CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Trifluridine and Tipiracil (Lonsurf®)

Version: 1.0

EFFECTIVE DATE: 3/1/2025

NantHealth® | Eviti®

Please note the following:

Trifluridine and Tipiracil (Lonsurf®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within 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.

Trifluridine and Tipiracil (Lonsurf): Discussion

Trifluridine and tipiracil consists of two components: trifluridine, a thymidine-based nucleoside analog, and tipiracil, a phosphorylase inhibitor. Tipiracil increases the exposure of trifluridine by preventing its breakdown. Once inside cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis, and inhibits cell proliferation.[1,2]

The most common adverse reactions for single agent trifluridine and tipiracil (≥10%) are neutropenia, anemia, thrombocytopenia, fatigue, nausea, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

Trifluridine and tipiracil is approved by the Food and Drug Administration (FDA) for the following cancer types: colorectal, gastric, and gastroesophageal junction.[1]

The National Comprehensive Cancer Network (NCCN) endorses trifluridine and tipiracil for the following cancer types: colon, esophageal, esophagogastric junction, gastric, and rectal.[3,4,5,6]

Trifluridine and Tipiracil: Definitions

- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than 30 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.
- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **RAS** - Binary molecular switches that cycle between active guanosine triphosphate (GTP)-bound and inactive guanosine diphosphate (GDP)-bound states during signal transduction. These switches are normally tightly controlled, but mutations in the RAS genes or their regulators render RAS proteins persistently active in RAS-related diseases.[7]
- **Vascular Endothelial Growth Factor (VEGF)** - A signaling protein that promotes the growth of new blood vessels. VEGF forms part of the mechanism that restores the blood

supply to cells and tissues when they are deprived of oxygenated blood due to compromised blood circulation.

- **Wild-Type** - The natural, unchanged (unmutated) form of the gene.

Trifluridine and Tipiracil: Policy

Note: Coverage of trifluridine and tipiracil will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

Trifluridine and Tipiracil will be considered for coverage when the following criteria are met:

Colon Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Single agent or in combination with bevacizumab for patients with metastatic disease who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-epidermal growth factor receptor (EGFR) therapy[1]; OR

For **NCCN** required criteria coverage:

4. Second-line and subsequent therapy as a single agent or in combination with bevacizumab for advanced or metastatic disease (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progressed on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb]) not previously treated with trifluridine/tipiracil in patients who have progressed through all available regimens besides fruquintinib, regorafenib or trifluridine/tipiracil with or without bevacizumab[3]; OR

Appendiceal Adenocarcinoma

For **NCCN** required criteria coverage:

5. Second-line and subsequent therapy as a single agent or in combination with bevacizumab for advanced or metastatic disease (proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progressed on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb]) not previously treated with trifluridine/tipiracil in patients who have progressed through all available regimens besides fruquintinib, regorafenib or trifluridine/tipiracil with or without bevacizumab.[3]

Esophageal Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Palliative therapy for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease and a Karnofsky performance score (KPS) ≥60% or an ECOG performance score ≤2 as third-line or subsequent therapy as a single agent.[4]; OR

Esophagogastric Junction/Gastroesophageal Junction Cancers

For **FDA** required criteria coverage:

4. Previously treated with at least two prior lines of chemotherapy for metastatic disease that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy; OR

For **NCCN** required criteria coverage:

5. Palliative therapy for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease and a Karnofsky performance score (KPS) ≥60% or an ECOG performance score ≤2 as third-line or subsequent therapy as a single agent.[4]

Gastric Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Previously treated with at least two prior lines of chemotherapy for metastatic disease that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy[1]; OR

For **NCCN** required criteria coverage:

4. Palliative third-line or subsequent therapy as a single agent for locoregional disease in patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease (including peritoneal only metastatic disease, including positive cytology) and a KPS ≥60% or an ECOG performance score ≤2.[5]

Rectal Cancer

1. At least 18 years of age; AND

2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Single agent or in combination with bevacizumab for metastatic disease who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy[1]; OR

For **NCCN** required criteria coverage:

4. Second-line and subsequent therapy as a single agent or in combination with bevacizumab, if not previously given, for advanced or metastatic disease (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progressed on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb]) not previously treated with trifluridine/tipiracil in patients who have progressed through all available regimens besides fruquintinib, regorafenib or trifluridine/tipiracil with or without bevacizumab.[6]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Trifluridine and Tipiracil: References

1. Trifluridine and Tipiracil (Lonsurf) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/207981s012lbl.pdf. Accessed March 6, 2025.
2. Burness et al. Trifluridine/Tipiracil: A Review in Metastatic Colorectal Cancer. https://pubmed.ncbi.nlm.nih.gov/27568360/. Accessed March 6, 2025.
3. National Comprehensive Cancer Network. Colon Cancer. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed March 6, 2025.
4. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed March 6, 2025.
5. National Comprehensive Cancer Network. Gastric Cancer. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed March 6, 2025.
6. National Comprehensive Cancer Network. Rectal Cancer. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed March 6, 2025.
7. Simanshu et al. RAS Proteins and Their Regulators in Human Disease. https://pmc.ncbi.nlm.nih.gov/articles/PMC5555610/. Accessed March 6, 2025.

Trifluridine and Tipiracil: Coding (CPT®, ICD-10, and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

Code	Description
C15.9	Esophageal cancer
C16.0	Esophagogastric junction cancer
C16.9	Gastric cancer
C18.1	Appendiceal adenocarcinoma
C18.9	Colon cancer
C20.0	Rectal cancer
J8999	Trifluridine and tipiracil

Trifluridine and Tipiracil: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	3/1/2025
2	Policy Review Dates:	
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee:	3/20/2025
6	Revision Changes:	