trifluridine/tipiracil (Lonsurf®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO069

Description

Lonsurf combines trifluidine and tipiracil. Trifluidine is an orally administered nucleoside analog that is incorporated into DNA to interfere with DNA synthesis and proliferation; while, tipiracil increases exposure to trifluridine by inhibiting thymidine phosphorylase.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
trifluridine/tipiracil (Lonsurf)	Stomach or esophagogastric adenocarcinoma – metastatic, previously treated	15 mg/6.14 mg tablets	80 tablets/28 days
	Colorectal cancer – metastatic, previously treated	20 mg/8.19 mg tablets	80 tablets/28 days

Initial Evaluation

I. **Trifluridine/tipiracil (Lonsurf)** may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist or a gastroenterologist; **AND**
   C. A diagnosis of one of the following:
      1. **Colorectal cancer**; **AND**
         i. The disease is metastatic (i.e., stage IV); **AND**
         ii. The member has been previously treated with a fluoropyrimidine (e.g., fluorouracil, capecitabine, S-1), oxaliplatin, and irinotecan-based chemotherapy; **AND**
         iii. The tumor has been tested and is documented to be KRAS mutant-type; **OR**
            a. The tumor has been tested and is documented to be KRAS wild-type; **AND**
               i. The member has been previously treated with an anti-EGFR therapy (e.g., cetuximab, panitumumab); **AND**

iv. Trifluridine/tipiracil (Lonsurf) will be used as monotherapy; **OR**
   a. Trifluridine/tipiracil (Lonsurf) will be used in combination with an anti-VEGF biological therapy (e.g., bevacizumab); **OR**

2. **Gastric or gastroesophageal junction adenocarcinoma**; **AND**
   i. The disease is metastatic (i.e., stage IV); **AND**
   ii. The member has received at least two prior lines of chemotherapy that have included a fluoropyrimidine (e.g., fluorouracil, capecitabine, S-1), a platinum therapy (e.g., cisplatin, carboplatin, oxaliplatin), and one of the following: a taxane (e.g., docetaxel, paclitaxel) or irinotecan; **AND**
   iii. The tumor is HER2- overexpression negative (HER2-negative); **OR**
      a. The tumor is HER2- overexpression positive (HER-2 positive); **AND**
         i. The member has received prior HER2/neu-targeted therapy (e.g., trastuzumab); **AND**
   iv. Provider attests that trifluridine/tipiracil (Lonsurf) is being requested as a third-line or subsequent therapy; **AND**
   v. Trifluridine/tipiracil (Lonsurf) will be used as monotherapy

II. Trifluridine/tipiracil (Lonsurf) is considered investigational when used for all other conditions, including but not limited to:
   A. Combination therapy with other oncolytic agents not outlined above
   B. Colorectal, gastric, or gastroesophageal cancer at a dose <20 mg/m2 orally twice daily
   C. Non adenocarcinoma gastric or gastroesophageal junction (e.g., squamous cell type)
   D. Gastric or gastroesophageal junction adenocarcinoma prior to at least two previous lines of chemotherapy and prior to use of all of the following: a fluoropyrimidine, a platinum therapy, and one of the following – taxane or irinotecan
   E. Biliary track cancers
   F. Tumors that are not colorectal, gastric or gastroesophageal in nature

Renewal Evaluation

I. Member has a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation of member's current body surface area is provided in meters squared; **AND**
IV. Trifluridine/tipiracil (Lonsurf) is being used at or above a dose of 20 mg/m2; **AND**
V. The member has not experienced disease progression while on trifluridine/tipiracil (Lonsurf); **OR**

- Documentation of compelling clinical evidence of benefit is provided if therapy is to be continued in the setting of progression.

Supporting Evidence

I. Trifluidine is an orally administered nucleoside analog that is incorporated into DNA to interfere with DNA synthesis and proliferation, and tipiracil increases exposure to trifluridine by inhibiting thymidine phosphorylase. The clinical trials for FDA-approval of trifluridine/tipiracil (Lonsurf) were in patients 18 years and older; therefore, there is a lack of safety and efficacy data from clinical trials for use in pediatric patients.

II. Many treatment options exist for the conditions listed in this policy. Initial and next line therapies in these settings is contingent upon patient specific characteristics. Given the complexities surrounding diagnosis and treatment choices, targeted drug therapies should be prescribed by, or in consultation with, a specialist.

III. Pivotal clinical trials for FDA-approved indications evaluated safety and efficacy of trifluridine/tipiracil (Lonsurf) as monotherapy in heavily pretreated patients. The therapies listed in the above criteria had been tried and failed by the majority of patients enrolled in the clinical trials.

IV. **Colorectal Cancer (CRC)**

- 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. Patients had received at least 2 prior regimens of standard chemotherapy and were refractory to, or failing, all of the following within three months: Fluoropyrimidine, irinotecan and oxaliplatin, anti-VEGF biologic therapy, anti-EGFR therapy (if *RAS* wild type). Eight hundred total patients were enrolled and 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. The primary outcome was overall survival (OS) measured every 8 weeks until defined endpoint. Secondary outcome measures were progression-free survival (PRS) and percentage of patients with adverse events. The median OS improved from 5.3 months with placebo to 7.1 months with LONSURF, and the hazard ratio for death in the LONSURF group versus the placebo group was 0.68 (95% confidence interval [CI], 0.58 to 0.81; P<0.001).
- Currently, trifluridine/tipiracil (Lonsurf) is approved by the FDA for use in monotherapy in both metastatic gastric cancer and metastatic colorectal cancer, mCRC. The NCCN revised their opinion on this for the mCRC guidelines allowing therapy with bevacizumab in combination with trifluridine/tipiracil (Lonsurf) versus requiring failure of bevacizumab first or requiring trifluridine/tipiracil (Lonsurf) to be used as monotherapy. The panel had this decision from a review of the following

information: A phase I single-arm, open label study (C-TASK FORCE) where all patients (n=25) enrolled were refractory/intolerant to fluoropyrimidine, irinotecan, oxaliplatin, anti-VEGF therapy, and anti-EGFR therapy (if wild-type *KRAS*). The endpoint was PFS at 16 weeks which was 42.9%. Based on this information, a Danish phase II trial was done with 93 mCRC patients comparing trifluridine/tipiracil (Lonsurf) with and without bevacizumab. After a median follow-up of 10 months, the median PFS (primary endpoint) was 2.6 months for trifluridine/tipiracil (Lonsurf) alone compared to 4.6 months in combination with bevacizumab (HR, 0.45; 95% CI, 0.29-0.72; P = .0015). A retrospective study of 57 patients with refractory mCRC showed similar results, with an improved median OS for trifluridine/tipiracil (Lonsurf) with bevacizumab versus without (14.4 months vs. 4.5 months; P < .001). Based on this data, the panel added +/- use of bevacizumab as a treatment option for patients progressing through standard therapies. This same treatment is currently being evaluated in a phase III trial, SUNLIGHT, due for completion in 2023.

V. **Gastric or gastroesophageal junction adenocarcinoma**

- 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. 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. Five hundred and seven total patients received either 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. The primary outcome was OS and secondary outcomes were PFS and adverse events. Median overall survival was 5.7 months (95% CI 4·8-6·2) in the trifluridine/tipiracil (Lonsurf) group and 3.6 months (3·1-4·1) in the placebo group (hazard ratio 0·69 [95% CI 0·56-0·85]; one-sided p=0·00029, two-sided p=0·00058). Presently, molecular testing for HER2 status, microsatellite instability status, and PD-L1 expression are used in the clinical management of locally advanced, unresectable, and metastatic EGJ cancers. HER2 testing is recommended for all patients with esophageal or EGJ cancer at the time of diagnosis if metastatic disease is documented or suspected.
- There is no globally accepted standard for first-line treatment of HER2/neu negative gastric or gastroesophageal adenocarcinoma. When these indications were added to the policy, NCCN guidelines were not updated to provide recommendations for

this agent. Clinical trial experience with extensive patient treatment history is the basis for addition into the policy.

VI. The recommended dosage for trifluridine/tipiracil (Lonsurf) is 35mg/m2/dose orally twice a day; however, due to the medication's adverse events, dose decreases are common and from the package insert, a maximum of 3 dose reductions are permitted. It is recommended to permanently discontinue trifluridine/tipiracil (Lonsurf) in patients who are unable to tolerate a dose of 20 mg/m2 orally twice daily and to not escalate dosage after it has been reduced. There is one exception to the 20mg/m2 and that is those with severe renal impairment (CrCl 15-29), who can go to 15mg/m2 and then should discontinue if unable to be tolerated.

Investigational or Not Medically Necessary Uses

All indications listed below have not been sufficiently studied for safety and efficacy, or have inconclusive evidence regarding safety and efficacy for use of trifluridine/tipiracil (Lonsurf).

I. Combination therapy with other oncolytic agents
II. Colorectal cancer prior to the metastatic setting, and/or prior to use of a fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy regimen, and/or prior to use of an anti-VEGF biological therapy, and/or if the member is KRAS mutant-type use prior to an anti-EGFR therapy
III. Colorectal, gastric, or gastroesophageal cancer at a dose < 20 mg/m2 orally twice daily
IV. Non adenocarcinoma gastric or gastroesophageal junction (e.g., squamous cell type)
V. Gastric or gastroesophageal junction adenocarcinoma prior to at least two previous lines of chemotherapy and prior to use of all of the following: a fluoropyrimidine, a platinum therapy, and one of the following – taxane or irinotecan
VI. Biliary track cancers
VII. Tumors that are not colorectal, gastric, or gastroesophageal in nature

References

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8. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancer guideline Version 2.2022. Available at: gastric cancer (nccn.org) Accessed March 07, 2022.
9. National Comprehensive Cancer Network. Colon Cancer guideline Version1.2022. Available at: colon cancer (nccn.org). Accessed March 9, 2022.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
regorafenib (Stivarga)	Colorectal Cancer
encorafenib (Braftovi)	

Policy Implementation/Update:

Action and Summary of Changes	Date
Reformatted existing policy to match current standards. Updated renewal section to match requirements across other anti-cancer policies. Reviewed and updated references for building a better supportive evidence section. Included addition under mCRC for combination use with Avastin (bevacizumab). Updated initial approval duration from 3 months to 6 months.	10/2022
Added new indication of stomach and esophagogastric adenocarcinoma based on clinical trial data that demonstrated overall survival in the third line treatment setting.	03/2019
Policy originally created and effective	5/2015