Trifluridine and Tipiracil (Lonsurf®) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.	C18	00382a	CDS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

The recommended starting dose of Lonsurf® in adults is 35 mg/m^2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle until disease progression or unacceptable toxicity occurs.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1,2,3,4,5 8,9,10,11,12	Lonsurf®	35 mg / m^2 BD* expressed in terms of trifluridine	PO within 1 hour after completion of morning and evening meals	N/a	Repeat every 28 days
*The dosage must not exceed 80 mg/dose See **table 1**: Starting dose calculation according to body surface area.					
If doses are missed or held, the patient must not make up for missed doses					
Lonsurf ® is available as tablets containing either 15 mg/6.14 mg and 20mg/8.19mg of trifluridine and tipiracil (as hydrochloride) respectively					

Table 1: Starting dose calculation according to body surface area (BSA)

Starting Dose	BSA (m^2)	Dose in mg (x 2 daily)	Tablets per dose (X2 daily)		Total daily dose (mg)
			15mg / 6.14mg	20mg/8.19mg	
35mg/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

ELIGIBILITY:

- Indications as above
- ECOG status 0-1
- Adequate haematological, hepatic and renal function

EXCLUSIONS:

- Hypersensitivity to trifluridine, tipiracil or any of the excipients
- Pregnancy*
- Lactation

*See Supportive Care for further details

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Proteinuria by dipstick analysis

Regular tests:

- FBC, renal and liver profile prior to each cycle or as clinically indicated
- Proteinuria by dipstick analysis prior to each cycle or as clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Dosing adjustments may be required based on individual safety and tolerability.
- A maximum of 3 dose reductions are permitted to a minimum dose of 20mg/m^2 twice daily.
- Dose escalation is not permitted after it has been reduced.
- In the event of haematological and/or non-haematological toxicities patients should follow the dose interruption, resumption and reduction criteria stated in Table 2, Table 3 and Table 7

Haematological:

Table 2: Dose interruption and resumption criteria for haematological toxicities related to myelosuppression

Parameter	Interruption Criteria	Resumption Criteria[a]
ANC	**< 0.5 × 10^9/L**	**≥ 1.5 × 10^9/L**
Platelets	**< 50 × 10^9/L**	**≥ 75 × 10^9/L**

[a] Resumption criteria applied to the start of the next cycle for all patients regardless of whether or not the interruption criteria were met.

Table 3: Recommended dose modifications for Lonsurf® in case of haematological adverse reactions

Adverse Reaction	Recommended Dose Modification
Febrile neutropenia	• Interrupt dosing until toxicity resolves to Grade 1 or baseline. • When resuming dosing, decrease the dose level by 5 mg/m^2/dose from the previous dose level
ANC < 0.5 × 10^9/L or platelets < 25× 10^9/L that results in more than 1 week's delay in start of next cycle	• Dose reductions are permitted to a minimum dose of 20 mg/m^2/dose twice daily. • Do not increase dose after it has been reduced.

Table 4: Dose reductions according to body surface area (BSA)

Reduced dose	BSA (m^2)	Dose in mg (x 2 daily)	Tablets per dose		Total daily dose (mg)
			15mg/6.14mg	20mg/8.19mg	
Level 1 dose reduction: From 35 mg/m^2 to 30 mg/m^2					
30mg/m^2	< 1.09	30	2	0	60
	1.09-1.24	35	1	1	70
	1.25-1.39	40	0	2	80
	1.40-1.54	45	3	0	90
	1.55-1.69	50	2	1	100
	1.70-1.94	55	1	2	110
	1.95-2.09	60	0	3	120
	2.10-2.28	65	3	1	130
	≥ 2.29	70	2	2	140
Level 2 dose reduction: From 30 mg/m^2 to25 mg/m^2					
25mg/m^2	<1.10	25 [a]	2[a]	1 [a]	50 [a]
	1.10-1.29	30	2	0	60
	1.30-1.49	35	1	1	70
	1.50-1.69	40	0	2	80
	1.70-1.89	45	3	0	90
	1.90-2.09	50	2	1	100
	2.10-2.29	55	1	2	110
	≥2.3	60	0	3	120
Level 3 dose reduction: From 25 mg/m^2 to 20 mg/m^2					
20mg/m^2	<1.14	20	0	1	40
	1.14-1.34	25 [a]	2[a]	1 [a]	50 [a]
	1.35-1.59	30	2	0	60
	1.60-1.94	35	1	1	70
	1.95-2.09	40	0	2	80
	2.10-2.34	45	3	0	90
	≥2.35	50	2	1	100

[a] At a total daily dose of 50mg, patients should take 1 x 20mg/8.19mg tablet in the morning and 2x15mg/6.14mg tablets in the evening

Renal and Hepatic Impairment:

Table 5: Dose modification of Lonsurf® in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
Cr Cl (ml/min)	**Recommended dose**		**Recommended dose**
30-89 (mild or moderate)	No adjustment of the starting dose is recommended	**Mild**	No adjustment of the starting dose is recommended
15-29 (severe renal impairment)	A starting dose of 20mg/m^2 twice daily is recommended. One dose reduction to a minimum dose of 15mg/m^2 twice daily is permitted based on individual safety and tolerability (see Table 6). Dose escalation is not permitted after it has been reduced.	**Moderate/ Severe**	Administration is not recommended in patients with baseline moderate or severe hepatic impairment (National Cancer Institute [NCI] Criteria Group C and D defined by total bilirubin > 1.5 x ULN) as, a higher incidence of Grade 3 or 4 hyperbilirubinaemia is observed in patients with baseline moderate hepatic impairment, although this is based on very limited data
<15 (end stage renal disease or requiring dialysis)	Not recommended		

Table 6: Starting dose and dose reduction in patients with severe renal impairment according to body surface area (BSA)

Reduced dose	BSA (m^2)	Dose in mg (x 2 daily)	Tablets per dose		Total daily dose (mg)
			15mg/6.14mg	20mg/8.19mg	
Starting dose					
20mg/m^2	< 1.14	20	0	1	40
	1.14–1.34	25[a]	2[a]	1[a]	50[a]
	1.35-1.59	30	2	0	60
	1.60-1.94	35	1	1	70
	1.95-2.09	40	0	2	80
	2.10-2.34	45	3	0	90
	≥ 2.35	50	2	1	100
Dose reduction: From 20mg/m^2 to 15mg/m^2					
15mg/m^2	<1.15	15	1	0	30
	1.15-1.49	20	0	1	40
	1.50-1.84	25[a]	2[a]	1[a]	50[a]
	1.85-2.09	30	2	0	60
	2.10-2.34	35	1	1	70
	≥2.35	40	0	2	80

[a] At a total daily dose of 50mg, patients should take 1 x 20mg/8.19mg tablet in the morning and 2x15mg/6.14mg tablets in the evening

Management of adverse events:

Table 7: Dose Modification for Lonsurf® in case of adverse reaction

Adverse reactions	Recommended dose modification
Non-haematologic Grade 3 or Grade 4 adverse reaction; except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhoea responsive to antidiarrhoeal medicinal products	• Interrupt dosing until toxicity resolves to Grade 1 or baseline. • When resuming dosing, decrease the dose level by 5 mg/m^2/dose from the previous dose level • Dose reductions are permitted to a minimum dose of 20mg/m^2/dose twice daily. • Do not increase dose after it has been reduced

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (**Refer to local policy).**

PREMEDICATIONS: None recommended

OTHER SUPPORTIVE CARE:

- Patients should be advised that Lonsurf® has minor influence on the ability to drive and use machines. Fatigue, dizziness or malaise may occur during treatment.
- **Adequate contraception**;
  - Women: Trifluridine may cause foetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking Lonsurf® and for up to 6 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking Lonsurf® and for 6 months after stopping treatment. It is currently unknown whether Lonsurf may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier contraceptive method.
  - Men with a partner of child-bearing potential must use effective contraception during treatment and for up to 6 months after discontinuation of treatment.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.
This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Infections and Bone marrow suppression:** Serious infections have been reported following treatment with Lonsurf®. Given that the majority were reported in the context of bone marrow suppression, the patient's condition should be monitored closely, and appropriate measures, such as antimicrobial agents and granulocyte-colony stimulating factor (G-CSF), should be administered as clinically indicated.
- **Gastrointestinal toxicity:** Patients with nausea, vomiting, diarrhoea and other gastrointestinal toxicities should be carefully monitored, and anti-emetic, anti-diarrhoeal and other measures, such as fluid/electrolyte replacement therapy, should be administered as clinically indicated. Dose modifications (delay and/or reduction) should be applied as necessary.
- **Lactose intolerance:** Lonsurf® contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

DRUG INTERACTIONS:

- Trifluridine is a substrate of thymidine phosphorylase. Caution is required when using medicinal products that are human thymidine kinase substrates.
- *In vitro* studies indicated that trifluridine, tipiracil hydrochloride and 5-[trifluoromethyl] uracil (FTY) did not inhibit the activity of human cytochrome P450 (CYP) isoforms.
- *In vitro* evaluation indicated that trifluridine, tipiracil hydrochloride and FTY had no inductive effect on human CYP isoforms.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Trifluridine/Tipiracil (Lonsurf ®) - L01BC59

REFERENCES:

1. Mayer R Van Cutsem E et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. N Engl J Med 2015;372:1909-19.
2. Lonsurf ®Summary of Product Characteristics. EMA. Accessed Dec 2020. Available at https://www.ema.europa.eu/en/documents/product-information/lonsurf-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	1/02/2017		Dr Maccon Keane
2	16/01/2019	Updated to new NCCP template. Updated details as per smpc update regarding drug strengths and rounding Updated dose modification in hepatic impairment as per SmPC Updated drug interactions	Prof Maccon Keane
3	06/01/2021	Updated dose modification in renal impairment as per SmPC, amended drug interactions.	Prof. Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.