Clinical Policy: Trifluridine/Tipiracil (Lonsurf)

Reference Number: CP.PHAR.383
Effective Date: 11.16.16
Last Review Date: 08.22
Line of Business: Commercial, HIM, 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-vascular endothelial growth factor (VEGF) biological therapy, and if RAS wild-type, an anti-epidermal growth factor receptor (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.

It is the policy of health plans affiliated with Centene Corporation® 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 (including appendiceal adenocarcinoma);
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. 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. For brand Lonsurf requests, member must use generic trifluridine/tipiracil, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Prescribed as a single agent or in combination with bevacizumab*;
   **Prior authorization may be required*
8. Documentation of member's body surface area (m^2);
9. Request meets one of the following (a or b):*
   a. Dose does not exceed 70 mg/m^2 per day up to a maximum of 160 mg per day (based on the trifluridine component; round dose to the nearest 5 mg increment given 15 and 20 mg tablets) on Days 1 through 5 and 8 through 12 of each 28-day cycle;
   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:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

B. Gastric Cancer or Gastroesophageal Junction Adenocarcinoma (must meet all)**:**
1. Diagnosis of gastric cancer (GC) or GEJ adenocarcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. One of the following (a or b):
   a. Disease is metastatic, advanced, unresectable, or recurrent;
   b. Member is not a candidate for surgery;
5. Documentation of HER2/neu gene status;
6. 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.*
7. 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.*
8. For brand Lonsurf requests, member must use generic trifluridine/tipiracil, if available, unless contraindicated or clinically significant adverse effects are experienced;
9. Prescribed as a single agent;
10. Documentation of member's body surface area (m^2);
11. Request meets one of the following (a or b):*
    a. Dose does not exceed 70 mg/m^2 per day up to a maximum of 160 mg per day (based on the trifluridine component; round dose to the nearest 5 mg increment given 15 and 20 mg tablets) on Days 1 through 5 and 8 through 12 of each 28-day cycle;

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:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

C. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit, 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. For brand Lonsurf requests, member must use generic trifluridine/tipiracil, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. Documentation of member's body surface area (m^2);
5. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed 70 mg/m^2 per day up to a maximum of 160 mg per day (based on the trifluridine component) on Days 1 through 5 and 8 through 12 of each 28-day cycle;
   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:
Medicaid/HIM – 12 months
Commercial –12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies –

CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid, 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 for all relevant lines of business 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/m^2 IV on day 1, 1,200 mg/m^2 for 2 days OR 225 mg/m^2 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/m2 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 on Days 1-14. Repeat every 21 days for 8 cycles. **GC/GEJ adenocarcinoma** 1000-1,250 mg/m^2 PO BID on Days 1-14 of every 21-day cycle OR	2500 mg/m^2/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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	
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 80 mg/m^2 IV 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 IV in combination with 5-FU based chemotherapy	130 mg/m^2
FOLFOX = Infusional 5-FU/leucovorin /Eloxatin™ (oxaliplatin)	**CRC** Eloxatin (oxaliplatin) 85 mg/m^2 IV on Day 1; leucovorin 200 mg/m^2 IV on Days 1 & 2, followed by 5-FU 400 mg/m^2 IV bolus, followed by 5-FU 600 mg/m^2 IV on Days 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 5-FU 1,200 mg/m^2 IV 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 2,600 mg/m^2 IV continuous infusion on Day 1. Repeat cycle every 14 days.	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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
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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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 4, 2022.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed April 4, 2022.
3. National Comprehensive Cancer Network. Colon Cancer Version 1.2022. Available at: http://www.nccn.com. Accessed April 4, 2022.
4. National Comprehensive Cancer Network. Rectal Cancer Version 1.2022. Available at: http://www.nccn.com. Accessed April 4, 2022.
5. National Comprehensive Cancer Network. Gastric Cancer Version 2.2022. Available at: http://www.nccn.com. Accessed April 4, 2022.
6. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers Version 2.2022. Available at: http://www.nccn.com. Accessed April 4, 2022.
7. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed April 4, 2022.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2018 annual review: policies combined for Commercial and Centene Medicaid (new); off-label unresectable CRC added per NCCN; age and specialist requirements added; KRAS changed to RAS mutation per NCCN encompassing KRAS and NRAS; Cyramza and Stivarga added as anti-VEGF therapies per NCCN; dosing changed from 80 mg per dose to 160 mg per day to encompass BID regimen; continuation of care statement added; references reviewed and updated.	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; references reviewed and updated.	05.14.19	08.19
3Q 2020 annual review: added HIM line of business; 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; modified HIM.PHAR.21 to HIM.PA.154; added oral oncology generic redirection if available; references reviewed and updated.	04.05.21	08.21
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less	01.20.22	05.22
3Q 2022 annual review: per NCCN, added appendiceal adenocarcinoma as a type of colon cancer that is eligible for coverage, added requirement for use as a single agent (CRC, GC/GEJ) or in combination with bevacizumab (CRC), and added pathway for approval if member is not a surgical candidate for GC/GEJ; per PI, revised max dosing criterion to include body-weight dosing and allow therapy only on Days 1-5 and 8-12 of every 28-day cycle; added requirement for documentation of body surface area for dose calculation purposes; references reviewed and updated.	04.04.22	08.22

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. The Health Plan makes no representations and

accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.