.
Table 5  Adverse Reactions (≥5%) in Patients Receiving LONSURF and at a Higher Incidence (>2%) than in Patients Receiving Placebo in TAGS

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LONSURF (N=335)</th>
<th>Placebo (N=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4* (%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>34</td>
<td>9</td>
</tr>
<tr>
<td>Infections†</td>
<td>23</td>
<td>5</td>
</tr>
</tbody>
</table>

*No Grade 4 definition for nausea or fatigue in NCI CTCAE, version 4.03.
†Incidence reflects 46 preferred terms in the Infections and Infestations system organ class.

Table 6  Laboratory Abnormalities in TAGS

<table>
<thead>
<tr>
<th>Laboratory Parameter*</th>
<th>LONSURF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>66</td>
<td>38</td>
</tr>
<tr>
<td>Anemia†</td>
<td>63</td>
<td>19</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>34</td>
<td>6</td>
</tr>
</tbody>
</table>

*Worst Grade at least one Grade higher than baseline, with percent based on number of patients with post-baseline samples which may be <335 (LONSURF) or 168 (placebo)
†Anemia: No Grade 4 definition in CTCAE, v4.03

In TAGS, pulmonary emboli occurred more frequently in LONSURF-treated patients (3.1%) compared to 1.8% for patients on placebo.
Additional Clinical Experience

Interstitial lung disease was reported in 15 (0.2%) patients, 3 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 [see Clinical Pharmacology (12.2)], 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 human exposures at the recommended clinical dose (see Data). There are no available data on LONSURF use 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 ≥50 mg/kg (approximately 0.33 times the FTD 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

There are no data on the presence of trifluridine, tipiracil or its metabolites in human milk or its effects on the breastfed child or on milk production. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk (see Data). Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with LONSURF and for 1 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

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating LONSURF [see Use in Specific Populations (8.1)].

Contraception

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

Females

Advise females of reproductive potential to use effective contraception during treatment with LONSURF and for at least 6 months after the final dose.

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.

Juvenile Animal Toxicity 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 ≥ 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m² twice daily).

8.5 Geriatric Use

In RECOURSE and TAGS, 868 patients received LONSURF; 45% were 65 years of age or over, while 10% were 75 and over. No overall differences in effectiveness were observed in patients 65 or older versus younger patients. Patients 65 years of age or older who received LONSURF had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (46% vs. 32%), Grade 3 anemia (22% vs. 16%), and Grade 3 or 4 thrombocytopenia (7% vs. 4%).

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min as determined by the Cockcroft-Gault formula). Reduce the dose of LONSURF for patients with severe renal impairment (CLcr of 15 to 29 mL/min) [see Dosage and Administration (2.3)]. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.
8.7 Hepatic Impairment

No adjustment to the starting dosage of LONSURF is recommended for patients with mild hepatic impairment. Do not initiate LONSURF in patients with baseline moderate or severe (total bilirubin >1.5 times ULN and any AST) hepatic impairment [see Clinical Pharmacology (12.3)].

11 DESCRIPTION

LONSURF contains trifluridine and tipiracil hydrochloride at a molar ratio of 1:0.5.

Trifluridine

Trifluridine, a nucleoside metabolic inhibitor, is described chemically as 2’-deoxy-5-(trifluoromethyl) uridine and has the following structural formula:

![Trifluridine 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-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 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 (trifluridine and tipracil) tablets for oral use contain 15 mg of trifluridine and 6.14 mg of tipracil equivalent to 7.065 mg of tipiracil hydrochloride or 20 mg of trifluridine and 8.19 mg of tipracil equivalent to 9.420 mg of tipiracil hydrochloride.

LONSURF tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, ferric oxide, and magnesium stearate. The tablets 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 had no large effect (i.e. >20 ms) in the mean QTc interval when compared to placebo and no exposure-QT relationship was identified. Two of 42 patients (4.8%) had QTc >500 msec and 2.4% had a QTc increase from baseline >60 msec.

12.3 Pharmacokinetics

After twice daily dosing of LONSURF, systemic exposure (AUC) of trifluridine increased more than dose-proportionally over the dose range of 15 mg/m² (0.43 times the recommended dose) to 35 mg/m².

The accumulation of trifluridine was 3-fold for AUC₀₋₁₂hr and 2-fold for Cₘₐₓ at steady state while no accumulation was observed for tipiracil.

Administration of a single dose of LONSURF 35 mg/m² increased the mean AUC₀₋ₗₐₛₜ of trifluridine by 37-fold and Cₘₐₓ by 22-fold with reduced variability compared to administration of a single dose of trifluridine 35 mg/m² alone.
Absorption
Following a single oral administration of LONSURF at 35 mg/m² in patients with cancer, the mean time to peak plasma concentration (T_{max}) of trifluridine was around 2 hours.

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

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

Elimination
After administration of LONSURF 35 mg/m², the mean elimination half-life (t_{1/2}) 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.

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 [14C]-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 <3% for both. The unchanged trifluridine was <3% of administered dose recovered in the urine and feces.

After single oral administration of LONSURF (60 mg) with [14C]-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
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.

Patients with Renal Impairment
In a dedicated renal impairment study, all patients received LONSURF 35 mg/m² twice daily except for patients with severe renal impairment who received 20 mg/m² twice daily. Mild renal impairment (CLean of 60 to 89 mL/min as determined by the Cockcroft-Gault formula) had no clinically important effect on steady-state AUC_{0-last} of trifluridine and tipiracil. Moderate renal impairment (CLean of 30 to 59 mL/min) increased steady-state AUC_{0-last} of trifluridine by 56% and tipiracil by 139% compared to normal renal function (CLean ≥ 90 mL/min). Severe renal
impairment (CLcr of 15 to 29 mL/min) increased the dose-normalized steady-state AUC\textsubscript{0-last} of trifluridine by 140% and tipiracil by 614% compared to normal renal function. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

*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 ≤ ULN and AST > ULN or total bilirubin <1 to 1.5 times ULN and any AST) to moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST) and patients with normal hepatic function (total bilirubin and AST ≤ ULN); however, 5 of 6 patients with moderate hepatic impairment experienced Grade 3 or 4 increased bilirubin levels. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with severe hepatic impairment [see Dosage Modifications (2.2), Use in Specific Populations (8.6)].

**Drug Interaction Studies**

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 Metastatic Colorectal Cancer

The efficacy of LONSURF was evaluated in RE COURSE (NCT01607957), an international, randomized, double-blind, placebo-controlled study conducted in patients with previously treated metastatic colorectal cancer (mCRC). Key eligibility criteria included prior treatment with at least 2 lines of standard chemotherapy for metastatic CRC, ECOG performance status (PS) 0-1, absence of brain metastasis, and absence of ascites requiring drainage in the past four weeks.

Patients were randomized 2:1 to receive LONSURF 35 mg/m\textsuperscript{2} 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. 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). The major efficacy outcome measure was overall survival (OS) and an additional efficacy outcome measure was progression-free survival (PFS).

A total of 800 patients were randomized to LONSURF (N=534) with best supportive care (BSC) or matching placebo (N=266) plus BSC. The median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, and all patients had baseline ECOG 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.

Efficacy results are summarized in Table 7 and Figure 1.

### Table 7  Efficacy Results from RECOURSE

<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 events, 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>
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</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), 2-sided
Figure 1   Kaplan-Meier Curves of Overall Survival in RECOURSE

14.2 Metastatic Gastric Cancer

The efficacy of LONSURF was evaluated in TAGS (NCT02500043), an international, randomized, double-blind, placebo-controlled study in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma previously treated with at least 2 prior regimens for advanced disease. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Other key eligibility criteria included ECOG performance status (PS) 0 or 1. Patients were randomized 2:1 to receive LONSURF 35 mg/m² orally twice daily on Days 1-5 and 8-12 of each 28-day cycle with best supportive care (BSC) or matching placebo with BSC until disease progression or unacceptable toxicity. Randomization was stratified by ECOG PS at baseline (0 vs. 1), prior ramucirumab (yes vs. no), and geographic region (Japan vs. rest of world). The major efficacy outcome measure was OS and an additional outcome measure was PFS.

A total of 507 patients were randomized to LONSURF (N=337) or placebo (N=170). The median age was 63 years, 73% were male, 70% and 16% were White and Asian respectively, and 38% had a baseline ECOG PS of 0. Seventy-one percent of patients had gastric tumors, 29% had GEJ tumors, and two patients had gastric/GEJ tumors. All patients received platinum-based chemotherapy, 99% received fluoropyrimidine-based therapy, 91% received a taxane, 55% received irinotecan, and 33% received ramucirumab. The HER2 status was negative in 62%, positive in 19%, and unknown in 20% of patients. Among the 94 patients with HER2 positive tumors, 89% received prior anti-HER2 therapy.

Efficacy results are summarized in Table 8 and Figure 2.
Table 8  Efficacy Results from TAGS

<table>
<thead>
<tr>
<th></th>
<th>LONSURF (N=337)</th>
<th>Placebo (N=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths, N (%)</td>
<td>244 (72)</td>
<td>140 (82)</td>
</tr>
<tr>
<td>Median OS (months)(^a) (95% CI)(^b)</td>
<td>5.7 (4.8, 6.2)</td>
<td>3.6 (3.1, 4.1)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.69 (0.56, 0.85)</td>
<td></td>
</tr>
<tr>
<td>p-value(^c)</td>
<td>0.0006</td>
<td></td>
</tr>
<tr>
<td><strong>Progression-Free Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events, N (%)</td>
<td>287 (85)</td>
<td>156 (92)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.56 (0.46, 0.68)</td>
<td></td>
</tr>
<tr>
<td>p-value(^c)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Kaplan-Meier estimates
\(^b\) Methodology of Brookmeyer and Crowley
\(^c\) Stratified log-rank test (strata: ECOG PS, prior ramucirumab treatment, region), 2-sided

Figure 2  Kaplan-Meier Curves of Overall Survival in TAGS

15  REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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 patients 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 patients that LONSURF is available in two strengths and they may receive both strength tablets to provide the prescribed dosage.

Advise patients to take LONSURF with food [see Dosage and Administration (2.1)].

Advise patients that anyone else who handles their medication should wear gloves [see References (15)].
Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.2), Use in Specific Populations (8.3)].

Advise female patients of reproductive potential to use effective contraception during treatment with LONSURF and for at least 6 months after the final dose [see Warnings and Precautions (5.2), Use in Specific Populations (8.3)].

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 Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)].

Lactation

Advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose [see Use in Specific Populations (8.2)].