BlueCross BlueShield Arizona

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PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
ORIGINAL EFFECTIVE DATE:	**1/21/2016**
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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.**

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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 a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     a. 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

     b. 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

     c. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

  4. **ALL** of the following baseline tests have been completed before initiation of treatment:
     a. Negative pregnancy test in a woman of childbearing potential
     b. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1

  5. Individual has failure, contraindication or intolerance to all available regimens **except** regorafenib or trifluridine-tipiracil, previous chemotherapy regimens may include:
     a. Fluoropyrimidine-, Oxaliplatin-, Irinotecan-based chemotherapy regimen
     b. Anti-VEGF biological therapy – such as bevacizumab (Avastin) or ramucirumab (Cyramza) or ziv-aflibercept (Zaltrap)
     c. If has RAS wild-type (is negative for the RAS mutation), an anti-EGFR therapy – such as cetuximab (Erbitux) or panitumumab (Vectibix)

  6. Individual does not have end-stage renal disease (CrCl less than 156 mL/min)

  7. Individual does not have baseline moderate or severe (total bilirubin >1.5 times ULN and any AST) hepatic impairment

  8. There are no significant interacting drugs

  Initial approval duration: 6 months

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- **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 a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

  2. Individual's condition has responded while on therapy
     a. Response is defined as:
        i. Documented evidence of efficacy, disease stability and/or improvement
        ii. No evidence individual has developed any significant unacceptable adverse drug reactions that may exclude continued use

  3. Requested dose is at least a dose of 20 mg/m^2 twice daily or 15 mg/m^2 in a patient with severe renal impairment (CrCl 15-29 mL/min)

  4. Individual has been adherent with the medication

  5. Individual has not developed any significant adverse drug effects that may exclude continued use
     a. Significant adverse effect such as:
        i. Severe or life-threatening myelosuppression after dose modification
        ii. There have not been more than 3 dose reductions due to toxicity

  6. Individual does not have end-stage renal disease (CrCl less than 156 mL/min)

  7. Individual does not have moderate or severe (total bilirubin >1.5 times ULN and any AST) hepatic impairment

  8. There are no significant interacting drugs

  Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-cancer Medications**

  2. **Off-Label Use of Cancer Medications**

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,

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and if RAS wild-type, an anti-EGFR therapy. Lonsurf is also 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.

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.

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 (trifluridine/tipiracil)
Xeloda (capecitabine, generics available)

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Topoisomerase inhibitors:
Camptosar (irinotecan, generics available)

Taxanes:
Docetaxel

Resources:

Lonsurf (trifluridine and tipiracil) product information, revised by Taiho Pharmaceutical Co., Ltd. 12-2019. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 09, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon Cancer Version 3.2021 – Updated September 10, 2021. Available at https://www.nccn.org. Accessed December 09, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Rectal Cancer Version 2.2021 – Updated September 10, 2021. Available at https://www.nccn.org. Accessed December 09, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Esophageal and Esophagogastric Junction Cancers Version 4.2021 – Updated August 03, 2021. Available at https://www.nccn.org. Accessed December 09, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Gastric Cancer Version 5.2021 – Updated October 06, 2021. Available at https://www.nccn.org. Accessed December 09, 2021.

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.