Drug Monograph

A - Drug Name

trifluridine / tipiracil

COMMON TRADE NAME(S): Lonsurf®

back to top

B - Mechanism of Action and Pharmacokinetics

Trifluridine is a thymidine-based nucleoside analogue, which is metabolized intracellularly into its triphosphate form and incorporated into DNA, thereby interfering with DNA synthesis and inhibiting cell proliferation. **Tipiracil** hydrochloride is a thymidine phosphorylase inhibitor which prevents the metabolism of trifluridine, prolonging its exposure.

Absorption	Bioavailability	Trifluridine: at least 57% Tipiracil: at least 27%
	Effects with food	C_{max} decreased by 40% when taken with high-fat, high-calorie meal.
	Peak plasma levels	2 to 3 hours (in patients with advanced solid tumors)
Distribution	PPB	Trifluridine: 96% (mainly serum albumin) Tipiracil: < 8%
Metabolism	Trifluridine is mainly eliminated via thymidine phosphorylase.	

	Inactive metabolites	Yes
Elimination	Urine	Trifluridine: 55% (inactive metabolites) Tipiracil: 27%
	Feces	Trifluridine: < 3% (unchanged) Tipiracil: 50%
	Half-life	Trifluridine: 2.0 hours (at steady state) Tipiracil: 2.4 hours (at steady state)

back to top

C - Indications and Status

Health Canada Approvals:

- Colorectal cancer
- Gastric cancer / gastroesophageal cancer

Refer to the product monograph for a full list and details of approved indications.

back to top

D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

The adverse effects reported below were mainly from a placebo-controlled, Phase III study in refractory metastatic colorectal cancer, where the incidences are ≥ 2% from the control group. Incidences marked with an asterisk (*) were observed in pooled data of colorectal cancer patients. They also include potentially severe, life-threatening or post-marketing adverse events reported from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Venous thromboembolism (2%)	D

Dermatological	Alopecia (7%)	E
	Paronychia (rare)	E
	Rash (4%)	E D
Gastrointestinal	Anorexia (39%) (4% severe)	D
	Diarrhea (32%) (3% severe)	E
	Dyspepsia (3%)	E
	Mucositis (8%)	E
	Nausea, vomiting (50%) (2% severe)*	I
General	Fatigue (38%) (4% severe)*	E
Hematological	Myelosuppression ± infection, bleeding (58%) (severe, including febrile neutropenia (39%))*	E
Metabolic / Endocrine	↓ K (4%)	E
Nervous System	Dysgeusia (7%)	E
Renal	Proteinuria (4%)	E
Respiratory	Interstitial lung disease (<1%) /pneumonitis	L
	Other (4%) Nasopharyngitis	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for trifluridine / tipiracil include myelosuppression ± infection, bleeding, nausea, vomiting, anorexia, fatigue and diarrhea.

Trifluridine / tipiracil has resulted in increased incidences of **gastrointestinal toxicities**. Anti-emetic, anti-diarrheal and other measures, such as fluid / electrolyte replacement therapy, should be administered early after onset of toxicity and as clinically indicated.

Severe and life-threatening **myelosuppression** (including a fatal case) has been observed with trifluridine / tipiracil. Appropriate measures, such as antimicrobial agents and granulocyte-colony stimulating factor, should be administered as clinically indicated.

back to top

E - Dosing

Refer to protocol by which the patient is being treated.

Do not start treatment with trifluridine / tipiracil until ANC ≥ 1.5 x 10^9/L, platelets ≥ 75 x 10^9/L and non-hematological toxicities ≤ grade 1.

Adults:

Oral: 35*mg/m^2 BID on Days 1 to 5 and Days 8 to 12 of each 28-day cycle

*Based on the trifluridine component; up to a maximum of 80 mg per dose

Dose Level	Dose* (mg/m^2) BID
0	35
-1	30
-2	25
-3	20
-4	Discontinue

*Based on trifluridine component

Dose Calculation Based on Body Surface Area (BSA)

Dose	BSA (m^2)	Dose (mg)*	Number of tablets per dose		Total daily dose (mg)*
			15 mg**	20 mg**	
35 mg/m^2	< 1.07	35	1	1	70
	1.07 – 1.22	40	0	2	80
	1.23 – 1.37	45	3	0	90
	1.38 – 1.52	50	2	1	100
	1.53 – 1.68	55	1	2	110
	1.69 – 1.83	60	0	3	120

	1.84 – 1.98	65	3	1	130
	1.99 – 2.14	70	2	2	140
	2.15 – 2.29	75	1	3	150
	≥ 2.3	80	0	4	160

*Given twice daily
**Based on trifluridine component

Dose Level	BSA (m^2)	Dose (mg)*	Number of tablets per dose		Total Daily Dose (mg)*
			15 mg**	20 mg**	
-1 (30 mg/m^2)	< 1.09	30	2	0	60
	1.09 – 1.24	35	1	1	70
	1.25 – 1.39	40	0	2	80
	1.4 – 1.54	45	3	0	90
	1.55 – 1.69	50	2	1	100
	1.7 – 1.94	55	1	2	110
	1.95 – 2.09	60	0	3	120
	2.1 – 2.28	65	3	1	130
	≥ 2.29	70	2	2	140
-2 (25 mg/m^2)	<1.1	25***	2***	1***	50***
	1.1 – 1.29	30	2	0	60
	1.3 – 1.49	35	1	1	70
	1.5 – 1.69	40	0	2	80
	1.7 – 1.89	45	3	0	90
	1.9 – 2.09	50	2	1	100
	2.1 – 2.29	55	1	2	110
	≥ 2.3	60	0	3	120
-3 (20 mg/m^2)	<1.14	20	0	1	40
	1.14 – 1.34	25***	2***	1***	50***

	1.35 – 1.59	30	2	0	60
	1.6 – 1.94	35	1	1	70
	1.95 – 2.09	40	0	2	80
	2.1 – 2.34	45	3	0	90
	≥ 2.35	50	2	1	100

*Given twice daily
**Based on trifluridine component

***For total daily dose of 50 mg; patients should take 1 x 20 mg tablet in the morning and 2 x 15 mg tablets in the evening.

Dosage with Toxicity:

Toxicity	Action
Hematologic	
Grade 3 thrombocytopenia (platelets 25 to < 50 x 10^9/L) OR Grade 4 thrombocytopenia or neutropenia (platelets < 25 x 10^9/L or ANC < 0.5 x 10^9/L) requiring a ≤ 1 week delay in start of next cycle	Hold*; restart next cycle at same dose level
Grade 4 thrombocytopenia or neutropenia (platelets < 25 x 10^9/L or ANC < 0.5 x 10^9/L) requiring a > 1 week delay in start of next cycle	Hold*; restart next cycle at ↓ one dose level
Febrile neutropenia	Hold*; restart next cycle at ↓ one dose level
Non-hematologic	
Grade 3 or 4 non-hematologic; except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhea responding to antidiarrheal therapy	Hold*; restart next cycle at ↓ one dose level
Interstitial Lung Disease/Pneumonitis (treatment-related)	Hold and investigate. If confirmed, discontinue permanently

*Restart when platelets recovered to ≥ 75 x 10^9/L and ANC recovered to ≥ 1.5 x 10^9/L and non-hematological toxicities ≤ grade 1. Do not re-escalate dose after it has been reduced.

Dosage with Hepatic Impairment:

Higher incidence of grade 3 or 4 hyperbilirubinemia was observed in patients with moderate hepatic impairment.

Hepatic Impairment	Bilirubin		AST	Starting Dose
Mild	≤ ULN	and	> ULN	No adjustment required
	< 1 – 1.5 x ULN	and	Any	
Moderate	> 1.5 – 3 x ULN	and	Any	Not recommended for use
Severe	> 3 x ULN			

Dosage with Renal Impairment:

Patients with moderate renal impairment (creatinine clearance = 30 - 59 mL/min) had a higher incidence (difference of at least 5%) of ≥ grade 3 adverse events (hemoglobin and leukocytes decreases) and serious adverse events compared to patients with normal or mild renal impairment.

<table>
<tr><th>Creatinine Clearance (mL/min)</th><th>Starting Dose</th></tr>
<tr><td>≥ 60</td><td>No adjustment required</td></tr>
<tr><td>30 - 59</td><td>No adjustment required; monitor closely for hematological toxicity and dose adjust accordingly</td></tr>
<tr><td>15 - 29</td><td>
<table>
<tr><th>Dose Level</th><th>Starting Dose* (mg/m^2) BID</th></tr>
<tr><td>0</td><td>20</td></tr>
<tr><td>-1</td><td>15</td></tr>
<tr><td>-2</td><td>Discontinue</td></tr>
</table>
</td></tr>
</table>

*Based on the trifluridine component

Dosage	BSA (m^2)	Dose (mg)*	Tablets per Dose		Total Daily Dose (mg)*
			15 mg**	20mg**	
20 mg/m^2	< 1.14	20	0	1	40
	1.14 to 1.34	25***	2 in the evening***	1 in the morning***	50***
	1.35 to 1.59	30	2	0	60
	1.6 to 1.94	35	1	1	70
	1.95 to 2.09	40	0	2	80
	2.1 to 2.34	45	3	0	90
	≥ 2.35	50	2	1	100
15 mg/m^2	< 1.15	15	1	0	30
	1.15 to 1.49	20	0	1	40
	1.5 to 1.84	25***	2 in the evening***	1 in the morning***	50***
	1.85 to 2.09	30	2	0	60
	2.1 to 2.34	35	1	1	70
	≥ 2.35	40	0	2	80

*Given twice daily
**Based on trifluridine component

***For total daily dose of 50 mg; patients should take 1 x 20 mg tablet in the morning and 2 x 15 mg tablets in the evening.

< 15 (End Stage Renal Disease)	Not studied, no data available

Dosage in the elderly:

No adjustments of starting dose needed. No overall differences in effectiveness were reported based on age (≥65 years of age versus <65 years); higher incidences of severe myelosuppression were observed in patients aged ≥ 65 compared with those < 65. Efficacy and safety data in patients ≥ 75 years old is limited.

Dosage based on ethnicity:

No dose adjustments required. Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been rarely observed in one clinical trial of Asian patients as well as post marketing. There is limited data in African American patients.

Children:

Not indicated; safety and effectiveness have not been established.

back to top

F - Administration Guidelines

- Trifluridine / tipiracil should be given orally with a glass of water, within one hour of completion of morning and evening meals.
- If a dose is missed or held, the patient should not make up for the missed dose.
- Store at room temperature (15 - 30°C) in its original packaging.

back to top

G - Special Precautions

Contraindications:

- Patients who have a known hypersensitivity to the drug or to any of its excipients

Other Warnings/Precautions:

- Contains lactose; carefully consider use in patients with hereditary lactase, glucose or galactose disorders
- Use with caution in patients who received prior radiotherapy; may be at higher risk of

hematological adverse effects

Other Drug Properties:

- Carcinogenicity: Unknown
  No long term carcinogenicity studies. Trifluridine / tipiracil is genotoxic in bacteria and mice; treat as potential carcinogen.

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Trifluridine / tipiracil is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose.
  Women using a hormonal contraceptive must also use a barrier contraceptive, as it is unknown whether trifluridine / tipiracil may reduce the effectiveness of hormonal contraceptives.
- Genotoxicity: Probable
- Excretion into breast milk: Probable
  Trifluridine / tipiracil are excreted in milk in animal studies. Breastfeeding is not recommended during treatment and for **1 day** after the last dose.
- Fertility effects: Unlikely

back to top

H - Interactions

Trifluridine is not metabolized by CYP P450 enzyme. Trifluridine, tipiracil and its metabolite FTY did not inhibit or induce the CYP enzymes 3A4, 1A2 or 2B6 *in vitro* studies.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Human thymidine kinase substrates (eg. zidovudine)	↓ efficacy of antiviral product	Compete with trifluridine for activation via thymidine kinases	Caution; monitor for decreased efficacy of antiviral, consider switching to alternative antiviral that is not human thymidine kinase substrate (eg. lamivudine, abacavir etc.)
CNT1, ENT1 and ENT2 inhibitors or inducers (eg. zidovudine)	Unknown	Trifluridine is a substrate of these nucleoside transporters	Caution

OCT2 and MATE1 inhibitors (eg. cimetidine, dolutegravir)	↑ tipiracil concentration	Tipiracil is a substrate of these transporters	Caution

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, before each cycle and at each visit (including Day 15)
Renal function tests	Baseline and at each visit
Liver function tests	Baseline and at each visit
Proteinuria (by dipstick)	Baseline and as clinically indicated
Clinical toxicity assessment for infection, bleeding, venous thromboembolism, GI and respiratory effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- trifluridine / tipiracil - For the treatment of metastatic gastric cancer (mGC) or adenocarcinoma of the gastroesophageal junction (GEJ) in adult patients, according to clinical criteria
- trifluridine / tipiracil - In combination with bevacizumab for treatment of metastatic colorectal cancer, according to clinical criteria

back to top

K - References

Mayer RJ et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015;372:1909-19.

Product monograph: Lonsurf® (trifluridine and tipiracil). Taiho Pharma Canada Incorporated, January 23, 2018.

Product monograph: Lonsurf® (trifluridine and tipiracil). Taiho Oncology Incorporated, October 2020.

November 2024 Updated Supplementary Public Funding section

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO

and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top