Clinical Policy Title:	trifluridine/tipiracil
Policy Number:	RxA.396
Drug(s) Applied:	Lonsurf®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

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

It 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^2/dose by mouth twice daily 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. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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;
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 Approval

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 andmore 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
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Fluoropyrimidine, platinum, and irinotecan therapeutic agents and examples of regimens		
5 FU (fluorouracil)*	**CRC** 400 mg/m^2 intravenously on day 1, 1,200 mg/m^2 for 2 days **GC/GEJ adenocarcinoma** 750-1,000 mg/m^2 intravenously daily on Days 2-4 of every 28-day cycle in combination with cisplatin OR 2,000 mg/m2 intravenously on Day 1 of every 14-day cycle in combination with leucovorin and cisplatin OR 800 mg/m^2 intravenously on Days 1-5 of every 28-day cycle	2,400 mg/m^2
capecitabine (Xeloda®)*	**CRC** 1,250 mg/m2 orally twice daily on Days 1-14. Repeat every 21 days for 8 cycles. **GC/GEJ adenocarcinoma** 1000-1,250 mg/m2 orally twice daily on Days 1-14 of every 21-day cycle OR 1,000 mg/m2 orally twice daily on Days 1-14 in combination with cisplatin 80 mg/m2 intravenously on Day 1 of every 21-day cycle OR 1,000 mg/m2 orally twice daily on Days 1-14 in combination with oxaliplatin 130 mg/m2 intravenously on Day 1 of every 21-day cycle	2500 mg/m^2/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
irinotecan (Camptosar®)	**CRC** 125 mg/m^2 intravenously in combination with 5-FU based chemotherapy **GC/GEJ adenocarcinoma** 180 mg/m^2 intravenously on Day 1 of each 14-day cycle in combination with leucovorin and fluorouracil OR 80 mg/m^2 intravenously on Day 1 weekly for 6 weeks followed by 2 weeks off treatment, in combination with leucovorin and fluorouracil	350 mg/m^2
oxaliplatin	85 mg/m^2 intravenously in combination with 5-FU based chemotherapy	130 mg/m^2
FOLFOX = Infusional 5-FU/leucovorin /oxaliplatin	**CRC** Eloxatin (oxaliplatin) 85 mg/m2 intravenously on Day 1; leucovorin 200 mg/m2 intravenously on Days 1 & 2, followed by 5-FU 400 mg/m2 intravenous bolus, followed by 5-FU 600 mg/m2 intravenously on Days 1 & 2. Repeat cycle every 14 days. **Gastric cancer/GEJ adenocarcinoma** Eloxatin (oxaliplatin) 85 mg/m2 intravenously on Day 1; leucovorin 400 mg/m2 intravenously on Day 1; 5-FU 400 mg/m2 intravenous bolus on Day 1, followed by 5-FU 1,200 mg/m2 intravenously on Days 1 & 2. Repeat cycle every 14 days. OR Eloxatin (oxaliplatin) 85 mg/m2 intravenously on Day 1; leucovorin 200 mg/m2 intravenously on Day 1; 5-FU 2,600 mg/m2 intravenous continuous infusion on Day 1. Repeat cycle every 14 days.	Varies
FOLFIRI = Infusional 5FU/leucovorin/ irinotecan (Camptosar®)	**CRC** Irinotecan 180 mg/m^2 intravenously over 90 minutes day 1; leucovorin 400 mg/m^2 intravenously over 2 hours day 1 followed by 5-FU 400 mg/m^2 intravenous bolus over 2-4 minutes, followed by 2.4-3 gm/m^2 intravenous 5-FU continuous infusion over 46 hours. Repeat cycle every 14 days. **GC/GEJ adenocarcinoma** Irinotecan 180 mg/m^2 intravenously on Day 1; leucovorin 400 mg/m^2 intravenously on Day 1; 5-FU 400 mg/m^2 intravenous bolus on Day 1, followed by 1200 mg/m^2 intravenous continuous infusion on Days 1 and 2. Repeat cycle every 14 days.	Varies
Anti-VEGF therapy for CRC		

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Avastin® (bevacizumab)	5 or 10 mg/kg intravenously every 14 days in combination with 5-FU based chemotherapy	20 mg/kg
Cyramza® (ramucirumab)	8 mg/kg intravenously every 2 weeks plus FOLFIRI regimen	10 mg/kg per dose
Stivarga® (regorafenib)	160 mg orally once daily on Days 1-21 of each 28-day cycle	160 mg/day
Zaltrap® (ziva flibercept)	160 mg orally once daily for the first 21 days of each 28-day cycle	160 mg/day
Anti-EGFR therapy for CRC		
Erbitux® (cetuximab)	400 mg/m^2 intravenously for initial dose, then weekly infusions of 250 mg/m^2 intravenously	400 mg/m^2
Vectibix® (panitumumab)	6 mg/kg intravenously every 2 weeks	9 mg/kg every 3 weeks
HER2/neu therapy for GC or GEJ adenocarcinoma		
Herceptin® (trastuzumab)	With chemotherapy: 8 mg/kg intravenous loading dose on Day 1 of cycle 1, then 6 mg/kg intravenously every 21 days OR 6 mg/kg intravenous loading dose on Day 1 of cycle 1, then 4 mg/kg intravenously every 14 days	8 mg/kg/dose
Taxanes for GC or GEJ adenocarcinoma		
docetaxel	75-100 mg/m^2 intravenously on Day 1 of every 21-day cycle	100 mg/m^2
paclitaxel	135-250 mg/m^2 intravenously on Day 1 of every 21-day cycle OR 80 mg/m^2 intravenously on Day 1 weekly of every 28day cycle OR 80 mg/m^2 intravenously on Days 1, 8, and 15 of every 28-day cycle	250 mg/m^2

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.
*5-FU and capecitabine are examples of fluoropyrimidine chemotherapeutic agents.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None reported.

- Boxed Warning(s):
  - None reported.

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: https://www.lonsurf.com/. Accessed June 3,2021.
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3. National Comprehensive Cancer Network. Colon Cancer Version 2.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed June 3,2021.
4. National Comprehensive Cancer Network. Rectal Cancer Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed June 3,2021.
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7. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed June 3, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established	01/2020	03/06/2020
Policy was reviewed: 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.	07/29/2020	09/14/2020
Policy was reviewed: 1) Statement about provider sample, ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 2) Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance.." 3) Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic	06/03/2021	09/14/2021

name when the drug is available by generic only" 4) References were reviewed and updated.		