Clinical Policy: Trifluridine/Tipiracil (Lonsurf)
Reference Number: CP.PHAR.383
Effective Date: 11.16.16
Last Review Date: 08.19
Line of Business: Commercial, Medicaid

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.

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 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. 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:**
- Medicaid – 6 months
- Commercial – Length of Benefit

**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. 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.*
  6. 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*
  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:**
- Medicaid – 6 months
- Commercial – Length of Benefit

**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 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. 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:**
- Medicaid – 12 months
Commercial – Length of Benefit

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 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 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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/ Maximum Dose</th>
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</thead>
<tbody>
<tr>
<td>5 FU (fluorouracil)*</td>
<td>CRC: 400 mg/m² IV on day 1, 1,200 mg/m² for 2 days</td>
<td>2,400 mg/m²</td>
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<td></td>
<td>GC/GEJ adenocarcinoma: 750-1,000 mg/m² 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/m² IV on Days 1-5 of every 28-day cycle</td>
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<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Dose Limit/Maximum Dose</td>
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<tr>
<td>capcitabine (Xeloda®)*</td>
<td><strong>CRC</strong> 1,250 mg/m² PO BID on Days 1-14. Repeat every 21 days for 8 cycles.</td>
<td>2500 mg/m²/day</td>
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<td></td>
<td><strong>GC/GEJ adenocarcinoma</strong> 1000-1,250 mg/m² PO BID on Days 1-14 of every 21-day cycle OR 1,000 mg/m² PO BID on Days 1-14 in combination with cisplatin 80 mg/m² IV on Day 1 of every 21-day cycle OR 1,000 mg/m² PO BID on Days 1-14 in combination with oxaliplatin 130 mg/m² IV on Day 1 of every 21-day cycle</td>
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<tr>
<td>irinotecan (Camptosar®)</td>
<td><strong>CRC</strong> 125 mg/m² IV in combination with 5-FU based chemotherapy</td>
<td>350 mg/m²</td>
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<tr>
<td></td>
<td><strong>GC/GEJ adenocarcinoma</strong> 180 mg/m² IV on Day 1 of each 14-day cycle in combination with leucovorin and fluorouracil OR 80 mg/m² IV on Day 1 weekly for 6 weeks followed by 2 weeks off treatment, in combination with leucovorin and fluorouracil</td>
<td></td>
</tr>
<tr>
<td>oxaliplatin</td>
<td>85 mg/m² IV in combination with 5-FU based chemotherapy</td>
<td>130 mg/m²</td>
</tr>
<tr>
<td>FOLFOX = Infusional 5-FU/leucovorin /Eloxatin™ (oxaliplatin)</td>
<td><strong>CRC</strong> Eloxatin (oxaliplatin) 85 mg/m² IV on Day 1; leucovorin 200 mg/m² IV on Days 1 &amp; 2, followed by 5-FU 400 mg/m² IV bolus, followed by 5-FU 600 mg/m² IV on Days 1 &amp; 2. Repeat cycle every 14 days. <strong>Gastric cancer/GEJ adenocarcinoma</strong> Eloxatin (oxaliplatin) 85 mg/m² IV on Day 1; leucovorin 400 mg/m² IV on Day 1; 5-FU 400 mg/m² IV bolus on Day 1, followed by 5-FU 1,200 mg/m² IV on Days 1 &amp; 2. Repeat cycle every 14 days. OR</td>
<td>Varies</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Dose Limit/ Maximum Dose</td>
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<tr>
<td><strong>Eloxatin (oxaliplatin)</strong> 85 mg/m² IV on Day 1; leucovorin 200 mg/m² IV on Day 1; 5-FU 2,600 mg/m² IV continuous infusion on Day 1. Repeat cycle every 14 days.</td>
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<tr>
<td><strong>FOLFIRI = Infusional 5-FU/leucovorin/irinotecan (Camptosar®)</strong></td>
<td><strong>CRC</strong> Irinotecan 180 mg/m² IV over 90 minutes on Day 1; leucovorin 400 mg/m² IV over 2 hours on Day 1 followed by 5-FU 400 mg/m² IV bolus over 2-4 minutes, followed by 2.4-3 gm/m² IV 5-FU continuous infusion over 46 hours. Repeat cycle every 14 days.</td>
<td>Varies</td>
</tr>
<tr>
<td><strong>CRC</strong> Irinotecan 180 mg/m² IV on Day 1; leucovorin 400 mg/m² IV on Day 1; 5-FU 400 mg/m² IV bolus on Day 1, followed by 1200 mg/m² IV continuous infusion on Days 1 and 2. Repeat cycle every 14 days.</td>
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<tr>
<td><strong>GC/GEJ adenocarcinoma</strong></td>
<td>Irinotecan 180 mg/m² IV on Day 1; leucovorin 400 mg/m² IV on Day 1; 5-FU 400 mg/m² IV bolus on Day 1, followed by 1200 mg/m² IV continuous infusion on Days 1 and 2. Repeat cycle every 14 days.</td>
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<tr>
<td><strong>Anti-VEGF therapy for CRC</strong></td>
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<tr>
<td>Avastin (bevacizumab) 5 or 10 mg/kg IV every 14 days in combination with 5-FU based chemotherapy</td>
<td>20 mg/kg</td>
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<tr>
<td>Cyramza (ramucirumab) 8 mg/kg IV every 2 weeks plus FOLFIRI regimen</td>
<td>10 mg/kg per dose</td>
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<tr>
<td>Stivarga (regorafenib) 160 mg PO QD on Days 1-21 of each 28-day cycle</td>
<td>160 mg/day</td>
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<tr>
<td>Zaltrap (ziv-aflibercept) 160 mg PO QD for the first 21 days of each 28-day cycle</td>
<td>160 mg/day</td>
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<tr>
<td><strong>Anti-EGFR therapy for CRC</strong></td>
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<tr>
<td>Erbitux (cetuximab) 400 mg/m² IV for initial dose, then weekly infusions of 250 mg/m² IV</td>
<td>400 mg/m²</td>
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<tr>
<td>Vectibix (panitumumab) 6 mg/kg IV every 2 weeks</td>
<td>9 mg/kg every 3 weeks</td>
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<tr>
<td><strong>HER2/neu therapy for GC or GEJ adenocarcinoma</strong></td>
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<tr>
<td>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</td>
<td>8 mg/kg/dose</td>
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<tr>
<td><strong>Taxanes for GC or GEJ adenocarcinoma</strong></td>
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<tr>
<td>docetaxel 75-100 mg/m² IV on Day 1 of every 21-day cycle</td>
<td>100 mg/m²</td>
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</tbody>
</table>
**CLINICAL POLICY**
**Trifluridine/Tipiracil**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
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<tbody>
<tr>
<td>paclitaxel</td>
<td>135-250 mg/m² IV on Day 1 of every 21-day cycle OR 80 mg/m² IV on Day 1 weekly of every 28-day cycle OR 80 mg/m² IV on Days 1, 8, and 15 of every 28-day cycle</td>
<td>250 mg/m²</td>
</tr>
</tbody>
</table>

*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**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
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<tbody>
<tr>
<td>Metastatic CRC, GC, and GEJ adenocarcinoma</td>
<td>35 mg/m²/dose PO BID on Days 1 through 5 and Days 8 through 12 of each 28-day cycle</td>
<td>160 mg/day (based on the trifluridine component)</td>
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</tbody>
</table>

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

**VII. References**
**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.