

<b>Clinical Policy Title:</b>	trifluridine/tipiracil
<b>Policy Number:</b>	RxA.396
<b>Drug(s) Applied:</b>	Lonsurf®
<b>Original Policy Date:</b>	03/06/2020
<b>Last Review Date:</b>	09/14/2020
<b>Line of Business Policy Applies to:</b>	All lines of business

## Background

Trifluridine/tipiracil (Lonsurf®) is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor.

Lonsurf® is indicated for the treatment of adult patients with:

- Metastatic colorectal cancer (CRC) previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy;
- Metastatic gastric or gastroesophageal junction (GEJ) 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.

## Dosing Information

Drug name	Indication	Dosing Regimen	Maximum Dose
Trifluridine/Tipiracil (Lonsurf®)	Metastatic CRC, GC, and GEJ adenocarcinoma	35 mg/m <sup>2</sup> /dose PO BID on Days 1 through 5 and Days 8 through 12 of each 28-day cycle	160 mg/day (based on the trifluridine component)

## Dosage Forms

- Tablets: 15 mg trifluridine/6.14 mg tipiracil, 20 mg trifluridine /8.19 mg tipiracil.

## Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

### I. Initial Approval Criteria

#### A. Colorectal Cancer (must meet all):

1. Diagnosis of metastatic or unresectable CRC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Documentation of RAS (KRAS or NRAS) wild-type gene status;
5. Failure of the following agents,\* unless contraindicated or clinically significant adverse effects are experienced:
  - a. 5-fluorouracil or capecitabine;
  - b. Oxaliplatin and irinotecan;

This clinical policy has been developed to authorize, modify, or determine coverage for individuals with similar conditions. Specific care and treatment may vary depending on individual need and benefits covered by the plan. This policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. This document may contain prescription brand name drugs that are trademarks of pharmaceutical manufacturers that are not affiliated with RxAdvance.

- c. An anti-VEGF agent: Avastin®, Cyramza®, Stivarga® or Zaltrap®;
- d. If tumor expresses the RAS wild-type gene, an anti-EGFR agent: Erbitux® or Vectibix®;  
*\*Prior authorization may be required.*
6. Attestation of obtaining complete blood counts prior to and on Day 15 of each cycle and more frequently as clinically indicated;
7. Request meets one of the following (a or b):
  - a. Dose does not exceed 160 mg per day (based on the trifluridine component; round dose to the nearest 5 mg increment given 15 and 20 mg tablets);
  - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber *must submit supporting evidence*).

**Approval duration**

**Commercial:** 6 months

**Medicaid:** 6 months

**B. Gastric Cancer or Gastroesophageal Junction Adenocarcinoma (must meet all):**

1. Diagnosis of metastatic, unresectable, or recurrent gastric cancer (GC) or GEJ adenocarcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Documentation of HER2/neu gene status;
5. Attestation of obtaining complete blood counts prior to and on Day 15 of each cycle and more frequently as clinically indicated;
6. Failure of at least two of the following agents,\* unless contraindicated or clinically significant adverse effects are experienced:
  - a. 5-fluorouracil or capecitabine;
  - b. Cisplatin, carboplatin, or oxaliplatin;
  - c. Docetaxel, paclitaxel, or irinotecan;*\*Prior authorization may be required.*
7. If tumor is HER2/neu-positive (i.e., HER2-overexpressing): Failure of Herceptin®, unless contraindicated or clinically significant adverse effects are experienced;  
*\*Prior authorization may be required for Herceptin®*
8. Request meets one of the following (a or b):
  - a. Dose does not exceed 160 mg per day (based on the trifluridine component; round dose to the nearest 5 mg increment given 15 and 20 mg tablets);
  - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber *must submit supporting evidence*).

**Approval duration**

**Commercial:** 6 months

**Medicaid:** 6 months

**II. Continued Therapy**

**A. All Indications in Section I (must meet all):**

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. Attestation of obtaining complete blood counts prior to and on Day 15 of each cycle and more frequently as clinically indicated;
4. If request is for a dose increase, request meets one of the following (a or b):
  - a. New dose does not exceed 160 mg per day (based on the trifluridine component).

- b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

**Approval duration**

**Commercial:** 12 months

**Medicaid:** 6 months

**III. Appendices**

**APPENDIX A: Abbreviation/Acronym Key**

5-FU: 5-fluorouracil

CRC: colorectal carcinoma

EGFR: epidermal growth factor receptor

FDA: Food and Drug Administration

GC: gastric cancer

GEJ: gastroesophageal junction

VEGF: vascular endothelial growth factor

**APPENDIX B: Therapeutic Alternatives**

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.*

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
<b>Fluoropyrimidine, platinum, and irinotecan therapeutic agents and examples of regimens</b>		
5 FU (fluorouracil)*	<p><b>CRC</b> 400 mg/m<sup>2</sup> IV on day 1, 1,200 mg/m<sup>2</sup> for 2 days</p> <p><b>GC/GEJ adenocarcinoma</b> 750-1,000 mg/m<sup>2</sup> IV daily on Days 2-4 of every 28-day cycle in combination with cisplatin OR 2,000 mg/m<sup>2</sup> IV on Day 1 of every 14-day cycle in combination with leucovorin and cisplatin OR 800 mg/m<sup>2</sup> IV on Days 1-5 of every 28-day cycle</p>	2,400 mg/m <sup>2</sup>

capecitabine (Xeloda®)*	<p><b>CRC</b> 1,250 mg/m<sup>2</sup> PO BID on Days 1-14. Repeat every 21 days for 8 cycles.</p> <p><b>GC/GEJ adenocarcinoma</b> 1000-1,250 mg/m<sup>2</sup> PO BID on Days 1-14 of every 21-day cycle OR 1,000 mg/m<sup>2</sup> PO BID on Days 1-14 in combination with cisplatin 80 mg/m<sup>2</sup> IV on Day 1 of every 21-day cycle OR 1,000 mg/m<sup>2</sup> PO BID on Days 1-14 in combination with oxaliplatin 130 mg/m<sup>2</sup> IV on Day 1 of every 21-day cycle</p>	2500 mg/m <sup>2</sup> /day
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irinotecan (Camptosar®)	<p><b>CRC</b> 125 mg/m<sup>2</sup> IV in combination with 5-FU based chemotherapy</p> <p><b>GC/GEJ adenocarcinoma</b> 180 mg/m<sup>2</sup> IV on Day 1 of each 14-day cycle in combination with leucovorin and fluorouracil OR 80 mg/m<sup>2</sup> IV on Day 1 weekly for 6 weeks followed by 2 weeks off treatment, in combination with leucovorin and fluorouracil</p>	350 mg/m <sup>2</sup>
oxaliplatin	85 mg/m <sup>2</sup> IV in combination with 5-FU based chemotherapy	130 mg/m <sup>2</sup>
FOLFOX = Infusional 5-FU/leucovorin /oxaliplatin	<p><b>CRC</b> Eloxatin (oxaliplatin) 85 mg/m<sup>2</sup> IV on Day 1; leucovorin 200 mg/m<sup>2</sup> IV on Days 1 &amp; 2, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus, followed by 5-FU 600 mg/m<sup>2</sup> IV on Days 1 &amp; 2. Repeat cycle every 14 days.</p> <p><b>Gastric cancer/GEJ adenocarcinoma</b> Eloxatin (oxaliplatin) 85 mg/m<sup>2</sup> IV on Day 1; leucovorin 400 mg/m<sup>2</sup> IV on Day 1; 5-FU 400 mg/m<sup>2</sup> IV bolus on Day 1, followed by 5-FU 1,200 mg/m<sup>2</sup> IV on Days 1 &amp; 2. Repeat cycle every 14 days. OR</p>	Varies

	Eloxatin (oxaliplatin) 85 mg/m <sup>2</sup> IV on Day 1; leucovorin 200 mg/m <sup>2</sup> IV on Day 1; 5-FU 2,600 mg/m <sup>2</sup> IV continuous infusion on Day 1. Repeat cycle every 14 days.	
FOLFIRI = Infusional 5FU/leucovorin/ irinotecan (Camptosar®)	<p><b>CRC</b> Irinotecan 180 mg/m<sup>2</sup> IV over 90 minutes day 1; leucovorin 400 mg/m<sup>2</sup> IV over 2 hours day 1 followed by 5-FU 400 mg/m<sup>2</sup> IV bolus over 2-4 minutes, followed by 2.4-3 gm/m<sup>2</sup> IV 5-FU continuous infusion over 46 hours. Repeat cycle every 14 days.</p> <p><b>GC/GEJ adenocarcinoma</b> Irinotecan 180 mg/m<sup>2</sup> IV on Day 1; leucovorin 400 mg/m<sup>2</sup> IV on Day 1; 5-FU 400 mg/m<sup>2</sup> IV bolus on Day 1, followed by 1200 mg/m<sup>2</sup> IV continuous infusion on Days 1 and 2. Repeat cycle every 14 days.</p>	Varies

<b>Anti-VEGF therapy for CRC</b>		
Avastin® (bevacizumab)	5 or 10 mg/kg IV every 14 days in combination with 5-FU based chemotherapy	20 mg/kg
Cyramza® (ramucirumab)	8 mg/kg IV every 2 weeks plus FOLFIRI regimen	10 mg/kg per dose
Stivarga® (regorafenib)	160 mg PO QD on Days 1-21 of each 28-day cycle	160 mg/day
Zaltrap® (zivaflibercept)	160 mg PO QD for the first 21 days of each 28-day cycle	160 mg/day
<b>Anti-EGFR therapy for CRC</b>		
Erbitux® (cetuximab)	400 mg/m <sup>2</sup> IV for initial dose, then weekly infusions of 250 mg/m <sup>2</sup> IV	400 mg/m <sup>2</sup>
Vectibix® (panitumumab)	6 mg/kg IV every 2 weeks	9 mg/kg every 3 weeks
<b>HER2/neu therapy for GC or GEJ adenocarcinoma</b>		
Herceptin® (trastuzumab)	With chemotherapy: 8 mg/kg IV loading dose on Day 1 of cycle 1, then 6 mg/kg IV every 21 days OR 6 mg/kg IV loading dose on Day 1 of cycle 1, then 4 mg/kg IV every 14 days	8 mg/kg/dose
<b>Taxanes for GC or GEJ adenocarcinoma</b>		

docetaxel	75-100 mg/m <sup>2</sup> IV on Day 1 of every 21-day cycle	100 mg/m <sup>2</sup>
paclitaxel	135-250 mg/m <sup>2</sup> IV on Day 1 of every 21-day cycle OR 80 mg/m <sup>2</sup> IV on Day 1 weekly of every 28day cycle OR 80 mg/m <sup>2</sup> IV on Days 1, 8, and 15 of every 28-day cycle	250 mg/m <sup>2</sup>

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

\*5-FU and capecitabine are examples of fluoropyrimidine chemotherapeutic agents.

#### APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None.
- Boxed Warning(s):
  - None.

#### APPENDIX D: General Information

- 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
- Severe myelosuppression and embryo-fetal toxicity is a risk for patients.

#### References

1. Lonsurf Prescribing Information. Princeton, NJ: Taiho Oncology; December 2019. Available at: [www.taihooncology.com/us/prescribing-information](http://www.taihooncology.com/us/prescribing-information). Accessed July 29, 2020.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: [http://www.nccn.org/professionals/drug\\_compendium](http://www.nccn.org/professionals/drug_compendium). Accessed July 29, 2020.
3. National Comprehensive Cancer Network. Colon Cancer Version 2.2019. Available at: <http://www.nccn.com>. Accessed July 29, 2020.
4. National Comprehensive Cancer Network. Rectal Cancer Version 2.2019. Available at: <http://www.nccn.com>. Accessed July 29, 2020.
5. National Comprehensive Cancer Network. Gastric Cancer Version 1.2019. Available at: <http://www.nccn.com>. Accessed July 29, 2020.
6. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers Version 1.2019. Available at: <http://www.nccn.com>. Accessed July 29, 2020.
7. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed July 29, 2020.

Review/Revision History

Review/Revised Date

P&T Approval Date

Policy established	01/2020	03/06/2020
Policy was reviewed:	07/29/2020	09/14/2020
1) Policy title was updated.		
2) Indications were updated.		
3) Initial Approval criteria updated.		
4) Continued Therapy Approval criteria II.A.1 was rephrased.		
5) Appendices updated – General information updated.		
6) References were updated.		