Clinical Policy: Trifluridine/Tipiracil (Lonsurf)

Reference Number: ERX.SPA.237
Effective Date: 09.01.18
Last Review Date: 08.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

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

FDA Approved Indication(s)

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.

Policy/Criteria

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

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Lonsurf is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of metastatic or advanced CRC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Documented of RAS (KRAS or NRAS) wild-type gene status;
5. Member has progressed through all available regimens for CRC that include all the following agents,* unless clinically significant adverse effects are experienced or all are contraindicated:
   a. 5-fluorouracil or capecitabine;
   b. Oxaliplatin and irinotecan;
   c. An anti-VEGF agent: bevacizumab, 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. 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*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Commercial – Length of Benefit
Medicaid – 6 months

B. Gastric Cancer or Gastroesophageal Junction Adenocarcinoma (must meet all)**:**
1. Diagnosis of metastatic, unresectable, advanced, 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. Member has previously been treated with at least two prior lines of chemotherapy that include all of the following agents,* unless contraindicated or clinically significant adverse effects are experienced (a, b, and c):
   a. 5-fluorouracil or capecitabine;
   b. Cisplatin, carboplatin, or oxaliplatin;
   c. Docetaxel, paclitaxel, or irinotecan;
   **Prior authorization may be required.*
6. If tumor is HER2/neu-positive (i.e., HER2-overexpressing): Failure of trastuzumab, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for trastuzumab.*
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*).
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Commercial – Length of Benefit
Medicaid – 6 months

C. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, or documentation supports that member is currently receiving Lonsurf for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. 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*).
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Commercial – Length of Benefit
Medicaid – 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

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 and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Fluoropyrimidine, platinum, and irinotecan therapeutic agents and examples of regimens		
5 FU (fluorouracil)*	**CRC:** 400 mg/m2 IV on day 1, 1,200 mg/m^2 for 2 days OR 225 mg/m2 IV over 24 hours 5 to 7 days/week **GC/GEJ adenocarcinoma:** 750-1,000 mg/m^2 IV daily on Days 2-4 of every 28 day cycle in combination with cisplatin OR 2,000 mg/m^2 IV on Day 1 of every 14 day cycle in combination with leucovorin and cisplatin OR 800 mg/m^2 IV on Days 1-5 of every 28-day cycle	2,400 mg/m^2
capecitabine (Xeloda®)*	**CRC:** 1,250 mg/m^2 PO bid days 1-14. Repeat every 21 days for 8 cycles. **GC/GEJ adenocarcinoma:** 1,000-1,250 mg/m^2 PO bid on Days 1-14 of every 21-day cycle OR 1,000 mg/m^2 PO bid on Days 1-14 in combination with cisplatin 80 mg/m^2 IV on Day 1 of every 21-day cycle OR 1,000 mg/m^2 PO bid on Days 1-14 in combination with oxaliplatin 130 mg/m^2 IV on Day 1 of every 21-day cycle	2,500 mg/m^2 /day
irinotecan (Camptosar®)	**CRC:** 125 mg/m^2 IV in combination with 5-FU based chemotherapy **GC/GEJ adenocarcinoma:** 180 mg/m^2 IV on Day 1 of each 14 day cycle in combination with leucovorin and fluorouracil OR	350 mg/m^2

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	80 mg/m^2 IV on Day 1 weekly for 6 weeks followed by 2 weeks off treatment, in combination with leucovorin and fluorouracil	
oxaliplatin	85 mg/m^2 IV in combination with 5-FU based chemotherapy	130 mg/m^2
FOLFOX = infusional 5-FU/leucovorin(LV) /Eloxatin™ (oxaliplatin)	**CRC:** Eloxatin (oxaliplatin) 85 mg/m^2 IV over 2 hours day 1; leucovorin 200 mg/m^2 IV over 2 hours day 1 & 2, followed by 5-FU 400 mg/m^2 IV bolus over 2-4 minutes, followed by 600 mg/m^2 IV 5-FU continuous infusion over 22 hours on day 1 & 2. Repeat cycle every 14 days. **Gastric cancer/GEJ adenocarcinoma:** Eloxatin (oxaliplatin) 85 mg/m^2 IV on Day 1; leucovorin 400 mg/m^2 IV on Day 1; 5-FU 400 mg/m^2 IV bolus on Day 1, followed by 1,200 mg/m^2 IV 5-FU continuous infusion over 24 hours on Days 1 & 2. Repeat cycle every 14 days. OR Eloxatin (oxaliplatin) 85 mg/m^2 IV on Day 1; leucovorin 200 mg/m^2 IV on Day 1; 5-FU 2600 mg/m^2 IV continuous infusion on Day 1. Repeat cycle every 14 days.	Varies
FOLFIRI = infusional 5-FU/leucovorin/ irinotecan (Camptosar®)	**CRC:** Irinotecan 180 mg/m^2 IV over 90 minutes day 1; leucovorin 400 mg/m^2 IV over 2 hours day 1 followed by 5-FU 400 mg/m^2 IV bolus over 2-4 minutes, followed by 2.4-3 gm/m^2 IV 5-FU continuous infusion over 46 hours. Repeat cycle every 14 days. **GC/GEJ adenocarcinoma:** Irinotecan 180 mg/m^2 IV on Day 1; leucovorin 400 mg/m^2 IV on Day 1; 5-FU 400 mg/m^2 IV bolus on Day 1, followed by 1200 mg/m^2 IV continuous infusion on Days 1 and 2. Repeat cycle every 14 days.	Varies
Anti-VEGF therapy – for CRC		
Avastin, Mvasi, Zirabev (bevacizumab, bevacizumab-awwb, bevacizumab-bvzr)	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 (ziv-aflibercept)	4 mg/kg IV every 14 days in combination with FOLFIRI	4 mg/kg every 2 weeks
Anti-EGFR therapy – for CRC		
Erbitux (cetuximab)	400 mg/m^2 IV for initial dose, then weekly infusions of 250 mg/m^2 IV	400 mg/m^2

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Vectibix (panitumumab)	6 mg/kg IV every 2 weeks	9 mg/kg every 3 weeks
HER2/neu therapy – for GC or GEJ adenocarcinoma		
Herceptin, Herzuma, Kanjinti, Ogivri, Ontruzant, Trazimera (trastuzumab, trastuzumab-pkrb,anns,dttb,dkst,qyyp)	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
Taxanes – for GC or GEJ adenocarcinoma		
docetaxel	75-100 mg/m^2 IV on Day 1 of every 21-day cycle	100 mg/m^2
paclitaxel	135-250 mg/m^2 IV on Day 1 of every 21-day cycle OR 80 mg/m^2 IV on Day 1 weekly of every 28-day cycle OR 80 mg/m^2 IV on Days 1, 8, and 15 of every 28-day cycle	250 mg/m^2

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
None reported

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Metastatic CRC, GC, and GEJ adenocarcinoma	35 mg/m^2/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)

VI. Product Availability
Tablets: 15 mg trifluridine/6.14 mg tipiracil, 20 mg trifluridine/8.19 mg tipiracil

VII. References
1. Lonsurf Prescribing Information. Princeton, NJ: Taiho Oncology; December 2019. Available at: www.taihooncology.com/us/prescribing-information. Accessed April 5, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed April 5, 2021.
3. National Comprehensive Cancer Network. Colon Cancer Version 2.2021. Available at: http://www.nccn.com. Accessed April 5, 2021.
4. National Comprehensive Cancer Network. Rectal Cancer Version 1.2021. Available at: http://www.nccn.com. Accessed April 5, 2021.
5. National Comprehensive Cancer Network. Gastric Cancer Version 2.2021. Available at: http://www.nccn.com. Accessed April 5, 2021.
6. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers Version 2.2021. Available at: http://www.nccn.com. Accessed April 5, 2021.
7. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed April 5, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	05.08.18	08.18
Criteria added for new FDA indication: gastric cancer and GEJ adenocarcinoma; references reviewed and updated.	04.09.19	05.19
3Q 2019 annual review: recurrent added to GC/GEJ per NCCN; added Medicaid line of business with 6/12 month approval durations; references reviewed and updated.	05.14.19	08.19
3Q 2020 annual review: added advanced CRC, GC, and GEJ per NCCN guidelines; changed T/F of Herceptin to trastuzuamb allowing usage of biosimilars as supported by NCCN guidelines; updated Appendix B; references reviewed and updated.	05.05.20	08.20
3Q 2021 annual review: for GC/GEJ adenocarcinoma clarified two prior lines of chemotherapy required per label and NCCN compendium; for CRC clarified per label and NCCN compendium that member has progressed through all available regimens; for CRC removed coverage for unresectable disease per NCCN compendium; references reviewed and updated.	04.05.21	08.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.