Appendix

S-1 Clinical profile of tegafur/gimeracil/oteracil for the treatment of patients with mCRC for whom fluoropyrimidines (FP) cannot be continued due to Hand Foot Syndrome (HFS) or cardiotoxicity that developed in the adjuvant or metastatic setting.[1]

Profile Element	Description
Product	A fixed dose combination of three active substances: • Tegafur, which after absorption is converted into the anti-cancer substance 5-FU • Gimeracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor to prevent degradation of 5-FU by the body (resulting in similar 5FU levels and prolonged half-life) ; • Oteracil, an orotate phosphoribosyltransferase (OPRT) inhibitor (to reduce gastro-intestinal toxicity of metabolites of 5FU). The combination of tegafur, gimeracil, and oteracil is set at 1:0.4:1 molar ratio as optimum in order to maintain 5-FU exposure and thus sustain anti-tumour activity while reducing toxicity associated with 5-FU alone
Indication	**Current Indication:** Indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin **New Indication:** (*as monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab)* for the treatment of patients with metastatic colorectal cancer for whom fluoropyrimidines cannot be continued due to Hand Foot Syndrome (HFS) or cardiotoxicity that developed in the adjuvant or metastatic setting.
Mechanism of action	Tegafur is a prodrug of 5-FU with good oral bioavailability. Following oral administration, tegafur is gradually converted to 5-FU in vivo, mainly by CYP2A6 enzyme activity in the liver. Once activated within cancer cells, 5-FU inhibits DNA synthesis and disrupt RNA functions Cardiotoxicity and HFS are caused by metabolites of IV-5-FU and CAP (capecitabine) which are formed upon degradation by DPD. Product X contains an inhibitor of the enzyme DPD and allows therefore for a lower amount of tegafur, resulting in a lower concentration of these toxic metabolites.
Route of administration & dosing regimen	Oral Capsule: Full dose treatment regimen (with or without bevacizumab) is 30 mg/m2 bid for monochemotherapy or 25 mg/m2 for combination treatment with irinotecan or oxaliplatin for 14 days with 7 days break in three week regimens

Adapted from SmPC Teysuno 2022

Cardiotoxicity	Description
Multi-centre retrospective observational cohort study	• A recently published multi-centre retrospective observational cohort study [Osterlund 2021] at 13 centers in 6 countries involving 200 "switch patients", treated between 2011 and 2020 • The primary endpoint was recurrence of cardiac toxicity after switch to Product X-based treatment due to 5-fluorouracil- or capecitabine (CAP)-related cardiotoxicity. Secondary endpoints included cardiac risk factors, diagnostic work-up, treatment details and outcomes, and timelines of cardiotoxicity. • Initial cardiotoxicity was associated with CAP (n=170), continuous infusion IV-5-FU (n=22), or bolus 5-FU (n=8) * • Baseline cardiovascular comorbidities were present in 99 (50%) patients.
	Results: • *99% of patients who switched to Product X were able to complete planned fluoropyrimidine-based therapy* • *After switch to Product X, recurrent cardiotoxicity was observed in eight (4%) patients (competing risk 95% confidence interval [CI] 2·02–7·89). Events were limited to grade 1-2 and occurred at a median of 16 days (IQR 7-67) from therapy switch.* • *The efficacy of Product X after switch in this study population was in line with previous reports for IV-5-FU and CAP with a 5-year survival rate of 83% in colorectal cancer and a median overall survival for the subgroup of patients with mCRC (n=53) of 26 months (95% CI 22-31)* • *Overall tolerability was comparable with IV-5-FU and CAP based regimens. However, non-cardiac adverse event rates were higher with Product X treatment, probably due to the large difference in treatment duration between CAP/5-FU regimens (median 5 days) and Product X regimens (median 147 days exposure to treatment)*
Published case series (Kwakman, 2017) & Recent RWE Data	Published case series (Kwakman, 2017) of patients switched after CAP-induced coronary artery vasospasm to Product X concludes that • Product X can be administered at full dose in all patients irrespective of the combination regimen • Interval between discontinuation of CAP and initiation of Product X ranged from 1 week to 2 years • Patients received a median of 4 cycles (range 2-15) of Product X which was well tolerated • None of the 7 patients experienced any recurrence of cardiac toxicity while on Product X Furthermore a retrospective data analysis from the Dutch Prospective Colorectal Cancer Cohort involving over 10,000 patients identified 47 patients who could not continue CAP and were switched to Product X from between June 1st 2016 and June 15th 2021. Ten of these switched for reasons of cardiac toxicity, which did not recur in any of them after switch to Product X

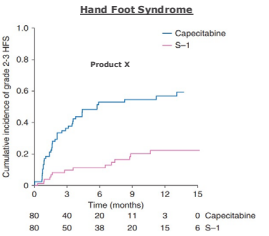
Osterlund et al, Continuation of fluoropyrimidine treatment with S-1 after cardiotoxicity on capecitabine- or 5-fluorouracil-based therapy, ESMO Open March, 2022

Kwakman et al, Case series of patients treated with the oral fluoropyrimidine S-1 after capecitabine-induced coronary artery vasospasm, EJC, 81(2017) 130-134

Hand-Foot syndrome	Description
Recent RWE Data	• A retrospective data analysis from the Dutch Prospective Colorectal Cancer Cohort involving over 10,000 patients identified 47 patients who could not continue CAP and were switched to Product X from between June 1st 2016 and June 15th 2021
	Results: **HFS** / **During capecitabine n (%)** / **After switch to Product X n (%)** None: 9 (19) / 31 (66) Grade 1: 2 (4) / 15 (32) Grade 2: 26 (55) / 1 (2) Grade 3: 10 (21) / 0 (0) • *Median PFS (Median time from initiation of treatment with CAP to first documented progression of disease after initiation of treatment with Product X) was 414 days (95% confidence interval 332-568 days), concordant with expected treatment outcomes.* • *Product X was well tolerated* • *No difference in outcomes was observed between subgroup who switched for HFS (n=36) vs. the whole group.*
Retrospective study (Kwakman, 2017)	• A retrospective study of 52 patients from 6 centres in The Netherlands and Denmark with any type of cancer who switched from capecitabine to Product X (given as single agents or in combination schedules) because of HFS were reviewed to assess the tolerability of Product X in patients with grade 2 or 3 HFS due to capecitabine • The primary endpoint was the incidence of any grade HFS upon treatment switch to Product X • A total of 49 patients (94%) started Product X treatment at a full dose of 30 mg/m2 bid for monochemotherapy or 25 mg/m2 for combination treatment.
	Results: • *A total of 49 patients (94%) experienced a lower grade of HFS upon treatment with Product X compared to the capecitabine-induced grade of HFS, with 29 patients (56%) experiencing a complete resolution of HFS-related symptoms*

RWA data on file, Nordic Pharma 2021

Kwakman et al, Tolerability of oral fluoropyrimidine S-1 after HFS-rel. discontinuation of capecitabine in western cancer patients, Acta Oncol. 2017, 1023-26

Hand-Foot syndrome	Description
SALTO study	• Randomized phase III trial of Product X versus capecitabine in the first-line treatment of metastatic colorectal cancer • Patients with previously untreated mCRC and planned treatment with fluoropyrimidine monochemotherapy were randomized 1 : 1 to receive either capecitabine or Product X, with bevacizumab optional in both groups. • The primary endpoint was the incidence of any grade HFS, as assessed by both physicians and patients (diaries). • Secondary endpoints included grade 3 HFS, other toxicities, relative dose intensity, progression-free survival, response rate and overall survival. • A total of 161 patients were randomized in 27 centres.
	Results: **Hand Foot Syndrome**  **Figure 1.** Cumulative inci **Product X** timating the probability of developing HFS grades 2 and 3 in patients over time. **PFS and OS** **Median follow-up of 40.3 months** Product X / Capecitabine Median OS: 17.0 months (95% CI13.0-20.1) / 17.1 months (95% CI) 14.3-23.5 / HR 1.07, 95% CI 0.76-1.49, p=0.70 PFS: 8.4 months / 8.2 months • There was no significant difference in median PFS (secondary endpoint). A recent publication reports the long-term data after a median of 40.3 months • Overall tolerability was comparable between Product X and CAP treatment

Kwakman et al, Randomized phase III trial of S-1 versus capecitabine in the first-line treatment of metastatic colorectal cancer (SALTO), Annals of Oncology 28: 1288–1293, 2017

	Description

Meta-analysis	• A recent meta-analysis (Derksen et al) included ten phase II/III RCT's (n=2,117) with a total of 1,062 patients who received Product X-based therapy and 1,055 patients receiving 5FU/CAP-based therapy. Nine studies were conducted in Asia, and one study was conducted in Europe. Primary outcome was PFS (reported in six studies) and secondary outcomes were OS and ORR (reported in six and ten studies respectively)
	
	Results:
	• *Thorough meta-analysis with conservative non-inferiority margin of 1.25 and a 99% confidence interval demonstrated that in the treatment of mCRC, Product X based therapy:*
	  ◦ *is non-inferior to 5FU/Cap-based therapy regarding PFS (HR_{total} 0.95, 99%CI 0.83–1.08)*
	  ◦ *is at least as effective as 5FU/Cap-based therapy in terms of OS. (HR_{total} 0.93, 99%CI 0.81–1.07)*
	  ◦ *is at least as effective as 5FU/Cap-based therapy in terms of ORR. (RR_{total} 1.06, 99%CI 0.90–1.24)*
	
	• *No significant heterogeneity between the Asian and Caucasian populations was detected in these studies for PFS (I^2 = 12%, P = 0.34).) and OS (I^2 = 0%, P = 0.82), moderate heterogeneity was detected for ORR (I^2 = 48%, P = 0.04), demonstrating that patients from these different regions can be pooled.*
	
	• *It was concluded that given the proven non-inferiority Product X can be indicated for patients that show intolerable toxicity on current standard first-line treatment with a IV5FU or CAP backbone.*

Derksen et al, Systematic review and non-inferiority meta-analysis of randomised phase II/III trials on S-1-based therapy vs 5-fluorouracil- or capecitabine-based therapy, European Journal of Cancer 166 (2022) 73-86

1 https://www.ema.europa.eu/nl/documents/product-information/teysuno-epar-product-information_nl.pdf