09-J2000-46

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Reviewed: 01/09/19

Revised: 05/15/19

Subject: Trifluridine-Tipiracil (Lonsurf®) Capsule

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Trifluridine is a thymidine-based nucleoside analog that inhibits cell proliferation of cancer cells by interference with DNA synthesis. Tipiracil prevents degradation of trifluridine through inhibition of its metabolism by thymidine phosphorylase and increases trifluridine exposure. Trifluridine and tipiracil demonstrated activity in fluorouracil resistant tumors and both KRAS wild-type and mutant human colorectal cancer xenografts in mice.

Trifluridine and tipiracil (Lonsurf®) was FDA approved in September 2015 for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

Trifluridine and tipiracil was evaluated in a phase III, double blind study of 800 patients with adenocarcinoma of the colon or rectum. Patients were eligible for the study if they had received at least two prior regimens of chemotherapy which included a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and if KRAS wild-type tumors, cetuximab or panitumumab. The median overall survival with trifluridine and tipiracil was 7.1 months as compared to 5.3 months with placebo and the hazard ratio for death was 0.68 ($p<0.001$). The median progression-free survival was 2 months with trifluridine and tipiracil as compared to 1.7 months. The hazard ratio for progression was 0.48 ($p<0.001$).

The National Comprehensive Cancer Network (NCCN) guidelines for colon and rectal cancer support the use of trifluridine and tipiracil for unresectable advanced or metastatic disease not previously treated with the agent. NCCN recommends use after first disease progression following FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) with or without bevacizumab in patients with disease positive for the KRAS/NRAS mutation. NCCN also supports the use of trifluridine and tipiracil for second disease

progression following treatment with irinotecan- and oxaliplatin-based regimens as well as FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) with or without bevacizumab (in patients with mutant or wild type tumors). The NCCN guidelines also support use in the treatment of esophageal, esophagogastric junction, and gastric cancers.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

I. Initiation of trifluridine and tipiracil (Lonsurf®) **meets the definition for medical necessity** for members diagnosed with ANY of the following conditions when ALL associated criteria are met:

A. **Colon or Rectal Cancer**

1. Trifluridine and tipiracil (Lonsurf®) will be used as a single agent
2. Member has metastatic or unresectable advanced disease
3. Member has not previously received trifluridine and tipiracil (Lonsurf®)
4. Member meets **ONE** of the following:
    a. Trifluridine and tipiracil (Lonsurf®) is used following disease progression with FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan) +/- bevacizumab **AND** the member's disease is positive for the KRAS/NRAS mutation
    b. Trifluridine and tipiracil (Lonsurf®) is used as third-line or subsequent (i.e., fourth line or greater) therapy for disease progression after previous treatment with **THREE** or more of the following agents (combination use or in separate regimens):
        i. Anti-EGFR therapy (e.g., panitumumab or cetuximab) if KRAS/NRAS gene is normal (i.e., without mutation, also known as wild type).
        ii. Anti-VEGF therapy (e.g., bevacizumab, ziv-aflibercept or ramucirumab).
        iii. Fluoropyrimidine-containing chemotherapy (e.g., fluorouracil or capecitabine).
        iv. Irinotecan-containing chemotherapy
        v. Oxaliplatin-containing chemotherapy
        vi. Regorafenib (Stivarga®)
5. The dosage does not exceed 35 mg/m2/dose twice daily based on trifluridine component (maximum of 80 mg of trifluridine component per dose) on days 1 through 5 and days 8 through 12 of a 28 day cycle

B. Esophageal, gastric or gastroesophageal junction adenocarcinoma

1. Trifluridine and tipiracil (Lonsurf®) will be used as a single agent

2. **ONE** of the following:
    a. Member has unresectable locally advanced disease
    b. Member has recurrent or metastatic disease
    c. Member is not a surgical candidate
3. Member's ECOG performance status is 0-2 or KPS is greater than or equal to 60%
4. Member has not previously received trifluridine and tipiracil (Lonsurf®)
5. Trifluridine and tipiracil (Lonsurf®) is used as third-line or subsequent (i.e., fourth line or greater) therapy after previous treatment with THREE or more of the following agents (combination use or in separate regimens):
    a. Fluoropyrimidine-containing chemotherapy (e.g., fluorouracil or capecitabine).
    b. Irinotecan-containing chemotherapy
    c. Oxaliplatin-containing chemotherapy
    d. Taxane-containing chemotherapy
    e. HER2-targeted therapy
6. The dosage does not exceed 35 mg/m2/dose twice daily based on trifluridine component (maximum of 80 mg of trifluridine component per dose) on days 1 through 5 and days 8 through 12 of a 28 day cycle

C. Other FDA-approved or NCCN supported diagnosis (not previously listed above)
    1. ONE of the following is met:
        a. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
        b. Indication AND usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
    2. Dose does not exceed the maximum FDA-approved dose

Duration of approval: 180 days

II. Continuation of trifluridine and tipiracil (Lonsurf®) **meets the definition of medical necessity** for colon or rectal cancer, esophageal cancer, gastric cancer, gastroesophageal junction cancer, or other FDA-approved or NCCN supported diagnosis when the following criteria are met:
    A. The member's disease has not progressed while receiving treatment with trifluridine and tipiracil (Lonsurf®)
    B. The member has been previously approved by Florida Blue or another health plan in the past 2 years, OR the member has previously met all indication-specific criteria for coverage
    C. The dose does not exceed 35 mg/m^2/dose twice daily based on trifluridine component (maximum of 80 mg of trifluridine component per dose) and is prescribed on days 1 through 5 and days 8 through 12 of a 28 day cycle

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

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

Trifluridine and tipiracil is indicated for the treatment of 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.

The recommended starting dose is 35 mg/m^2 up to a maximum of 80 mg (trifluridine component) orally twice daily. The dose should be taken within 1 hour after completion of morning and evening meals on days 1-5 and days 8-12 of each 28 day cycle until disease progression or unacceptable toxicity. The dose should be rounded to the nearest 5 mg increment.

Special handling and disposal procedures are recommended due to cytotoxicity.

Dose Adjustments

Do not initiate therapy until:

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

Withhold therapy within a treatment cycle for any of the following:

- Absolute neutrophil count (ANC) is less than 500/mm^3 or febrile neutropenia
- Platelets are less than or equal to 50,000/mm^3
- Grade 3 or 4 non-hematological adverse reaction

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

- Febrile neutropenia
- Uncomplicated Grade 4 neutropenia (which has recovered to greater than or equal to 1,500/mm^3) or thrombocytopenia (which has recovered to greater than or equal to 75,000/mm^3) that results in more than 1 week delay in start of next cycle
- Non-hematological Grade 3 or 4 adverse reaction except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication

A maximum of 3 dose reductions are permitted to a minimum dose of 20 mg/m^2 twice daily. Do not escalate the dose after it has been reduced.

Drug Availability

- 15 mg trifluridine/6.14 mg tipiracil tablet
- 20 mg trifluridine/8.19 mg tipiracil tablet

PRECAUTIONS:

Contraindications

- None

Precautions/Warnings

- Severe Myelosuppression: Obtain complete blood counts prior to and on day 15 of each cycle. Reduce dose and/or hold therapy as clinically indicated.
- Embryo-Fetal Toxicity: Fetal harm can occur. Advise women of potential risk to a fetus.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

C9399	Unclassified drugs or biologicals
J8999	Prescription drug, oral, chemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity

C15.3 – C15.9	Malignant neoplasm of esophagus
C16.0 – C16.9	Malignant neoplasm of stomach
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction

C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C78.00 – 78.02	Secondary malignant neoplasm of unspecified lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
D37.1	Neoplasm of uncertain behavior of stomach
D37.8	Neoplasm of uncertain behavior of other specified digestive organs
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the guideline creation.

DEFINITIONS:

VEGF - Vascular endothelial growth factor.

EGFR - Epidermal growth factor receptor.

RELATED GUIDELINES:

Bevacizumab (Avastin®) Injection, 09-J0000-66

Capecitabine (Xeloda®) Tablets, 09-J1000-42

Human EGFR Inhibitors (cetuximab; panitumumab) IV, 09-J0000-94

Irinotecan HCl (Camptosar®) IV, 09-J0000-99

KRAS Mutation Analysis, 05-86000-28

Oxaliplatin (Eloxatin®) IV, 09-J1000-00

Ramucirumab (Cyramza™) Injection, 09-J2000-14

Regorafenib (Stivarga®) IV, 09-J1000-83

Ziv-aflibercept (Zaltrap®) IV, 09-J1000-80

OTHER:

Table 1: Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/09/19.

GUIDELINE UPDATE INFORMATION:

01/15/16	New Medical Coverage Guideline.
05/15/16	Updated position statement with self-administration statement.
01/15/17	Review and revision to guideline consisting of updating position statement and references.
01/15/18	Review and revision to guideline consisting of updating position statement, coding and references.
02/15/19	Review and revision to guideline consisting of updating position statement and references.
05/15/19	Revision to guideline consisting of updating position statement, coding and references