DRUG NAME: Trifluridine-tipiracil

SYNONYM(S): TAS-102[1]

COMMON TRADE NAME(S): LONSURF®

CLASSIFICATION: antimetabolite

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Trifluridine-tipiracil is an orally administered antimetabolite comprised of an antineoplastic thymidine-based nucleoside analogue (trifluridine), and a thymidine phosphorylase inhibitor (tipiracil).[1-4] Unlike other fluoropyrimidines such as fluorouracil and capecitabine, trifluridine is not metabolized by the dihydropyrimidine dehydrogenase (DPD) enzyme.[5] Once inside the cell, trifluridine is phosphorylated by thymidine kinase and incorporated into DNA, thereby interfering with DNA synthesis and preventing cell proliferation. Tipiracil enhances the oral availability of trifluridine by inhibiting its rapid degradation and subsequent first-pass metabolism by thymidine phosphorylase.[1-4]

PHARMACOKINETICS:

Oral Absorption	trifluridine: bioavailability = 57%, t_{max} = 2 h; tipiracil: bioavailability = 27%, t_{max} = 3 h; food effect: high-fat, high-calorie food intake reduces trifluridine C_{max} and tipiracil C_{max} and AUC by 40%	
Distribution	cross blood brain barrier?	no information found
	volume of distribution[6]	trifluridine: 21 L; tipiracil: 333 L
	plasma protein binding	trifluridine: > 96% (mainly serum albumin); tipiracil: < 8%
Metabolism	independent of cytochrome P450 enzymes	
	active metabolite(s)	no information found
	inactive metabolite(s)	trifluridine: 5-trifluoromethyl uracil (FTY) and others; tipiracil: 6-hydroxymethyluracil
Excretion	negative correlation between serum albumin levels and trifluridine clearance	
	urine	trifluridine: 55%; tipiracil: 27%
	feces	trifluridine: <3%; tipiracil: 50%
	terminal half life	trifluridine: 2 h; tipiracil: 2.4 h
	clearance	trifluridine: 3 L/h; tipiracil: 90 L/h

Adapted from standard reference[1,3,4] unless specified otherwise.

USES:

Primary uses:

*Colorectal cancer

*Gastric cancer

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- patients who have had ***prior radiotherapy*** may experience more hematological and myelosuppression related adverse reactions, including febrile neutropenia[3]

Special populations:
- ***patients aged 65 years or older*** may experience more grade 3 or 4 hematologic adverse events compared to younger patients[3,4]

Carcinogenicity: no information found

Mutagenicity: Mutagenic in Ames test and mammalian *in vitro* mutation test. Trifluridine-tipiracil is clastogenic in mammalian *in vivo* chromosome test.[3,4]

Fertility: In animal studies, dose related increases in the corpus luteum and implanting embryo counts were observed but did not affect female fertility. No effect on male fertility was observed.[3,4]

Pregnancy: In animal studies, trifluridine-tipiracil was teratogenic when administered during organogenesis at maternal exposures both lower than and approximately equal to the expected human exposure following recommended doses. Findings included decreased fetal weight, embryolethality, and various structural anomalies. Female patients of childbearing potential should use effective contraception during treatment and for at least six months after the last dose. Male patients with female partners of reproductive potential should use effective contraception for at least three to six months after the last dose.[2-4]

Breastfeeding is not recommended due to the potential secretion into breast milk. In animal studies, trifluridine, tipiracil, and/or their metabolites were present in breast milk. Women should wait at least one day after the last dose before breastfeeding.[2-4]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important[7]. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia (see paragraph following **Side Effects** table)	***anemia*** (40-45%, severe 16-19%)
	febrile neutropenia (2-4%)
	leukopenia (5-17%, severe 2-7%)
	lymphopenia (6%, severe 2%)
	neutropenia (29-39%, severe 20-23%)
	pancytopenia (2%, severe 2%)
	thrombocytopenia (7-10%, severe 2%)
cardiac	palpitations (2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
gastrointestinal	*emetogenic potential:* low[8]
	abdominal pain (15-21%, severe 2%)
	diarrhea (23-32%, severe 3%)
	dyspepsia (3%)
	hematemesis (2%, severe 1%)
	hemorrhage, gastrointestinal (2%, severe 1%)
	nausea (37-48%, severe 2-3%)
	stomatitis (5-8%, severe <1%)
	vomiting (25-28%, severe 2-4%)
general disorders and administration site conditions	asthenia (18%, severe 3%)
	chills (1%)
	fatigue (27-35%, severe 4-7%)
	influenza-like illness (2%)
	malaise (4%)
	pyrexia (8-19%, severe 1%)
hepatobiliary	liver disorder (1%)
infections and infestations	herpes zoster (2%, severe <1%)
	infections (23-27%, severe 5-6%)[4]; fatal events have been reported
	nasopharyngitis (2-4%)
	neutropenic sepsis (1%, severe 1%); fatal events have been reported
	oral candidiasis (2%)
	upper respiratory tract infection (3%)
	urinary tract infection (3%, severe 1%)
investigations	hyperbilirubinemia (3%, severe 2%)
metabolism and nutrition	***appetite decrease*** (34-39%, severe 4-9%)
	hypoalbuminemia (7%, severe 1%)
	hypocalcemia (3%)
	hypokalemia (3-4%, severe 1-2%)
musculoskeletal and connective tissue	arthralgia, myalgia (4%)
	musculoskeletal pain (3%)
nervous system	dysgeusia (3-7%)
	paresthesia (2%)
	peripheral neuropathy (2%)
	somnolence (3%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
psychiatric	anxiety (3%)
renal and urinary	proteinuria (4%)
respiratory, thoracic and mediastinal	epistaxis (1%)
	interstitial lung disease/pneumonitis (severe <1%); fatal events have been reported
	pleural effusion (4%, severe 2%)
	pulmonary embolism (2-3%, severe 2%)
skin and subcutaneous tissue	alopecia (4-7%)
	dry skin (2%)
	pruritis (2%)
	rash (4%)
vascular	hypotension (2%)

Adapted from standard reference[3,4,9,10] unless specified otherwise.

Myelosuppression can be severe or life-threatening. Fatal events related to neutropenic infection, sepsis, or septic shock have occurred. Monitor closely for signs of infection and treat as indicated. Manage myelosuppression with granulocyte-colony stimulating factor if appropriate and/or dose reductions or treatment interruptions of trifluridine-tipiracil as indicated.[1,3,4]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
human thymidine kinase substrates (e.g., zidovudine)[3]	may decrease efficacy of human thymidine kinase substrate	competition with trifluridine for activation via thymidine kinase	avoid combination if possible (consider alternative antiviral therapy); if not possible, monitor for decreased efficacy of human thymidine kinase substrate
zidovudine[3]	possible attenuation of anti-tumour activity and reduced efficacy of trifluridine-tipiracil	*in vitro* attenuation of cell growth inhibitory effects of trifluridine	avoid combination if possible (consider alternative antiviral therapy)

Tipiracil is an *in vitro* substrate for Organic Cation Transporter 2 (OCT2) and Multidrug and Toxic Compound Extrusion Protein-1 (MATE1); monitor for increased trifluridine-tipiracil toxicity when used concomitantly with OCT2 and MATE1 inhibitors.[3]

Trifluridine is an *in vitro* substrate for nucleoside transporters CNT1, ENT1 and ENT2; clinical significance is unknown.[3]

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SUPPLY AND STORAGE:

Oral: Taiho Pharma Canada Inc. supplies trifluridine-tipiracil as 15 mg-6.14 mg and 20 mg-8.19 mg film-coated tablets. Tablets contain lactose. Store at room temperature.[3]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral:

Cycle Length:

4 weeks[11-13]:

35 mg/m² based on the trifluridine component (range 15-35 mg/m²) ***PO twice daily for five consecutive days from days 1 to 5 and repeated from days 8 to 12***
(total dose per cycle 700 mg/m² [range 300-700 mg/m²])

Round dose to the nearest 5 mg increment[4]

Maximum = 80 mg per dose (based on the trifluridine component)

Administer with food (i.e., within 1 hour of completion of morning and evening meals).[3]

For Dose Dispensing table: refer to protocol by which patient is being treated; in the absence of a protocol, the table below may be used to calculate the dose according to Body Surface Area (BSA):[3,4]

Dose	BSA (m^2)	Dose (mg) (given BID)	Number of tablets per dose		Total daily dose (mg)
			15 mg tablet*	20 mg tablet*	
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
	≥2.30	80	0	4	160

* based on the trifluridine component (see **Supply and Storage)**:
15 mg tablet = trifluridine-tipiracil 15 mg-6.14 mg tablet
20 mg tablet = trifluridine-tipiracil 20 mg-8.19 mg tablet

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Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated

Dosage in renal failure: modify according to protocol by which patient is being treated; in the absence of a protocol, the following recommendations can be used:

Creatinine Clearance (mL/min)	Dose adjustment
≥60	no adjustment required[3,4]
30-59	no adjustment required; monitor for increased hematologic toxicity[3]
15-29	20 mg/m^2 (based on the trifluridine component) PO BID on days 1-5 and 8-12 of each cycle[4,11]
<15	avoid; no information found

calculated creatinine clearance = $\frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure[11]*:* modify according to protocol by which patient is being treated; in the absence of a protocol, the following recommendations can be used:

Degree of Baseline Impairment	Total Bilirubin	AST	Dose adjustment
mild	<1.5 ULN	--	no adjustment required
moderate	1.5-3 x ULN	--	avoid; higher incidence of developing grade 3 or 4 hyperbilirubinemia
severe	>3 x ULN	any	avoid; no information found

Dosage in dialysis: no information found

Children: safety and efficacy not established[3]

REFERENCES:

1. Lexi-Drugs® - Lexicomp Online (database on the Internet). Trifluridine and Tipiracil. Wolters Kluwer Clinical Drug Information Inc., 2020. Available at: http://online.lexi.com. Accessed 7 April, 2020
2. AHFS Drug Information® - Lexicomp Online (database on the Internet). Trifluridine and Tipiracil Hydrochloride. Wolters Kluwer Clinical Drug Information Inc., 2020. Available at: http://online.lexi.com. Accessed 7 April, 2020
3. Taiho Pharma Canada Inc. LONSURF® product monograph. Oakville, Ontario; November 18 2019
4. Taiho Oncology Inc. LONSURF® full prescribing information. Princeton, NJ, USA; December 2019
5. Schouten JF, Willems J, Sanders, S. J. W. J., et al. Standard-Dose Trifluridine/Tipiracil as Safe Treatment Alternative in Metastatic Colorectal Cancer Patients With DPD Deficiency. Clin Colorectal Cancer 2021;20(4):359–363
6. Les Laboratoires Servier. LONSURF® product monograph (EU). Surenes, France; 25 April 2016
7. Howard Lim MD. BC Cancer Agency Gastrointestinal Tumour Group. Personal communication. July 2,2020
8. BC Cancer. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; December 1 2018
9. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015;372:1909-1919

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10. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2018;19(11):1437-1448
11. Taiho Pharma Canada Inc. LONSURF® product monograph. Oakville, Ontario; October 29 2020
12. BC Cancer Gastrointestinal Tumour Group. (GIAVTTB) BC Cancer Protocol Summary for Therapy of Advanced Colorectal Cancer Using Trifluridine-Tipiracil and Bevacizumab. Vancouver, British Columbia: BC Cancer; November 1 2024
13. BC Cancer Gastrointestinal Tumour Group. (GIGAVTT) BC Cancer Protocol Summary for Third- or Later-Line Therapy of Advanced Gastroesophageal Carcinoma Using Trifluridine-Tipiracil. (previously GIGAVTRFT). Vancouver, British Columbia: BC Cancer; November 1 2024

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