

Trifluridine-tipiracil (LONSURF®) Criteria for Use May 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

The following recommendations are based on current medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vaww.pbm.va.gov> for further information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive Trifluridine-tipiracil*

- Care not provided by a VA or VA purchased care (e.g. Choice Program, Fee Basis) oncology provider
- Inability to swallow/tolerate oral medications
- History of non-compliance with medication, follow up or laboratory monitoring
- Known malabsorption condition
- Hypersensitivity to **Trifluridine**-tipiracil or its excipients (lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, magnesium stearate)
- ECOG Performance Status ≥ 2

Inclusion Criteria *The answers to all of the following must be fulfilled in order to meet criteria.*

- Patient with diagnosis of metastatic colorectal cancer AND (all of the following sub-criterion must be met)
 - Received prior treatment or is not a candidate to receive a fluoropyrimidine-based regimen
 - Received prior treatment or is not a candidate to receive an oxaliplatin-based regimen
 - Received prior treatment or is not a candidate to receive an irinotecan-based regimen
 - Received prior treatment or is not a candidate to receive an anti-VEGF agent (i.e. bevacizumab or ziv-aflibercept)
 - If KRAS wild type, received an anti-EGFR agent (i.e. cetuximab or panitumumab), if medically eligible

AND

- Goals of care and role of Palliative Care consult has been discussed and documented
- Life expectancy > 3 months
- ECOG* Performance Status 0 or 1
- Adequate baseline bone marrow, liver and renal function defined as the following [ULN is local laboratory range for parameter]*:
 - Hemoglobin value ≥ 9.0 g/dL
 - ANC $\geq 1,500/\text{mm}^3$
 - Platelet count $\geq 100,000/\text{mm}^3$
 - Total bilirubin $\leq 1.5 \times$ ULN
 - ALT and AST $\leq 3.0 \times$ ULN unless due to liver metastasis, then $\leq 5 \times$ ULN; See Issues for Consideration
 - CrCl > 30 mL/min

* RECURSE Study Group Protocol (Mayer et al., N Engl J Med 2015; 372: 1909)

- For women of childbearing potential **and** their partners:
 - Pregnancy should be excluded prior to receiving **Trifluridine**-tipiracil and the patient provided contraceptive counseling on potential risk vs. benefit of taking **Trifluridine**-tipiracil if patient were to become pregnant
 - Effective contraception should be used by both men and women during **Trifluridine**-tipiracil treatment and for at least 3 months after the final dose

Dosage and Administration

Note: Doses should be based upon **Trifluridine** component

Dosage

- **Trifluridine**-tipiracil 35 mg/m²/dose (to maximum 80 mg **Trifluridine** component); Round dose to nearest 5 mg increment.
- Take dose orally twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle.
- Take within 1 hour after completion of morning and evening meals
- Do not take additional doses to make up for missed or held doses

Administration

- Drug is available in the following dosage forms:
 - 15mg **Trifluridine**/6.14mg tipiracil
 - 20mg **Trifluridine**/8.19mg tipiracil
- **Trifluridine**-tipiracil is cytotoxic; Follow special handling and disposal procedures
- **Trifluridine**-tipiracil tablets should be stored at room temperature; If stored outside original bottle, discard after 30 days

Dose modifications

CBC counts should be obtained prior to and on Day #15 of each cycle

- Do not initiate the cycle of **Trifluridine**-tipiracil until:
 - ANC $\geq 1,500/\text{mm}^3$ or febrile neutropenia is resolved
 - Platelets $\geq 75,000/\text{mm}^3$
 - Grade 3 or 4 non-hematological adverse reactions are resolved to Grade 0 or 1
- Within a treatment cycle, withhold **Trifluridine**-tipiracil for any of the following:
 - ANC $< 500/\text{mm}^3$ or febrile neutropenia
 - Platelets $< 50,000/\text{mm}^3$
 - Grade 3 or 4 non-hematological adverse reactions
- After recovery, resume **Trifluridine**-tipiracil after reducing dose by $5 \text{ mg}/\text{m}^2/\text{dose}$ from previous dose level, if the following occur:
 - Febrile neutropenia
 - Uncomplicated Grade 4 neutropenia (which has recovered to greater than or equal to $1,500/\text{mm}^3$) or thrombocytopenia (which has recovered to greater than or equal to $75,000/\text{mm}^3$) that results in more than 1 week delay in start of next cycle
 - Non-hematologic Grade 3 or Grade 4 adverse reaction [except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication]
- Max of 3 dose-reductions permitted to minimum dose $20 \text{ mg}/\text{m}^2$ twice daily. Do not escalate doses after it has been reduced

Recommended Monitoring

- Obtain complete blood cell count (CBC) with differential prior to and on Day 15 of each cycle.
- Renal function at baseline and prior to each cycle
- LFTs at baseline and prior to each cycle
- Fever and signs/symptoms of infection
- Assess toxicity prior to dispense of each 28-day cycle
- Evidence of disease response or progression via radiologic assessment with Response Evaluation Criteria in Solid Tumors (RECIST) every 8 weeks (2 cycles)

Issues for Consideration

- Dosing regimen may be complicated for some as drug is taken twice daily on non-consecutive days and may require multiple strengths to make up one dose. Ensure thorough patient and/or caregiver understanding of dosing regimen.
- Use cytotoxic handling and disposal precautions
- Subgroup analysis notes overall survival benefit in those who received ≥ 4 prior regimens
- Renal and Hepatic Dosing:
 - Not studied in patients with moderate to severe hepatic dysfunction or severe renal dysfunction
- Due to its metabolism pathway CYP-related drug interactions are not a concern

Discontinuation Criteria (any of the following)

- Evidence of disease progression via radiologic assessment with RECIST every 8 weeks (2 cycles)
- Non-compliance with therapy, laboratory or follow-up requests
- Decline in ECOG performance status to level unacceptable for patient to maintain quality of life*
- Persistent or recurring toxicity, despite dose modifications and patients requiring >3 dose reductions

*ECOG Performance Status *Am J Clin Oncol* 2982; 5: 649-655

0, fully active without restriction	3, confined to bed/chair more than 50% of time
1, restricted strenuous activity, but able to carry out light work	4, totally confined to bed/chair
2, ambulatory/capable self-care, unable to carry out work activities	5, dead

Prepared April 2016 by Carson Bechtold, Pharm.D., PGY2 Pharmacy Outcomes and Healthcare Analytics Resident, VISN 17 PBM

Contact person: Berni Heron, Pharm.D., BCOP National PBM Clinical Pharmacy Program Manager, Department of Veterans Affairs, Pharmacy Benefits Management