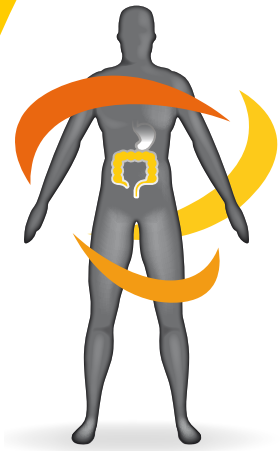
DOSING CARD



Teysuno®

TEGAFUR GIMERACIL OTERACIL

Also known as S-1

Adverse Event Reporting Information can be found at the foot of page 3.
Prescribing Information can be found on page 5.

Dosing table Teysuno® (aka S-1) in Metastatic Colorectal Cancer (mCRC)

Teysuno® (aka S-1) is indicated, as monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab, for the treatment of patients with metastatic colorectal cancer for whom it is not possible to continue treatment with another fluoropyrimidine due to hand-foot syndrome or cardiovascular toxicity that developed in the adjuvant or metastatic setting.

The recommended dose in mCRC for monotherapy is 30 mg/m^2 twice daily, morning and evening, for 14 consecutive days followed by a one-week pause (± bevacizumab 7.5 mg/kg on day 1). For combination therapy, the recommended dose is 25 mg/m^2 twice daily, morning and evening, for 14 consecutive days followed by a one-week pause (with on day 1 130 mg/m^2 oxaliplatin or 150-225 mg/m^2 irinotecan); 1 treatment cycle. This treatment cycle is repeated every 3 weeks. Teysuno® capsules should be swallowed with water at least 1 hour before or 1 hour after a meal.

Teysuno dose Monotherapy	**Total daily dose[a]**	**Each dose[a]**	**Number of capsules for each dose** (2 doses/day)	
Monotherapy standard dose[a]: 30 mg/m^2			**15 mg capsule[a]** (brown/white)	**20 mg capsule[a]** (white)
BSA ≥ 2.30 m^2	140 mg	70 mg	2	2
BSA = 2.10 – 2.29 m^2	130 mg	65 mg	3	1
BSA = 1.90 – 2.09 m^2	120 mg	60 mg		3
BSA = 1.70 – 1.89 m^2	110 mg	55 mg	1	2
BSA = 1.50 – 1.69 m^2	100 mg	50 mg	2	1
BSA = 1.30 – 1.49 m^2	80 mg	40 mg		2
BSA ≤ 1.29 m^2	70 mg	35 mg	1	1
Monotherapy First dose reduction[a]: to 25 mg/m^2			**15 mg capsule[a]** (brown/white)	**20 mg capsule[a]** (white)
BSA ≥ 2.30 m^2	120 mg	60 mg		3
BSA = 2.10 – 2.29 m^2	110 mg	55 mg	1	2
BSA = 1.90 – 2.09 m^2	100 mg	50 mg	2	1
BSA = 1.70 – 1.89 m^2	90 mg	45 mg	3	
BSA = 1.50 – 1.69 m^2	80 mg	40 mg		2
BSA = 1.30 – 1.49 m^2	70 mg	35 mg	1	1
BSA ≤ 1.29 m^2	60 mg	30 mg	2	

Teysuno dose Monotherapy	Total daily dose[a]	Each dose[a]	Number of capsules for each dose (2 doses/day)	
Monotherapy Second dose reduction[a]: to 20 mg/m²			**15 mg capsule[a]** (brown/white)	**20 mg capsule[a]** (white)
BSA ≥ 2.13 m²	90 mg	45 mg		
BSA = 1.88 – 2.12 m²	80 mg	40 mg		
BSA = 1.63 – 1.87 m²	70 mg	35 mg		
BSA = 1.30 – 1.62 m²	60 mg	30 mg		
BSA ≤ 1.29 m²	40 mg	20 mg		

Recommended dose reductions:

Elderly: No adjustment of the standard dose is recommended in patients ≥70 years old. For elderly, more vulnerable patients, in case of metastatic colorectal cancer and where it is not possible to continue treatment with another fluoropyrimidine due to hand-foot syndrome or cardiotoxicity, the recommended dose is 20 mg/m² (expressed as tegafur content) twice daily, morning and evening, for 14 consecutive days followed by 7 days rest, in combination with a reduced oxaliplatin dose (100 mg/m² on day 1 of a 3-week cycle).

Calculate the BSA to the second decimal

Source: SmPC Teysuno®

[a]Expressed as tegafur content

˙ *In combination therapy with 130 mg/m² oxaliplatin or 150-225 mg/m² irinotecan on day 1.*

˙˙ *Reduced dose in combination therapy with 100 mg/m² oxaliplatin or, depending on the starting dose, reduced dose irinotecan, on day 1.*

Adverse events should be reported.
Reporting forms and information can be found at **www.mhra.gov.uk/yellowcard**.
Adverse events should also be reported to **pv.uk@nordicpharma.com**

Dose reduction scheme

Metastatic Colorectal Cancer (mCRC)

Monotherapy

Standard dose and dose reductions allowed for Teysuno monotherapy in metastatic colorectal cancer.

Medicinal product	Standard dose		Dose reduction 1		Dose reduction 2
Teysuno	30 mg/m^2 [a]	↓	25 mg/m^2 [a]	↓	20 mg/m^2 [a]

Combination therapy

Standard dose and dose reductions allowed for Teysuno combination therapy in metastatic colorectal cancer.

Medicinal product	Standard dose		Dose reduction 1
Teysuno	25 mg/m^2 [a]	↓	20 mg/m^2 [a,e]
And/or			
Oxaliplatin[b,c,d]	130	↓	100[e]
Irinotecan[c,d]	150-225[f]	↓	No recommendations[g]

a. Expressed as tegafur content.

b. Chung KY, Saito K, Zergebel C, Hollywood E, Segal M, Saltz LB. Phase I study of two schedules of oral S-1 in combination with fixed doses of oxaliplatin and bevacizumab in patients with advanced solid tumors. Oncology. 2011;81(2):65-72.

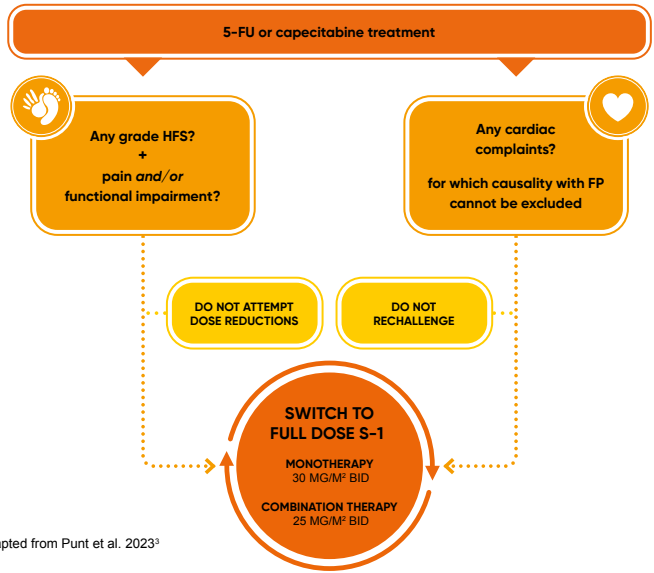
c. Winther SB, Zubcevic K, Qvortrup C, et al. Experience with S-1 in older Caucasian patients with metastatic colorectal cancer (mCRC): Findings from an observational chart review. Acta Oncol. 2016;55(7):881-885.

d. Österlund P, Kinos S, Pfeiffer P, et al. Continuation of fluoropyrimidine treatment with S-1 after cardiotoxicity on capecitabine- or 5-fluorouracil-based therapy in patients with solid tumours: a multi-centre retrospective observational cohort study. ESMO OPEN 2022, in press.

e. Winther SB, Liposits G, Skuladottir H, et al. Reduced-dose combination chemotherapy (S-1 plus oxaliplatin) versus full-dose monotherapy (S-1) in older vulnerable patients with metastatic colorectal cancer (NORDIC9): a randomised, open-label phase 2 trial. Lancet Gastroenterol Hepatol. 2019;4(5):376-388.

f. While the best dose of irinotecan is not known and is used in combination with Teysuno in ranges between 150-225 mg/m^2, the most relevant experience comes from irinotecan dosing of 180-200 mg/m^2

g. No recommendation can be made and dose reduction will be dependent on the starting dose



Adapted from Punt et al. 2023[3]

Click here for the
Teysuno Prescribing Information

Click here for the
UK SmPC

Switch guidelines S-1 in mCRC[3]

The **2022 ESMO guidelines for mCRC[2] recommend S-1** as an alternative fluoropyrimidine (FP) when intravenous 5-FU- or capecitabine-based chemotherapy cannot be continued due to cardiovascular toxicity (CVT) or Hand-foot syndrome (HFS). An international expert panel[3] reviewed the literature and reached a consensus on **guidance for using S-1 in daily practice for metastatic CRC patients experiencing HFS or CVT.**

Hand Foot Syndrome (HFS)

HFS is a very common problem during FP treatment, significantly impacting HRQoL, requiring dose reductions or interruptions. The panel agreed that pain and/or functional impairment due to HFS should be reason to intervention because:

1. The efficacy of reduced capecitabine doses is uncertain.
2. Grade 2 HFS recurs in about one-third of patients after dose reduction.
3. Switching to full-dose S-1 is well tolerated, effective and improves symptoms

The panel recommends switching to full-dose S-1 (30 mg/m² BID as monotherapy, 25 mg/m² BID in combination) **without prior capecitabine/5-FU dose reduction**. S-1 should ideally **start when HFS has decreased to grade 1**, as earlier use may be less effective in some patients.

Cardiovascular toxicity (CVT)

The expert panel[3] concluded that CVT is a potentially life-threatening event that occurs in 2%-4% of patients during FP treatment. A rechallenge of the FP under prophylaxis may reduce, but not prevent, recurrence and risk of death, but is laborious. Given the much lower recurrence rate and good tolerance of switching to S-1 at full dose in patients experiencing cardiac complaints, the panel recommended:

In patients who experience CVT during therapy with capecitabine or 5-FU, a switch to S-1 at full dose [30 mg/m² BID as monotherapy, 25 mg/m² BID in combination therapy] **is recommended without any attempt to rechallenge patients with capecitabine/5-FU**.

Conclusions

The panel concluded that **S-1 is well tolerated and can replace 5-FU or capecitabine when these agents are causing HFS or CVT that prevents or complicates their continued administration[3]**.

Dosing S-1 after switch

For both HFS and CVT, S-1 can be started at the full dose unless initial fluoropyrimidine was reduced for a reason other than HFS or cardiotoxicity (such as partial DPD deficiency or diarrhea). In these cases, the same relative dose reduction as that of capecitabine should be applied (see dose reduction scheme).

1. Teysuno Summary of Product Characteristics.
2. Cervantes A, Adam R, Roselló S, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34(1):10-32.
3. Punt CJA, Heinemann V, Maughan T, et al. Fluoropyrimidine-induced hand-foot syndrome and cardiotoxicity: recommendations for the use of the oral fluoropyrimidine S-1 in metastatic colorectal cancer. ESMO Open. 2023;8(2):101199.

NORDIC PHARMA

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