BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/21/16**
SECTION: DRUGS	**LAST REVIEW DATE: 1/18/18**
	LAST CRITERIA REVISION DATE: 1/18/18
	ARCHIVE DATE:

LONSURF (trifluridine-tipiracil) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

LONSURF (trifluridine-tipiracil) oral tablet (cont.)

Description:

Lonsurf is a combination of trifluridine, a thymidine nucleoside analogue, and tipiracil, a thymidine phosphorylase inhibitor. It is indicated for the treatment of metastatic colorectal cancer in patients 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.

Following Lonsurf uptake into cancer cells, trifluridine is incorporated into DNA, thereby interfering with DNA synthesis and inhibiting cell proliferation. Inclusion of tipiracil results in increased levels of trifluridine by inhibiting its metabolism by thymidine phosphorylase.

Colorectal cancer:

- CRC is the second leading cause of cancer-related death in the US
- Metastatic CRC (mCRC) accounts for approximately 20% of all CRC diagnoses, and has an estimated 5-year survival rate of 11.9%
- Survival of patients with mCRC can vary based on certain factors (such as RAS or BRAF mutations)
- About 35-45% of colorectal cancers have a mutated RAS oncogene, which is strong predictor that the cancer will not respond to EGFR inhibitors
- The National Comprehensive Cancer Network (NCCN) Colon Cancer and Rectal Cancer guidelines recommend one of five chemotherapy regimens for initial treatment, which contain various combinations of 5-fluorouracil, leucovorin, oxaliplatin, irinotecan and capecitabine
- Targeted biologic medications [such as Avastin (bevacizumab), Erbitux (cetuximab), or Vectibix (panitumumab)] may also be used as part of initial treatment
- Treatment for progressive disease varies based on the choice of prior therapy, but options may include Zaltrap (ziv-aflibercept), Cyramza (ramucirumab), Stivarga (regorafenib), Lonsurf (trifluridine/tipiracil), best supportive care, or enrollment in a clinical trial

LONSURF (trifluridine-tipiracil) oral tablet (cont.)

Definitions:

Ant- epidermal growth factor receptor (anti-EGFR)
- Erbitux (cetuximab)
- Vectibix (panitumumab)

Anti-vascular endothelial growth factor (anti-VEGF):
- Avastin (bevacizumab)
- Cyramza (ramucirumab)
- Stivarga (regorafenib)
- Zaltrap (ziv-aflibercept)

Platinum coordination complex:
- Eloxatin (oxaliplatin, generics available)

Pyrimidines
- Fluorouracil
- Lonsurf (trifluidine/tipiracil)
- Xeloda (capecitabine, generics available)

Topoisomerase inhibitors:
- Camptosar (irinotecan, generics available)

Lonsurf (trifluridine/tipiracil)

Medication class:
Antineoplastic Agent, Antimetabolite (pyrimidine analog), Thymidine Phosphorylase Inhibitor

FDA-approved indication(s):
- Treatment of metastatic colorectal cancer in patients 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

Recommended Dose:
- 35 mg/m^2/dose twice daily on days 1-5 and days 8-12 of each 28-day cycle, round dose to nearest 5 mg increment of trifluridine

Maximum dosage
- 80 mg/dose (based on the trifluridine component)

Available Dosage Forms:
- 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil tablets

Warnings, Precautions, and other Clinical Information:
- Do not use Lonsurf in patients with baseline moderate (total bilirubin > 1.5-3x ULN with any AST) or severe (total bilirubin > 3x ULN with any AST) hepatic impairment

LONSURF (trifluridine-tipiracil) oral tablet (cont.)

- Do not initiate Lonsurf until the ANC is $\geq$ 1,500/mm^3 or febrile neutropenia is resolved
- Do not initiate Lonsurf until the platelet count is $\geq$ 75,000/mm^3
- Withhold Lonsurf for ANC < 500/mm^3< 500/mm^3 or febrile neutropenia
- Withhold Lonsurf for platelet count < 50,000/mm^3
- Lonsurf may cause severe or persistent nausea, vomiting, and diarrhea; anti-emetics and anti-diarrhreals may be necessary
- A maximum of 3 dose reductions are permitted to a minimum dose of 20 mg/m^2 twice daily, do not escalate Lonsurf dose after it has been reduced
- The pharmacokinetic of Lonsurf has not been studied in patients with severe renal Impairment (CrCl < 30 mL/min) or end-stage renal disease
- Woman of child bearing potential should be warned against becoming pregnant
- Woman of childbearing potential should use effective contraception
- Woman who is breast feeding an infant or child should stop breast feeding
- Male on Lonsurf with a female partner of child bearing potential should use a condom

Criteria:

- **Criteria for initial therapy:** Lonsurf (trifluridine-tipiracil) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is an Oncologist
2. Individual is 18 years of age or older
3. A confirmed diagnosis of metastatic colorectal cancer
4. Individual has failure, contraindication or intolerance to **ALL** of the following previous chemotherapy regimens:
    - Previous chemotherapy regimens include:
        - Fluoropyrimidine-, Oxaliplatin-, Irinotecan-based chemotherapy regimen
        - Anti-VEGF biological therapy – such as bevacizumab(Avastin) or ramucirumab (Cymraza) or ziv-aflibercept (Zaltrap)
        - If has RAS wild-type (is negative for the RAS mutation), an anti-EGFR therapy – such as cetuximab (Erbitux) or panitumumab (Vectibix)
            1. Some examples of regimens may include: [note not an all-inclusive list]
                a. FOLFOX with or without bevacizumab
                b. CAPEOX with or without bevacizumab
                c. FOLFOX with cetuximab or panitumumab
                d. FOLFIRI with or without bevacizumab
                e. FOLFIRI with cetuximab or panitumumab
                f. FOLFOXIRI with or without bevacizumab
                g. 5FU/leucovorin with or without bevacizumab
                h. Capecitabine with or without bevacizumab
5. **ALL** of the following baseline tests have been completed before initiation of treatment:

LONSURF (trifluridine-tipiracil) oral tablet (cont.)

- Absolute neutrophil count is ≥ 1,500/mm^3
- Platelet count ≥ 75,000/mm^3

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Lonsurf (trifluridine-tipiracil) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by an Oncologist
2. Individual's condition has not worsened while on therapy
   - Worsening is defined as:
     - Cancer progression
3. Individual has been adherent with the medication
4. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use
   - Significant adverse effect such as:
     - Myelosuppression
       - Signs and symptoms may include: fever, chills, infection, unexplained bleeding or bruising, or unexplained weakness or shortness of breath

Renewal duration: 12 months

Resources:

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.

Lonsurf. Package Insert. Revised by manufacturer 09/2015. Accessed 09-22-2015, 12-01-2016

Lonsurf. Package Insert. Revised by manufacturer 03/2017. Accessed 12-27-2017

NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 2.2017, Mar 13, 2017. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer. Version 3.2017, Mar 13, 2017. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

BlueCross BlueShield of Arizona

An Independent Licensee of the Blue Cross and Blue Shield Association

Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

BlueCross BlueShield of Arizona

An Independent Licensee of the Blue Cross and Blue Shield Association

Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.