Trifluridine/Tipiracil (Lonsurf ®) (Colorectal/Gastric/GOJ)

Indication

Treatment of metastatic colorectal cancer in patients who have previously received, or are not suitable for other available therapies including; fluoropyrimidine-, oxaliplatin- and irinotecan- based chemotherapies and anti VEGF and anti EGFR agents.

(NICE TA405)

Treatment of metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma in patients who have had 2 or more treatment regimens.

(NICE TA852)

ICD-10 codes

Codes with a prefix C18-20

Regimen details

Days	Drug	Dose	Route
1-5 and 8-12	Trifluridine/Tipiracil (Lonsurf)	35mg/m^2 BD*	PO

* Doses are based on the trifluridine dose and are rounded to the nearest 5mg. Maximum dose is 80mg BD.

Cycle frequency

28 days

Number of cycles

Continued until disease progression or unacceptable toxicity.

Administration

Trifluridine/Tipiracil is available as two strengths of tablet:
15 mg tablet containing 15 mg /6.14 mg of trifluridine and tipiracil (as hydrochloride)
20mg tablet containing 20 mg /8.19 mg of trifluridine and tipiracil (as hydrochloride)

Dosing is based on the trifluridine dose and is rounded to the nearest 5mg. The dose must not exceed 80mg BD.

Tablets should be taken twice a day within 1 hour of morning and evening meals. The doses should be swallowed whole with a glass of water. It may be easier for patients to take the tablets Monday-Friday for ease of remembering treatment days, although this is not essential.

Doses should be prescribed as per the following table:

Body surface area (m^2)	**Dose (mg)**	**Tablets per dose**	
		15mg	**20mg**
≤ 1.07	35mg BD	1	1
1.07-1.22	40mg BD	0	2
1.23-1.37	45mg BD	3	0
1.38-1.52	50mg BD	2	1
1.53-1.68	55mg BD	1	2
1.69-1.83	60mg BD	0	3
1.84-1.98	65mg BD	3	1
1.99-2.14	70mg BD	2	2
2.15-2.29	75mg BD	1	3
≥2.30	80mg BD	0	4

Pre-medication

Nil

Emetogenicity

This regimen has moderate-low emetic potential

Additional supportive medication

Loperamide if required.
Antiemetics if required.
Topical emollients to prevent PPE
Proton pump inhibitor if required.

Extravasation

N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Proteinuria (dipstick)	Baseline

ECG+/- echocardiogram if significant cardiac history.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Proteinuria (dipstick)	As indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.5 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine clearance (CrCl)	> 30 mL/min
Bilirubin	≤ 1.5 x ULN

Dose modifications

A maximum of 3 dose reductions are permitted to a minimum dose of 20mg/m^2 BD. See SPC for BSA based dose banding tables at the different dose reduction levels.

Dose level	Dose
Full dose	35mg/m^2 BD
First dose reduction	30mg/m^2 BD
Second dose reduction	25mg/m^2 BD
Third dose reduction	20mg/m^2 BD

Once the dose has been reduced it should not be re-escalated.

- **Haematological toxicity**

To commence a new cycle neutrophils should be ≥ 1.5 x 10^9/L and platelets should be ≥ 75 x 10^9/L.

During a cycle, treatment should be withheld and recommenced as per the table below:

Haematological parameter	Interruption criteria	Resumption criteria
Neutrophils	< 0.5 x 10^9/L	≥ 1.5 x 10^9/L
Platelets	< 50 x 10^9/L	≥ 75 x 10^9/L

If febrile neutropenia or grade 4 neutropenia (< 0.5 x 10^9/L) or thrombocytopenia (< 25 x 10^9/L) resulting in more than 1 week's delay to start of next treatment:
- withhold treatment until resolves to ≤ grade 1 or baseline
- resume dosing when neutrophils ≥ 1.5x10^9/L and platelets ≥ 75x10^9/L at next dose reduction level

- **Renal impairment**

No dose adjustment in mild to moderate renal impairment (CrCl ≥ 30ml/min). For patients with severe renal impairment (CrCl 15-29ml/min) a starting dose of 20mg/m^2 twice daily is recommended with a further dose reduction to 15mg/m^2 twice daily permitted if required due to toxicity. Administration in end stage renal disease (CrCl < 15ml/min) is not recommended.

- **Hepatic impairment**

No dose modification in mild hepatic impairment. Trifluridine/Tipiracil is not recommended in moderate-severe hepatic impairment (Bilirubin > 1.5 x ULN) as limited data suggests higher incidence of G3 and 4 hyperbilirubinaemia in patients with moderate-severe hepatic impairment at baseline.

- **Other toxicities**

Any other ≥ grade 3 toxicity (except grade 3 nausea and/or vomiting controlled by anti-emetics or diarrhoea controlled by anti-diarrhoeals):
- withhold treatment until resolves to ≤ grade 1 or baseline
- resume with 5mg/m^2 BD dose reduction (to a minimum dose of 20mg/m^2 BD)
- the dose should not be increased following a dose reduction

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Hepatotoxicity
Embolism

- **Frequently occurring side effects**

Nausea and vomiting
Diarrhoea
Myelosuppression
Anorexia
Mucositis
Fatigue
Taste disturbance

- **Other side effects**

Dizziness
Headache
Alopecia
Rash
PPE
Deranged liver function
Electrolyte abnormalities
Proteinuria
Infections

Significant drug interactions – for full details consult product literature/ reference texts

Medicinal products that interact with nucleoside transporters CNT1, ENT1 and ENT2: use with caution, increased risk of toxicity.
Inhibitors of OCT2 or MATE1: use with caution, increased risk of toxicity.
Human thymidine kinase substrates, e.g., zidovudine: use with caution may reduce efficacy of trifluridine /tipiracil. If using antiviral medicinal products that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral medicinal product, and consider switching to an alternative antiviral medicinal product that is not a human thymidine kinase substrate, such as lamivudine, zalcitabine, didanosine and abacavir.
Hormonal contraceptives: it is unknown whether trifluridine /tipiracil may reduce the effectiveness of hormonal contraceptives. Therefore, women using hormonal contraceptive must also use a barrier contraceptive method.

Additional comments

Trifluridine/Tipiracil contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Trifluridine /Tipiracil.

References

- Summary of Product Characteristics Lonsurf®(Servier) accessed 29 February 2024 available at http://www.medicines.org.uk
- National Institute for Health and Care Excellence TA405 accessed 29 February 2024 via www.nice.org.uk
- National Institute for Health and Care Excellence TA852 accessed 29 February 2024 via www.nice.org.uk
- Mayer R, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. N Engl J Med 2015;372:1909-19.
- Shitara, K. et al. Trifluridine/tipiracil verusus 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.

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