

Tegafur/gimeracil/oteracil (Teysuno®) for the treatment of metastatic colorectal cancer

General information

Drug description [1]	Indication [2]
<p>Teysuno® (Tegafur/gimeracil, oteracil, S-1) is an oral fluoropyrimidine anti-cancer medicinal product. It is a fixed-dose combination of three active substances, tegafur, which after absorption is converted into the anti-cancer substance 5-fluorouracil (5-FU); gimeracil, a dihydropyrimidine dehydrogenase inhibitor to prevent degradation of 5-FU by the body; and, oteracil, an orotate phosphoribosyltransferase inhibitor that decreases the activity of 5-FU in normal gastrointestinal mucosa.</p>	<p>Teysuno® 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.</p>

Additional information/management of cardiovascular toxicity and hand-foot syndrome

- ❖ **Fluoropyrimidine Cardiotoxicity [3]**
 - The fluoropyrimidines, namely 5-FU and its oral prodrug, capecitabine, are the third most commonly used chemotherapeutic class for the treatment of solid tumours of glandular and squamous origin, such as head and neck, oesophageal, stomach, and bladder.
 - Use of fluoropyrimidines is standard of care for treatment of advanced colorectal cancers and may have synergetic effects with external beam radiation to enhance the radiosensitivity of tumours.
 - However, among conventional cytotoxic chemotherapies, 5-FU is likely one of the most common chemotherapeutic agents to cause cardiotoxicity, second only to anthracyclines.
 - When acute cardiotoxicity is suspected, it is recommended that fluoropyrimidines be stopped immediately, followed by treatment with aspirin, calcium channel blockers, and long-acting nitrates.
 - In general, reintroduction of the fluoropyrimidine after a known cardiotoxic event is not advised due to the risk of recurrence associated with complications including death, myocardial infarction, and the development of cardiogenic shock.
- ❖ **Hand-foot syndrome [4]**
 - Hand-foot syndrome is a common skin reaction to systemic therapy that should be anticipated with chemotherapeutic treatments such as pegylated liposomal doxorubicin, docetaxel, and fluoropyrimidines.
 - Although the hand-foot syndrome is not life-threatening, it can cause significant discomfort and impairment of function, especially in elderly patients, and may seriously impact QoL.
 - The incidence of hand-foot syndrome is dependent on the chemotherapeutic drug used, the treatment schedule, and the median duration of treatment.
 - Fluoropyrimidines are used for the treatment of many solid tumour types, including colorectal, gastric, pancreatic, oesophageal, breast, and head and neck cancer.
 - Intravenous 5-FU, capecitabine, and S-1 have shown comparable efficacy results in various tumour types, but the toxicity profiles of the 3 agents are distinct, especially for hand-foot syndrome.
 - The incidence of any grade hand-foot syndrome for intravenous 5-FU in phase 3 trials varies between 2.6% and 18%, while capecitabine is associated with rates of any grade hand-foot syndrome between 22% and 77%. S-1 has a reported incidence ranging from 5.4% to 45%, Capecitabine is associated with the highest incidence of grade 3 hand-foot syndrome, reported in up to 28% of patients.
 - Management of hand-foot syndrome in cancer treatment involves a combination of prevention, patient education, symptom amelioration, and dose intensity management.
 - The most effective way to manage hand-foot syndrome once it has emerged is dose intensity modification in the form of a dose delay or dose reduction, or even treatment discontinuation, an unfortunate and undesirable occurrence during cancer treatment. Alternatively, patients can be switched to a better tolerated regimen.

Regulatory status

EMA [2]	FDA [5]
<p>Approval status for this indication: On 16 December 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Teysuno®.</p>	<p>Approval status for this indication: Not approved.</p> <ul style="list-style-type: none"> ✓ Tegafur/gimeracil/oteracil: orphan status designation for the treatment of gastric cancer since 20 July 2006; not FDA approved for orphan indication.



<p>The CHMP adopted a new indication as follows:</p> <ul style="list-style-type: none"> ❖ Teysuno® is indicated in adults 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. <p>Other indications:</p> <ul style="list-style-type: none"> ❖ Teysuno® is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin. 	<p>Other indications: none</p>
Costs [6]	
<p>42 Teysuno® hard capsules 15mg/4.35mg/11.8mg = € 122.98 (ex-factory price)</p>	
<p>42 Teysuno® hard capsules 20mg/5.8mg/15.8mg = € 174.78 (ex-factory price)</p>	
Additional medication	
<p>Patients should be provided with outpatient prescriptions for anti-emetic and anti-diarrhoeal medicinal products [7].</p>	
Special warnings and precautions for use [7]	
<ul style="list-style-type: none"> ❖ Dose limiting toxicities include diarrhoea and dehydration. Most adverse reactions are reversible and can be managed by symptomatic therapy, dose interruptions and dose reductions. ❖ Bone marrow suppression <ul style="list-style-type: none"> • Treatment-related bone marrow suppression, including neutropaenia, leukopaenia, thrombocytopaenia, anaemia, and pancytopaenia, has been reported among patients treated with Teysuno® in combination with cisplatin. • Patients with low white blood cell counts should be monitored carefully for infection and risk of other complications of neutropenia and treated as medically indicated. • Patients with low platelet counts are at increased risk for bleeding and should be monitored carefully. The dose should be modified. ❖ Hepatitis B reactivation <ul style="list-style-type: none"> • Administration of Teysuno® in hepatitis B virus carriers, HBc antigen negative and HBc antibody positive patients, or HBs antigen negative and HBs antibody positive patients may result in reactivation of hepatitis B. • Patients should be tested for HBV infection before initiating treatment with Teysuno. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with Teysuno® should be closely monitored for signs and symptoms of active HBV infection throughout therapy, and follow-up monitoring for hepatic function tests or viral markers are recommended. ❖ Diarrhoea <ul style="list-style-type: none"> • Patients with diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Prophylactic treatment for diarrhoea should be administered as indicated. • Standard anti-diarrhoeal therapy (e.g., loperamide) and IV fluids/electrolytes should be initiated early when diarrhoea develops. Dose suspension/adjustment should be implemented with the occurrence of Grade 2 or higher diarrhoea if symptoms persist despite adequate treatment. ❖ Dehydration <ul style="list-style-type: none"> • Dehydration and any associated electrolyte disturbances should be prevented or corrected at onset. • Patients with anorexia, asthenia, nausea, vomiting, diarrhoea, stomatitis, and gastrointestinal obstruction should be monitored closely for signs of dehydration. • Dehydration should be managed aggressively with rehydration and other appropriate measures. If Grade 2 (or higher) dehydration occurs, treatment should be immediately suspended and the dehydration corrected. Treatment should not be resumed until dehydration and its underlying causes are corrected or adequately controlled. Dose modifications should be applied for the precipitating adverse reaction as necessary. ❖ Renal toxicity <ul style="list-style-type: none"> • Treatment with Teysuno® in combination with cisplatin may be associated with a transient decline of glomerular filtration rate caused primarily by pre-renal factors (e.g., dehydration, electrolyte imbalance, etc). 	

- Adverse reactions of Grade 3 or higher such as increased blood creatinine, decreased creatinine clearance, toxic nephropathy, and acute renal failure have all been reported in patients receiving Teysuno® in combination with cisplatin.
 - To detect early changes in renal function during treatment, renal parameters should be closely monitored. If deterioration of glomerular filtration rate is observed, Teysuno and/or cisplatin dose should be adjusted, and appropriate supportive measures taken.
 - Dehydration and diarrhoea may increase the risk of renal toxicity for cisplatin. Hyperhydration (forced diuresis) should be administered according to the cisplatin SmPC to reduce the risk of renal toxicity associated with cisplatin therapy.
 - Gimeracil increases 5-fluorouracil (5-FU) exposure by inhibiting DPD, the primary enzyme for metabolizing 5-FU. Gimeracil is primarily cleared by the kidney; so, in patients with renal insufficiency gimeracil renal clearance is decreased and 5-FU exposure thus increased. Treatment-related toxicities can be expected to increase as 5-FU exposure increases.
- ❖ **Severe renal impairment**
- Treatment with Teysuno® is not recommended in patients with severe renal impairment due to possibly higher incidence of adverse events of the blood and lymphatic system and the possibility of unexpectedly higher exposure to 5-FU as a result of fluctuations in renal function in these patients, unless the benefits clearly outweigh the risks.
- ❖ **Ocular toxicity**
- The most common treatment-related ocular disorders among patients in studies in Europe/United States of America treated with Teysuno® in combination with cisplatin were lacrimal disorders (8.8%), including increased lacrimation, dry eye, and acquired dacryostenosis.
 - Most ocular reactions will resolve or improve with suspension of medicinal product and proper treatment (instillation of artificial tears, antibiotic eye drops, implantation of glass or silicone tubes in lacrimal punctas or canaliculi, and/or use of spectacles rather than contact lenses). Efforts should be made to ensure early detection of ocular reactions, including an early ophthalmologic consultation in the event of any persistent or vision-reducing ocular symptoms such as lacrimation or corneal symptoms.
- ❖ **Coumarin-derivative anticoagulant**
- Patients receiving oral coumarin-derivative anticoagulant therapy must have their anticoagulant response (International Normalized Ratio for prothrombin time [INR] or prothrombin time [PT]) monitored closely and the anticoagulant dose adjusted accordingly.
 - The use of coumarin-derivative anticoagulant in clinical trials has been associated with elevated INR and gastrointestinal bleeding, bleeding tendency, haematuria, and anaemia in patients receiving Teysuno® therapy.
- ❖ **Brivudine**
- Brivudine must not be administered concomitantly with Teysuno®.
 - Fatal cases have been reported following capecitabine interaction. There must be at least a 4-week waiting period between end of treatment with brivudine and start of Teysuno® therapy. Treatment with brivudine can be started 24 hours after the last dose of Teysuno. In the event of accidental administration of brivudine to patients being treated with Teysuno®, effective measures should be taken to reduce the toxicity of Teysuno®. Immediate admission to hospital is recommended. All measures should be initiated to prevent systemic infections and dehydration.
- ❖ **DPD inducers**
- If a DPD inducer were to be concomitantly administered with Teysuno®, the exposure of 5-FU might not reach the efficacious level.
 - However, since no DPD inducers are currently known, the interaction between a DPD inducer and Teysuno® cannot be evaluated.
- ❖ **Phenotypic characterisation of DPD deficiency**
- For phenotypic characterisation of DPD deficiency the measurement of pre-therapeutic blood levels of the endogenous DPD substrate uracil in plasma is recommended.
 - Elevated pre-treatment uracil concentrations are associated with an increased risk of toxicity. Despite uncertainties on uracil thresholds defining complete and partial DPD deficiency, a blood uracil level ≥ 16 ng/ml and < 150 ng/ml should be considered indicative of partial DPD deficiency and associated with an increased risk for fluoropyrimidine toxicity. A blood uracil level ≥ 150 ng/ml should be considered indicative of complete DPD deficiency and associated with a risk for life-threatening or fatal fluoropyrimidine toxicity.
- ❖ **Microsatellite instability (MSI)**
- Teysuno® has not been studied in gastric cancer patients with MSI. The association between 5-FU sensitivity and MSI in patients with gastric cancer is unclear and the association between Teysuno® and MSI in gastric cancer is unknown.
- ❖ **Glucose/galactose intolerance/malabsorption**
- This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose/galactose malabsorption should not take this medicinal product.
- ❖ **Other oral fluoropyrimidines**
- No clinical trials are available comparing Teysuno® versus other oral 5-FU compounds. Therefore, Teysuno® cannot be used as a substitute for other oral 5-FU products.

Trial name	n	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
SALTO NCT01918852	161 (81 vs. 80)	capecitabine (1250 mg/m ² orally for patients <70 years; 1000 mg/m ² for patients ≥70 years, twice daily on days 1–14) with optional bevacizumab ¹	S-1 (30 mg/m ² orally twice daily on days 1–14) in 3-weekly cycles, with optional bevacizumab	incidence of any grade hand-foot syndrome, as assessed by both physicians and patients (diaries)	open-label, randomised, phase 3 trial	-	Dutch Colorectal Cancer Group	[8]
Efficacy (I vs. C)							Safety (I vs. C)	
<p>Incidence of any grade hand-foot syndrome (as assessed by local investigators): 73% vs. 45%; odds ratio (95% CI 0.31, 0.16-0.60), p=0.0005</p> <p>Incidence of grade 3 hand-foot syndrome: 21% vs. 4%, p=0.003</p> <p>Completed questionnaires in the patient diaries: 64% vs. 71%</p> <p>Incidence of any grade hand-foot syndrome (as assessed by patients): 84% vs. 58%; odds ratio 0.26 (95% CI 0.10–0.64), p=0.004</p> <p>Median time to first occurrence in patients developing grades 2 and 3 hand-foot syndrome: 2 months (IQR 1–4) vs. 3 months (IQR 1–7), p=0.13</p> <p>Co-treatment with bevacizumab in the capecitabine group was associated with a higher incidence of any grade and grade 3 hand-foot syndrome (not statistically significant); this trend was not observed in the S-1 group.</p> <p>Median relative dose intensity: 88% (IQR 76–99) vs. 95% (IQR 83–100); p=0.026</p> <p>After a median follow-up duration of 20.2 months, 90% of patients in the capecitabine group 88% patients in the S-1 group had progressed or died.</p> <p>Median PFS: 8.2 months (95% CI 6.4–10.3) vs. 8.4 months (6.4–10.6); HR 0.99, 95% CI 0.71–1.37, p=0.93</p> <p>PFS: 8.7 months capecitabine and S-1 WITH bevacizumab (7.8–10.8) vs. 6.6 months capecitabine and S-1 WITHOUT bevacizumab (5.3–8.5), HR 0.74, 95% CI 0.53–1.03, p=0.08</p> <p>Median PFS: capecitabine 6.6 months (5.5–8.5) vs. capecitabine plus bevacizumab 9.2 months (6.6–13.8); HR 0.61, 95% CI 0.38–0.97, p=0.04</p> <p>Median PFS: S-1 alone 6.4 months vs. S-1 plus bevacizumab 8.7 months, HR 0.91, 95% CI 0.56–1.47; p=0.69</p> <p>OS at 12 and 18 months: 67% (95% CI 57–78) and 50% (40–63) vs. 62% (53–74) and 41% (30–54), respectively; HR 1.23, 95% CI 0.82–1.86, p=0.32</p> <p>Overall objective response rate (in n=146): 47% vs. 32%; p=0.09</p> <p>Disease control: 95% vs. 89%, p=0.24)</p> <p>Results of an European cohort study [7]:</p>							<p>Death: n=1 (due to sepsis which was possibly related to treatment) vs. n=1 (due to bevacizumab-related bowel perforation)</p> <p>Hospitalization due to treatment-related AEs: n=2 vs. n=3</p> <p>Treatment discontinuation due to hand-foot syndrome: n=7 (10%) vs. n=0 (0%), p=0.013</p> <p>Results of an European cohort study [7]:</p> <ul style="list-style-type: none"> ❖ 200 patients with different solid tumours were switched from 5-FU or capecitabine based therapy because of cardiotoxicity to continue with Teysuno® based therapy ❖ Subgroup of metastatic colorectal cancer patients (n=53): <ul style="list-style-type: none"> • 92% of subgroup patients who developed cardiotoxicity while on capecitabine- or 5-FU-based chemotherapy could safely switch to S-1 and continue treatment, with recurrent cardiotoxicity (grade 1) seen in 8%. • Other AEs during S-1 treatment in this subgroup included: <ul style="list-style-type: none"> ○ grade 3-4 haematologic toxicity in 8% and ○ grade 2-4 non-haematologic adverse events in 36% (neuropathy 15%, infection 7%, thromboembolic event 6%, diarrhoea 4%, nausea 2%, hand-foot syndrome 2%). <p>Results of a retrospective cohort study from the Dutch colorectal cancer registry [7]:</p> <ul style="list-style-type: none"> ❖ Severity of hand-foot-syndrome decreased or completely resolved during treatment with S-1 	

¹ Co-treatment with bevacizumab was administered in 59% of patients (n=47 for capecitabine, n=48 for S-1).



<ul style="list-style-type: none"> ❖ 200 patients were switched from 5-FU or capecitabine based therapy because of cardiotoxicity to continue with Teysuno® based therapy. ❖ Subgroup of metastatic colorectal cancer patients (n=53): <ul style="list-style-type: none"> • With this switch, 100% of the patients were able to complete their planned chemotherapy. • In addition, for the colorectal cancer patients with metastatic disease, the median OS was 26 months (95% CI 22-31), with a 5-year survival rate of 12%. <p>Results of a retrospective cohort study from the Dutch colorectal cancer registry [7]:</p> <ul style="list-style-type: none"> ❖ 47 metastatic colorectal cancer patients switching to S-1 due to capecitabine-induced hand-foot syndrome (n=36) or cardiotoxicity (n=10) ❖ Median time from initiation of treatment with capecitabine to first documented progression of disease after initiation of treatment with S-1 was 414 days (95% confidence interval 332-568 days). 	<ul style="list-style-type: none"> ❖ No case of recurrence of cardiac toxicity was reported in any of the 10 patients that switched to S-1 due to cardiac AEs.
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ESMO-MCBS version 1.1 [9]

The ESMO-MCBS was not applicable due to the primary endpoint “incidence of any grade hand-foot syndrome” and the immature PFS and OS data.

Risk of bias (RCT) [10]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	Risk of bias
yes	-	No, open-label	unclear ²	yes ³	unclear

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Abbreviations: 5-FU=5-fluorouracil, AE=adverse event, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DPD=dihydropyrimidine dehydrogenase, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, HBV=hepatitis B virus, HR=hazard ratio, I=intervention, INR=international normalized ratio, MSI=microsatellite instability, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PT=prothrombin time, , SAE=serious adverse event

References:

1. European Medicines Agency (EMA). Teysuno: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/teysuno-epar-product-information_en.pdf].
2. European Medicines Agency (EMA). Medicines. Teysuno. [Available from: <https://www.ema.europa.eu/en/medicines/human/summaries-opinion/teysuno>].
3. Kanduri J, Asnani A. Fluoropyrimidine Cardiotoxicity. [Available from: <https://www.acc.org/latest-in-cardiology/articles/2019/04/05/07/34/fluoropyrimidine-cardiotoxicity>].
4. Kwakman J, et al. Management of cytotoxic chemotherapy-induced hand-foot syndrome. Oncol Rev 2020 Feb 18; 14(1): 442 Published online 2020 May 13.
5. U.S. Food and Drug Administration (FDA). Orphan Drug Designations and Approvals. [Available from: <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=225006>].
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: <https://warenverzeichnis.apoverlag.at/>].

² SALTO trial protocol is not available.

³ The Dutch Colorectal Cancer Group received an unrestricted grant from Nordic Pharma B.V.



7. European Medicines Agency (EMA). Teysuno: EPAR-Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/teysuno-epar-product-information_en.pdf].
8. Kwakman J, Simkens L, van Rooijen J, et al. Randomized phase III trial of S-1 versus capecitabine in the first-line treatment of metastatic colorectal cancer: SALTO study by the Dutch Colorectal Cancer Group. *Annals of Oncology* 28: 1288–1293, 2017. Published online 5 April 2017. [Available from: <https://doi.org/10.1093/annonc/mdx122>]
9. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. . *Annals of Oncology* 28: 2340–2366, 2017.
10. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: <https://www.eunetha.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf>].

