Pharma code position may vary as per folding machine suitability.

40 mm 40 mm

CAPTAB
Capecitabine

1659
4501659

A. Product Name

CAPTAB Capecitabine 150 mg Film Coated Tablets
CAPTAB Capecitabine 500 mg Film Coated Tablets

B. Name and Strength of Active Substance(s)

Capecitabine & 150 mg
Capecitabine & 500 mg

C. Product Description

CAPTAB Capecitabine 150 mg Film Coated Tablets is light pink colored, capsule shaped, biconvex film coated tablet debossed with CAP one side and 150 on other side.
Each film coated tablet contains: Capecitabine Ph.Eur......150 mg

CAPTAB Capecitabine 500 mg Film Coated Tablets is Dark pink colored, capsule shaped, biconvex film coated tablet debossed with CAP one side and 500 on other side.
Each film coated tablet contains: Capecitabine Ph.Eur......500 mg

D. Pharmacodynamics/Pharmacokinetics

D.1 Pharmacodynamic properties

Pharmacotherapeutic group: cytostatic (antimetabolite), ATC code: L01BC06

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Capecitabine is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found in tumour tissues, but also in normal tissues, albeit usually at lower levels. In human cancer xenograft models capecitabine demonstrated a synergistic effect in combination with docetaxel, which may be related to the upregulation of thymidine phosphorylase by docetaxel.

There is evidence that the metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxy uridylic acid to thymidylic acid, thereby interfering with the synthesis of deoxyribonucleic acid (DNA). The incorporation of 5-FU also leads to inhibition of RNA and protein synthesis. Since DNA and RNA are essential for cell division and growth, the effect of 5-FU may be to create a thymidine deficiency that provokes unbalanced growth and death of a cell. The effects of DNA and RNA deprivation are most marked on those cells which proliferate more rapidly and which metabolise 5-FU at a more rapid rate.

Colon and colorectal cancer:
Monotherapy with capecitabine in adjuvant colon cancer
Data from one multicentre, randomised, controlled phase III clinical trial in patients with stage III (Dukes' C) colon cancer supports the use of capecitabine for the adjuvant treatment of patients with colon cancer (XACT Study; M66001). In this trial, 1987 patients were randomised to treatment with capecitabine (1250 mg/m² twice daily for 2 weeks followed by a 1-week rest period and given as 3-week cycles for 24 weeks) or 5-FU and leucovorin (Mayo Clinic regimen: 20 mg/m² leucovorin IV followed by 425 mg/m² intravenous bolus 5-FU, on days 1 to 5, every 28 days for 24 weeks). Capecitabine was at least equivalent to IV 5-FU/LV in disease-free survival in per protocol population (hazard ratio 0.92; 95% CI 0.80-1.06). In the all-randomised population, tests for difference of capecitabine vs 5-FU/LV in disease-free and overall survival showed hazard ratios of 0.88 (95% CI 0.77 – 1.01; p = 0.068) and 0.86 (95% CI 0.74 – 1.01; p = 0.060), respectively. The median follow up at the time of the analysis was 6.9 years. In a preplanned multivariate Cox analysis, superiority of capecitabine compared with bolus 5-FU/LV was demonstrated. The following factors were pre-specified in the statistical analysis plan for inclusion in the model: age, time from surgery to randomization, gender, CEA levels at baseline, lymph nodes at baseline, and country. In the all-randomised population, capecitabine was shown to be superior to 5FU/LV for disease-free survival (hazard ratio 0.849; 95% CI 0.739 - 0.976; p = 0.0212), as well as for overall survival (hazard ratio 0.828; 95% CI 0.705 - 0.971; p = 0.0203).

Combination therapy in adjuvant colon cancer
Data from one multicentre, randomised, controlled phase 3 clinical trial in patients with stage III (Dukes' C) colon cancer supports the use of capecitabine in combination with oxaliplatin (XELOX) for the adjuvant treatment of patients with colon cancer (NO16968 study). In this trial, 944 patients were randomised to 3-week cycles for 24 weeks with capecitabine (1000 mg/m² twice daily for 2 weeks followed by a 1-week rest period) in combination with oxaliplatin (130 mg/m² intravenous infusion over 2-hours on day 1 every 3 weeks); 942 patients were randomised to bolus 5-FU and leucovorin. In the primary analysis for DFS in the ITT population, XELOX was shown to be significantly superior to 5-FU/LV (HR=0.80, 95% CI=[0.69; 0.93]; p=0.0045). The 3 year DFS rate was 71% for XELOX versus 67% for 5-FU/LV. The analysis for the secondary endpoint of RFS supports these results with a HR of 0.78 (95% CI=[0.67; 0.92]; p=0.0024) for XELOX vs. 5-FU/LV. XELOX showed a trend towards superior OS with a HR of 0.87 (95% CI=[0.72; 1.05]; p=0.1486) which translates into a 13% reduction in risk of death. The 5 year OS rate was 78% for XELOX versus 74% for 5-FU/LV. The efficacy data is based on a median observation time of 59 months for OS and 57 months for DFS. The rate of withdrawal due to adverse events was higher in the XELOX combination therapy arm (21%) as compared with that of the 5-FU/LV monotherapy arm (9%) in the ITT population.

Monotherapy with capecitabine in metastatic colorectal cancer
Data from two identically-designed, multicentre, randomised, controlled phase III clinical trials (SO14695; SO14796) support the use of capecitabine for first line treatment of metastatic colorectal cancer. In these trials, 603 patients were randomised to treatment with capecitabine (1250 mg/m² twice daily for 2 weeks followed by a 1-week rest period and given as 3-week cycles). 604 patients were randomised to treatment with 5-FU and leucovorin (Mayo regimen: 20 mg/m² leucovorin intravenous followed by 425 mg/m² intravenous bolus 5-FU, on days 1 to 5, every 28 days). The overall objective response rates in the all-randomised population (investigator assessment) were 25.7% (capecitabine) vs. 16.7% (Mayo regimen); p <0.0002. The median time to progression was 140 days (capecitabine) vs. 144 days (Mayo regimen). Median survival was 392 days (capecitabine) vs. 391 days (Mayo regimen). Currently, no comparative data are available on capecitabine monotherapy in colorectal cancer in comparison with first line combination regimens.

Combination therapy in first-line treatment of metastatic colorectal cancer
Data from a multicentre, randomised, controlled phase III clinical study (NO16966) support the use of capecitabine in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab for the first-line treatment of metastatic colorectal cancer. The study contained two parts: an initial 2-arm part in which 634 patients were randomised to two different treatment groups, including XELOX or FOLFOX-4, and a subsequent 2x2 factorial part in which 1401 patients were randomised to four different treatment groups, including XELOX plus placebo, FOLFOX-4 plus placebo, XELOX plus bevacizumab, and FOLFOX-4 plus bevacizumab.

Table 1 Treatment regimens in study NO16966 (mCRC)

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + Bevacizumab	Oxaliplatin	85 mg/m² intravenous 2 hr	Oxaliplatin on Day 1, every 2 weeks Leucovorin on Days 1 and 2, every 2 weeks 5-fluorouracil intravenous bolus/infusion, each on Days 1 and 2, every 2 weeks
	Leucovorin	200 mg/m² intravenous 2 hr	
	5-Fluorouracil	400 mg/m² intravenous bolus, followed by 600 mg/ m² intravenous 22 hr	
	Placebo or Bevacizumab	5 mg/kg intravenous 30-90 mins	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX+ Bevacizumab	Oxaliplatin	130 mg/m² intravenous 2 hr	Oxaliplatin on Day 1, every 3 weeks Capecitabine oral twice daily for 2 weeks (followed by 1 week off- treatment)
	Capecitabine	1000 mg/m² oral twice daily	
	Placebo or Bevacizumab	7.5 mg/kg intravenous 30-90 mins	Day 1, prior to XELOX, every 3 weeks
5-Fluorouracil: intravenous bolus injection immediately after leucovorin			

Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4-containing arms in the overall comparison was demonstrated in terms of progression-free survival in the eligible patient population and the intent-to-treat population (see table 2). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival (see table 2). A comparison of XELOX plus bevacizumab versus FOLFOX-4 plus bevacizumab was a pre-specified exploratory analysis. In this treatment subgroup comparison, XELOX plus bevacizumab was similar compared to FOLFOX-4 plus bevacizumab in terms of progression-free survival (hazard ratio 1.01; 97.5% CI 0.84 - 1.22). The median follow up at the time of the primary analyses in the intent-to-treat population was 1.5 years; data from analyses following an additional 1 year of follow up are also included in table 7. However, the on-treatment PFS analysis did not confirm the results of the general PFS and OS analysis: the hazard ratio of XELOX versus FOLFOX-4 was 1.24 with 97.5% CI 1.07 - 1.44. Although sensitivity analyses show that differences in regimen schedules and timing of tumour assessments impact the on-treatment PFS analysis, a full explanation for this result has not been found.

Table 2 Key efficacy results for the non-inferiority analysis of Study NO16966

PRIMARY ANALYSIS			
	XELOX/XELOX+P/ XELOX+BV (EPP*: N=967; ITT**: N=1017)	FOLFOX-4/FOLFOX-4+P/ FOLFOX-4+BV (EPP*: N = 937; ITT**: N= 1017)	
Population	Median Time to Event (Days)		HR (97.5% CI)
Parameter: Progression-free Survival			
EPP ITT	241 244	259 259	1.05 (0.94; 1.18) 1.04 (0.93; 1.16)
Parameter: Overall Survival			
EPP ITT	577 581	549 553	0.97 (0.84; 1.14) 0.96 (0.83; 1.12)
ADDITIONAL 1 YEAR OF FOLLOW UP			
Population	Median Time to Event (Days)		HR (97.5% CI)
Parameter: Progression-free Survival			
EPP ITT	242 244	259 259	1.02 (0.92; 1.14) 1.01 (0.91; 1.12)
Parameter: Overall Survival			
EPP ITT	600 602	594 596	1.00 (0.88; 1.13) 0.99 (0.88; 1.12)

*EPP=eligible patient population; **ITT=intent-to-treat population

In a randomised, controlled phase III study (CAIRO), the effect of using capecitabine at a starting dose of 1000 mg/m² for 2 weeks every 3 weeks in combination with irinotecan for the first-line treatment of patients with metastatic colorectal cancer was studied. 820 Patients were randomised to receive either sequential treatment (n=410) or combination treatment (n=410). Sequential treatment consisted of first-line capecitabine (1250 mg/m² twice daily for 14 days), second-line irinotecan (350 mg/m² on day 1), and third-line combination of capecitabine (1000 mg/m² twice daily for 14 days) with oxaliplatin (130 mg/m² on day 1). Combination treatment consisted of first-line capecitabine (1000 mg/m² twice daily for 14 days) combined with irinotecan (250 mg /m² on day 1) (XELIRI) and second-line capecitabine (1000 mg/m² twice daily for 14 days) plus oxaliplatin (130 mg/m² on day 1). All treatment cycles were administered at intervals of 3 weeks. In first-line treatment the median progression-free survival in the intent-to-treat population was 5.8 months (95%CI 5.1 - 6.2 months) for capecitabine monotherapy and 7.8 months (95%CI 7.0 - 8.3 months; p=0.0002) for XELIRI. However this was associated with an increased incidence of gastrointestinal toxicity and neutropenia during first-line treatment with XELIRI (26% and 11% for XELIRI and first line capecitabine respectively).

The XELIRI has been compared with 5-FU + irinotecan (FOLFIRI) in three randomised studies in patients with metastatic colorectal cancer. The XELIRI regimens included capecitabine 1000 mg/m² twice daily on days 1 to 14 of a three-week cycle combined with irinotecan 250 mg/m² on day1. In the largest study (BICC-C), patients were randomised to receive either open label FOLFIRI (n=144), bolus 5-FU (mIFL) (n=145) or XELIRI (n=141) and were additionally randomised to receive either double-blind treatment with celecoxib or placebo. Median PFS was 7.6 months for FOLFIRI, 5.9 months for mIFL (p=0.004) for the comparison with FOLFIRI), and 5.8 months for XELIRI (p=0.015). Median OS was 23.1 months for FOLFIRI, 17.6 months for mIFL (p=0.09), and 18.9 months for XELIRI (p=0.27). Patients treated with XELIRI experienced excessive gastrointestinal toxicity compared with FOLFIRI (diarrhoea 48% and 14% for XELIRI and FOLFIRI respectively).

In the EORTC study patients were randomised to receive either open label FOLFIRI (n=41) or XELIRI (n=44) with additional randomisation to either double-blind treatment with celecoxib or placebo. Median PFS and overall survival (OS) times were shorter for XELIRI versus FOLFIRI (PFS 5.9 versus 9.6 months and OS 14.8 versus 19.9 months), in addition to which excessive rates of diarrhoea were reported in patients receiving the XELIRI regimen (41% XELIRI, 5.1% FOLFIRI).

In the study published by Skof et al, patients were randomised to receive either FOLFIRI or XELIRI. Overall response rate was 49% in the XELIRI and 48% in the FOLFIRI arm (p=0.76). At the end of treatment, 37% of patients in the XELIRI and 26% of patients in the FOLFIRI arm were without evidence of the disease (p=0.56). Toxicity was similar between treatments with the exception of neutropenia reported more commonly in patients treated with FOLFIRI.

Montagnani et al used the results from the above three studies to provide an overall analysis of randomised studies comparing FOLFIRI and XELIRI treatment regimens in the treatment of mCRC. A significant reduction in the risk of progression was associated with FOLFIRI (HR, 0.76; 95%CI, 0.62-0.95; P <0.01), a result partly due to poor tolerance to the XELIRI regimens used.

Data from a randomised clinical study (Souglakos et al, 2012) comparing FOLFIRI + bevacizumab with XELIRI + bevacizumab showed no significant differences in PFS or OS between treatments. Patients were randomised to receive either FOLFIRI plus bevacizumab (Arm-A, n=167) or XELIRI plus bevacizumab (Arm-B, n-166). For Arm B, the XELIRI regimen used capecitabine 1000 mg/m² twice daily for 14 days + irinotecan 250 mg/m² on day 1. Median progression-free survival (PFS) was 10.0 and 8.9 months; p=0.64, overall survival 25.7 and 27.5 months; p=0.55 and response rates 45.5 and 39.8%; p=0.32 for FOLFIRI-Bev and XELIRI-Bev, respectively. Patients treated with XELIRI + bevacizumab reported a significantly higher incidence of diarrhoea, febrile neutropenia and hand-foot skin reactions than patients treated with FOLFIRI + bevacizumab with significantly increased treatment delays, dose reductions and treatment discontinuations.

Data from a multicentre, randomised, controlled phase II study (AIO KRK 0604) supports the use of capecitabine at a starting dose of 800 mg/m² for 2 weeks every 3 weeks in combination with irinotecan and bevacizumab for the first-line treatment of patients with metastatic colorectal cancer. 120 Patients were randomised to a modified XELIRI regimen with capecitabine 800 mg/m² twice daily for two weeks followed by a 7-day rest period), irinotecan (200 mg/m² as a 30 minute infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg as a 30 to 90 minute infusion on day 1 every 3 weeks ; 127 patients were randomised to treatment with capecitabine (1000 mg/m² twice daily for two weeks followed by a 7-day rest period), oxaliplatin (130 mg/m² as a 2 hour infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg as a 30 to 90 minute infusion on day 1 every 3 weeks). Following a mean duration of follow-up for the study population of 26.2 months, treatment responses were as shown below:

Table 3 Key efficacy results for AIO KRK study

	XELOX + bevacizumab (ITT: N=127)	Modified XELIRI+ bevacizumab (ITT: N= 120)	Hazard ratio 95% CI P value
Progression-free Survival after 6 months			
ITT 95% CI	76% 69 - 84%	84% 77 - 90%	-
Median progression free survival			
ITT 95% CI	10.4 months 9.0 - 12.0	12.1 months 10.8 - 13.2	0.93 0.82 - 1.07 P=0.30
Median overall survival			
ITT 95% CI	24.4 months 19.3 - 30.7	25.5 months 21.0 - 31.0	0.90 0.68 - 1.19 P=0.45

Combination therapy in second-line treatment of metastatic colorectal cancer
Data from a multicentre, randomised, controlled phase III clinical study (NO16967) support the use of capecitabine in combination with oxaliplatin for the second-line treatment of metastatic colorectal cancer. In this trial, 627 patients with metastatic colorectal carcinoma who have received prior treatment with irinotecan in combination with a fluoropyrimidine regimen as first line therapy were randomised to treatment with XELOX or FOLFOX-4. For the dosing schedule of XELOX and FOLFOX-4 (without addition of placebo or bevacizumab), refer to table 1. XELOX was demonstrated to be non-inferior to FOLFOX-4 in terms of progression-free survival in the per-protocol population and intent-to-treat population (see table 4). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival (see table 4). The median follow up at the time of the primary analyses in the intent-to-treat population was 2.1 years; data from analyses following an additional 6 months of follow up are also included in table 4.

Table 4 Key efficacy results for the non-inferiority analysis of Study NO16967

PRIMARY ANALYSIS			
	XELOX (PPP*: N=251; ITT**: N=313)	FOLFOX-4 (PPP*: N = 252; ITT**: N= 314)	
Population	Median Time to Event (Days)		HR (95% CI)
Parameter: Progression-free Survival			
PPP ITT	154 144	168 146	1.03 (0.87; 1.24) 0.97 (0.83; 1.14)
Parameter: Overall Survival			
PPP ITT	388 363	401 382	1.07 (0.88; 1.31) 1.03 (0.87; 1.23)
ADDITIONAL 6 MONTHS OF FOLLOW UP			
Population	Median Time to Event (Days)		HR (95% CI)
Parameter: Progression-free Survival			
PPP ITT	154 143	166 146	1.04 (0.87; 1.24) 0.97 (0.83; 1.14)
Parameter: Overall Survival			
PPP ITT	393 363	402 382	1.05 (0.88; 1.27) 1.02 (0.86; 1.21)

*PPP=per-protocol population; **ITT=intent-to-treat population

Advanced gastric cancer:
Data from a multicentre, randomised, controlled phase III clinical trial in patients with advanced gastric cancer supports the use of capecitabine for the first-line treatment of advanced gastric cancer (ML17032). In this trial, 160 patients were randomised to treatment with capecitabine (1000 mg/m² twice daily for 2 weeks followed by a 7-day rest period) and cisplatin (80 mg/m² as a 2-hour infusion every 3 weeks). A total of 156 patients were randomised to treatment with 5-FU (800 mg/m² per day, continuous infusion on days 1 to 5 every 3 weeks) and cisplatin (80 mg/m² as a 2-hour infusion on day 1, every 3 weeks). Capecitabine in combination with cisplatin was non-inferior to 5-FU in combination with cisplatin in terms of progression-free survival in the per protocol analysis (hazard ratio 0.81; 95% CI 0.63 - 1.04). The median progression-free survival was 5.6 months (capecitabine + cisplatin) versus 5.0 months (5-FU + cisplatin). The hazard ratio for duration of survival (overall survival) was similar to the hazard ratio for progression-free survival (hazard ratio 0.85; 95% CI 0.64 - 1.13). The median duration of survival was 10.5 months (capecitabine + cisplatin) versus 9.3 months (5-FU + cisplatin).

Data from a randomised multicentre, phase III study comparing capecitabine to 5-FU and oxaliplatin to cisplatin in patients with advanced gastric cancer supports the use of capecitabine for the first-line treatment of advanced gastric cancer (REAL-2). In this trial, 1002 patients were randomised in a 2x2 factorial design to one of the following 4 arms:

- ECF: epirubicin (50 mg/ m² as a bolus on day 1 every 3 weeks), cisplatin (60 mg/m² as a two hour infusion on day 1 every 3 weeks) and 5-FU (200 mg/m² daily given by continuous infusion via a central line).
- ECX: epirubicin (50 mg/m² as a bolus on day 1 every 3 weeks), cisplatin (60 mg/m² as a two hour infusion on day 1 every 3 weeks), and capecitabine (625 mg/m² twice daily continuously).
- EOF: epirubicin (50 mg/m² as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m² given as a 2 hour infusion on day 1 every three weeks), and 5-FU (200 mg/m² daily given by continuous infusion via a central line).
- EOX: epirubicin (50 mg/m² as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m² given as a 2 hour infusion on day 1 every three weeks), and capecitabine (625 mg/m² twice daily continuously).

The primary efficacy analyses in the per protocol population demonstrated non-inferiority in overall survival for capecitabine- vs 5-FU-based regimens (hazard ratio 0.86; 95% CI 0.8 - 0.99) and for oxaliplatin- vs cisplatin-based regimens (hazard ratio 0.92; 95% CI 0.80 - 1.1). The median overall survival was 10.9 months in capecitabine-based regimens and 9.6 months in 5-FU based regimens. The median overall survival was 10.0 months in cisplatin-based regimens and 10.4 months in oxaliplatin-based regimens.

Capecitabine has also been used in combination with oxaliplatin for the treatment of advanced gastric cancer. Studies with capecitabine monotherapy indicate that capecitabine has activity in advanced gastric cancer.

Colon, colorectal and advanced gastric cancer: meta-analysis
A meta-analysis of six clinical trials (studies SO14695, SO14796, M66001, NO16966, NO16967, M17032) supports capecitabine replacing 5-FU in mono- and combination treatment in gastrointestinal cancer. The pooled analysis includes 3097 patients treated with capecitabine-containing regimens and 3074 patients treated with 5-FU-containing regimens. Median overall survival time was 703 days (95% CI: 671; 745) in patients treated with capecitabine-containing regimens and 683 days (95% CI: 646; 715) in patients treated with 5-FU-containing regimens. The hazard ratio for overall survival was 0.94 (95% CI: 0.89; 1.00, p=0.0489) indicating that capecitabine-containing regimens are non-inferior to 5-FU-containing regimens.

Breast cancer:
Combination therapy with capecitabine and docetaxel in locally advanced or metastatic breast cancer
Data from one multicentre, randomised, controlled phase III clinical trial support the use of capecitabine in combination with docetaxel for treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy, including an anthracycline. In this trial, 255 patients were randomised to treatment with capecitabine (1250 mg/m² twice daily for 2 weeks followed by 1-week rest period and docetaxel 75 mg/m² as a 1 hour intravenous infusion every 3 weeks). 256 patients were randomised to treatment with docetaxel alone (100 mg/m² as a 1 hour intravenous infusion every 3 weeks). Survival was superior in the capecitabine + docetaxel combination arm (p=0.0126). Median survival was 442 days (capecitabine + docetaxel) vs. 352 days (docetaxel alone). The overall objective response rates in the all-randomised population (investigator assessment) were 41.6% (capecitabine + docetaxel) vs. 29.7% (docetaxel alone); p = 0.0058. Time to progressive disease was superior in the capecitabine + docetaxel combination arm (p<0.0001). The median time to progression was 186 days (capecitabine + docetaxel) vs. 128 days (docetaxel alone).

Monotherapy with capecitabine after failure of taxanes, anthracycline containing chemotherapy, and for whom anthracycline therapy is not indicated
Data from two multicentre phase II clinical trials support the use of capecitabine monotherapy for treatment of patients after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated. In these trials, a total of 236 patients were treated with capecitabine (1250 mg/m² twice daily for 2 weeks followed by 1-week rest period). The overall objective response rates (investigator assessment) were 20% (first trial) and 25% (second trial). The median time to progression was 93 and 98 days. Median survival was 384 and 373 days.

All indications:
A meta-analysis of 14 clinical trials with data from over 4700 patients treated with capecitabine monotherapy or capecitabine in combination with different chemotherapy regimens in multiple indications (colon, colorectal, gastric and breast cancer) showed that patients on capecitabine who developed hand-foot syndrome (HFS) had a longer overall survival compared to patients who did not develop HFS: median overall survival 1100 days (95% CI 1007;1200) vs 691 days (95% CI 638;754) with a hazard ratio of 0.61 (95% CI 0.56; 0.66).

Paediatric population:
The European Medicines Agency has waived the obligation to conduct studies with Capecitabine in all subsets of the paediatric population in adenocarcinoma of the colon and rectum, gastric adenocarcinoma and breast carcinoma.

D.2 Pharmacokinetic properties

The pharmacokinetics of capecitabine have been evaluated over a dose range of 502-3514 mg/m²/day. The parameters of capecitabine, 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-deoxy-5-fluorouridine (5'-DFUR) measured on days 1 and 14 were similar. The AUC of 5-FU was 30%-35% higher on day 14. Capecitabine dose reduction decreases systemic exposure to 5-FU more than dose-proportionally, due to non-linear pharmacokinetics for the active metabolite.

Absorption
After oral administration, capecitabine is rapidly and extensively absorbed, followed by extensive conversion to the metabolites, 5'-DFCR and 5'-DFUR. Administration with food decreases the rate of capecitabine absorption, but only results in a minor effect on the AUC of 5'-DFUR, and on the AUC of the subsequent metabolite 5-FU. At the dose of 1250 mg/m² on day 14 with administration after food intake, the peak plasma concentrations (C_{max} in μg/ml) for capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 4.67, 3.05, 12.1, 0.95 and 5.46 respectively. The time to peak plasma concentrations (T_{max} in hours) were 1.50, 2.00, 2.00, 2.00 and 3.34. The $AUC_{0-\infty}$ values in μg·h/ml were 7.75, 7.24, 24.6, 2.03 and 36.3.

Distribution
In vitro human plasma studies have determined that capecitabine, 5'-DFCR, 5'-DFUR and 5-FU are 54%, 10%, 62% and 10% protein bound, mainly to albumin.

Biotransformation
Capecitabine is first metabolised by hepatic carboxylesterase to 5'-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumour tissues. Further catalytic activation of 5'-DFUR then occurs by thymidine phosphorylase (ThyPase). The enzymes involved in the catalytic activation are found in tumour tissues but also in normal tissues, albeit usually at lower levels. The sequential enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations within tumour tissues. In the case of colorectal tumours, 5-FU generation appears to be in large part localised in tumour stromal cells. Following oral administration of capecitabine to patients with colorectal cancer, the ratio of 5-FU concentration in colorectal tumours to adjacent tissues was 3.2 (ranged from 0.9 to 8.0). The ratio of 5-FU concentration in tumour to plasma was 21.4 (ranged from 3.9 to 59.9, n=8) whereas the ratio in healthy tissues to plasma was 8.9 (ranged from 3.0 to 25.8, n=8). Thymidine phosphorylase activity was measured and found to be 4 times greater in primary colorectal tumour than in adjacent normal tissue. According to immunohistochemical studies, thymidine phosphorylase appears to be in large part localised in tumour stromal cells.

5-FU is further catabolised by the enzyme dihydropyrimidine dehydrogenase (DPD) to the much less toxic dihydro-5-fluorouracil (FUH_2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureidopropionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β-alanine (FBAL) which is cleared in the urine. Dihydropyrimidine dehydrogenase (DPD) activity is the rate limiting step. Deficiency of DPD may lead to increased toxicity of capecitabine.

Elimination
The elimination half-life ($t_{1/2}$ in hours) of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 0.85, 1.11, 0.66, 0.76 and 3.23 respectively. Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered capecitabine dose is recovered in urine. Faecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL, which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine unchanged

Combination therapy
Phase I studies evaluating the effect of capecitabine on the pharmacokinetics of either docetaxel or paclitaxel and vice versa showed no effect by capecitabine on the pharmacokinetics of docetaxel or paclitaxel (C_{max} and AUC) and no effect by docetaxel or paclitaxel on the pharmacokinetics of 5'-DFUR.

Pharmacokinetics in special populations
A population pharmacokinetic analysis was carried out after capecitabine treatment of 505 patients with colorectal cancer dosed at 1250 mg/m² twice daily. Gender, presence or absence of liver metastasis at baseline, Karnofsky Performance Status, total bilirubin, serum albumin, ASAT and ALAT had no statistically significant effect on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL.

Patients with hepatic impairment due to liver metastases: According to a pharmacokinetic study in cancer patients with mild to moderate liver impairment due to liver metastases, the bioavailability of capecitabine and exposure to 5-FU may increase compared to patients with no liver impairment. There are no pharmacokinetic data on patients with severe hepatic impairment.

Patients with renal impairment: Based on a pharmacokinetic study in cancer patients with mild to severe renal impairment, there is no evidence for an effect of creatinine clearance on the pharmacokinetics of intact drug and 5-FU. Creatinine clearance was found to influence the systemic exposure to 5'-DFUR (35% increase in AUC when creatinine clearance decreases by 50%) and to FBAL (114% increase in AUC when creatinine clearance decreases by 50%). FBAL is a metabolite without antiproliferative activity.

Elderly: Based on the population pharmacokinetic analysis, which included patients with a wide range of ages (27 to 86 years) and included 234 (46%) patients greater or equal to 65, age has no influence on the pharmacokinetics of 5'-DFUR and 5-FU. The AUC of FBAL increased with age (20% increase in age results in a 15% increase in the AUC of FBAL). This increase is likely due to a change in renal function.

Ethnic factors: Following oral administration of 825 mg/m² capecitabine twice daily for 14 days, Japanese patients (n=18) had about 36% lower C_{max} and 24% lower AUC for capecitabine than Caucasian patients (n=22). Japanese patients had also about 25% lower C_{max} and 34% lower AUC for FBAL than Caucasian patients. The clinical relevance of these differences is unknown. No significant differences occurred in the exposure to other metabolites (5'-DFCR, 5'-DFUR, and 5-FU).

E. Indication

Therapeutic Indication(s)
Breast Cancer:
Capecitabine in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Capecitabine is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of a taxane and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.
Capecitabine is indicated in combination with lapatinib ditosylate for the treatment of patients with advanced or metastatic breast cancer whose tumors over express HER2 and who have received prior therapy including an anthracycline, a taxane and trastuzumab.
Colon, Colorectal cancer:
Capecitabine is indicated for the treatment of patients with metastatic colorectal carcinoma.
Capecitabine is indicated as adjuvant treatment of patients following surgery of Stage III (Duke's Stage C) colon cancer.
Oesophagogastric Cancer:
Capecitabine is indicated as first-line treatment of patients with advanced oesophagogastric cancer in combination with a platinum-based regimen.

F. Recommended dose

Standard dosage
capecitabine tablets should be swallowed whole with water within 30 minutes after a meal. capecitabine tablets should not be crushed or cut. If patients cannot swallow capecitabine tablets whole and tablets must be crushed or cut, this should be done by a professional trained in the safe handling of cytotoxic drugs.

Monotherapy:
Colon, Colorectal and breast cancer
The recommended monotherapy starting dose of capecitabine is 1250 mg/ m² administered twice daily (morning and evening; equivalent to 2500 mg/m² total daily dose) for 2 weeks followed by a 7-day rest period.

Combination therapy
Breast Cancer
In combination with docetaxel
In combination with docetaxel, the recommended dose of capecitabine is 1250 mg/m² twice daily for 2 weeks followed by a 7-day rest period, combined with docetaxel at 75 mg/m² as a 1-hour intravenous infusion every 3 weeks.

Pre-medication according to the docetaxel labelling, should be started prior to docetaxel administration for patients receiving the capecitabine plus docetaxel combination.

In combination with lapatinib ditosylate

In combination with *lapatinib ditosylate*, the recommended dose of capecitabine is 2000 mg/m²/day administered orally in 2 doses 12 hours apart for 14 days (Day 1-14) in a repeating 21 day cycle combined with lapatinib ditosylate 1250 mg (5 tablets) given orally once daily from Day 1-21. (See manufacturer's prescribing information for lapatinib ditosylate for further information).

Colon, colorectal cancer
In combination with oxaliplatin and/or bevacizumab
In combination with oxaliplatin and/or bevacizumab the recommended dose of capecitabine is 1000 mg/m² twice daily for 2 weeks followed by a 7-day rest period. The first dose of capecitabine is given on the evening of day 1 and the last dose is given on the morning of day 15. Given as a 3-weekly schedule, on day 1 every 3 weeks bevacizumab is administered as a 7.5 mg/kg intravenous infusion over 30-90 minutes followed by oxaliplatin administered as a 130 mg/m² intravenous infusion over 2 hours.

Premedication to maintain adequate hydration and anti-emesis according to the oxaliplatin product information should be started prior to oxaliplatin administration for patients receiving the capecitabine plus oxaliplatin combination. Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

Gastric Cancer
In combination with platinum-based regimen:
In combination with a platinum-based compound the recommended dose of capecitabine for the treatment of advanced gastric cancer is 1000 mg/m² administered twice daily for 14 days followed by a 7 day rest period. The first dose of capecitabine should be given on the evening of day 1 and the last dose should be given on the morning of day 15. If epirubicin is added to this regimen the recommended dose of capecitabine is 625 mg/m² twice daily continuously. Epirubicin at a dose of 50 mg/m² should be given as a bolus on day 1 every 3 weeks. The platinum based compound (cisplatin at a dose of 60 mg/m² (triple regimen) - 80 mg/m² (double regimen) or oxaliplatin at a dose of 130 mg/m²) should be given on day 1 as a 2 hour intravenous infusion every 3 weeks.

Premedication to maintain adequate hydration and anti-emesis according to the cisplatin/oxaliplatin summary of product characteristics should be started prior to cisplatin/oxaliplatin administration for patients receiving the capecitabine plus cisplatin/oxaliplatin combination.

Dose calculation
capecitabine dose is calculated according to body surface area. The following tables show the standard and reduced dose calculations for a starting dose of capecitabine of either 1250 mg/m² or 1000 mg/m².

Table 5: Standard and reduced dose calculations according to body surface area for a starting dose of capecitabine of 1250 mg/m²

Dose level 1250 mg/m² (twice daily)					
	Full dose 1250 mg/m²	Number of tablets per administration (each administration to be given morning and evening)		Reduced dose (75%) 950 mg/m²	Reduced dose (50%) 625 mg/m²
Body surface area (m²)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤1.26	1500	-	3	1150	800
1.27 –1.38	1650	1	3	1300	800
1.39 –1.52	1800	2	3	1450	950
1.53 –1.66	2000	-	4	1500	1000
1.67 –1.78	2150	1	4	1650	1000
1.79 –1.92	2300	2	4	1800	1150
1.93 –2.06	2500	-	5	1950	1300
2.07 –2.18	2650	1	5	2000	1300
≥2.19	2800	2	5	2150	1450

Table 6: Standard and reduced dose calculations according to body surface area for a starting dose of capecitabine of 1000 mg/m²

Dose level 1000 mg/m² (twice daily)					
	Full dose 1000 mg/m²	Number of tablets per administration (each administration to be given morning and evening)		Reduced dose (75%) 750 mg/m²	Reduced dose (50%) 500 mg/m²
Body surface area (m²)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤1.26	1150	1	2	800	600
1.27 –1.38	1300	2	2	1000	600
1.39 –1.52	1450	3	2	1100	750
1.53 –1.66	1600	4	2	1200	800
1.67 –1.78	1750	5	2	1300	800
1.79 –1.92	1800	2	3	1400	900
1.93 –2.06	2000	-	4	1500	1000
2.07 –2.18	2150	1	4	1600	1050
≥2.19	2300	2	4	1750	1100

Dosage adjustments during treatment
General:
Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the capecitabine dose (treatment interruption or dose reduction). Once the dose has been reduced it should not be increased at a later time.

For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening treatment can be continued at the same dose without reduction or interruption.

Dosage modifications are not recommended for Grade 1 events. Therapy with capecitabine should be interrupted if a Grade 2 or 3 adverse drug reaction (ADR) occurs. Once the ADR has resolved or decreased in intensity to Grade 1, capecitabine therapy may be restarted at full dose or as adjusted according to Table 7. If a Grade 4 ADR occurs, therapy should be discontinued or interrupted until the ADR has resolved or decreased to Grade 1, and therapy should be restarted at 50% of the original dose. Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of capecitabine omitted for toxicity are not replaced.

Haematology:

Patients with baseline neutrophil counts of <1.5 X 10⁹/L and/or thrombocyte counts of <100 X 10⁹/L should not be treated with capecitabine. If unscheduled laboratory assessments during a treatment cycle show grade 3 or 4 haematologic toxicity, treatment with capecitabine should be interrupted.

The following table shows the recommended dose modifications following toxicity related to with capecitabine:

Table 7: Capecitabine dose reduction schedule

Toxicity NCIC grades*	Dose changes within a treatment cycle	Dose adjustment for next cycle (% of starting dose)
Grade 1	maintain dose level	maintain dose level
Grade 2		
1st appearance	interrupt until resolved to Grade 0-1	100%
2nd appearance		75%
3rd appearance		50%
4th appearance	discontinue treatment permanently	Not applicable
• Grade 3		
1st appearance	interrupt until resolved to Grade 0-1	75%
2nd appearance		50%
3rd appearance	discontinue treatment permanently	Not applicable
• Grade 4		
1st appearance	discontinue permanently *or* If physician deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0-1	50%
2nd appearance	discontinue permanently	Not applicable

*According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) Common Toxicity Criteria (version 1) or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 3.0. For hand-foot syndrome and hyperbilirubinemia,

The following are the recommended dose modifications for toxicity when Capecitabine and docetaxel are used in combination

Table 8: Capecitabine (X) in combination with docetaxel (T) dose reduction schedule

	Recommended Dose Modifications	
	Capecitabine dose changes within a treatment cycle	
Toxicity grade[1]	**Grade 1**	
	100% of starting dose (no interruption)	X: 100% of starting dose T: 100% (75 mg/m²)
Toxicity grade[1]	**Grade 2**	
1st appearance	Interrupt until resolved (grade 0 –1)	X: 100% of starting dose T: 100% (75 mg/m²)
2nd appearance of same toxicity	Interrupt until resolved (grade 0- 1)	X: 75% of starting dose T: Reduce to 55 mg/m²
3rd appearance of same toxicity	Interrupt until resolved (grade 0-1)	X: 50% of starting dose **T: Discontinue permanently**
4th appearance of same toxicity	**Discontinue permanently**	
Toxicity grade	**Grade 3**	
	If grade 3 haematological see section on haematological toxicity, otherwise:	
1st appearance	Interrupt until resolved (grade 0 – 1)	X: 75% of starting dose T: Reduce to 55 mg/m²
2nd appearance	Interrupt until resolved (grade 0 – 1)	X: 50% of starting dose **T: Discontinue permanently**
3rd appearance	**Discontinue permanently**	
Toxicity grade[1]	**Grade 4**	
	If G4 haematological see section on haematological toxicity, otherwise:	
1st appearance	Discontinue permanently *or* (if physician deems it to be in the best of interest of the patient) interrupt until resolved (grade 0-1)	X: Reduce to 50% **T: Discontinue permanently**
2nd appearance	**Discontinue permanently**	

*National Cancer Institute of Canada Common Toxicity Criteria were used except for hand-foot syndrome.

Specific dose adjustment in combination with docetaxel

Capecitabine and/or docetaxel dose modifications should be made according to the general dose modification scheme above, if nothing else is stated regarding specific dose adjustments. For those toxicities considered unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption. At the beginning of a treatment cycle, if either a docetaxel or a Capecitabine treatment delay is indicated, both docetaxel and Capecitabine administration should be delayed until the requirements for restarting both drugs are met. If docetaxel has to be discontinued, Capecitabine treatment can be resumed when the requirements for restarting Capecitabine are met.

Hematology: Treatment should only be re-administered when the neutrophil count is ≥1.5 x 10⁹/l (Grade 0 - 1). Patients with neutropenia <0.5 x 10⁹/l (Grade 4) for more than 1 week, or febrile (>38°C) neutropenia, should have the docetaxel dosage reduced from 75 mg/m² to 55 mg/m². If Grade 4 neutropenia or febrile neutropenia occurs at 55 mg/m² docetaxel, docetaxel should be discontinued. Patients with baseline neutrophil counts of <1.5 x 10⁹/l and/or thrombocyte counts of <1.0 x 10⁹/l should not be treated with the Capecitabine /docetaxel combination.

Hypersensitivity: Patients who develop severe hypersensitivity reactions (hypotension with a decrease of ≥ 20 mm Hg, or bronchospasm, or generalised rash/erythema) should stop treatment immediately and be given appropriate therapy. These patients should not be re challenged with the drug suspected to have caused hypersensitivity.

Peripheral neuropathy: For 1st appearance of Grade 2 toxicity, reduce the docetaxel dose to 55 mg/m². If Grade 3 toxicity appears, discontinue docetaxel treatment. In both instances follow the above dose modification scheme for Capecitabine.

Fluid retention: Severe (Grade 3 or 4) toxicity such as pleural effusion, pericardial effusion or ascites which is possibly related to docetaxel should be closely monitored. In case of appearance of such toxicity docetaxel treatment should be discontinued, Capecitabine treatment may be continued without dose modification.

Hepatic impairment: Docetaxel should generally not be given to patients with serum bilirubin above the upper limit of normal. The following modifications should be applied to the docetaxel dose in the event of abnormal values for ASAT, ALAT, and/or alkaline phosphatase levels:

Table 9: Modifications to the docetaxel dose

ASAT and/or ALAT values		Alkaline phosphatase values	Docetaxel dose modification
≤1.5 x UNL	and	≤5 x UNL	no dose modification
>1.5 x UNL — ≤2.5 x UNL	and	≤2.5 x UNL	no dose modification

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>2.5 x UNL — ≤5 x UNL	and	≤2.5 x UNL	reduce by 25% (not below 55 mg/m^2)
>1.5 x UNL — ≤5 x UNL	and	>2.5 x UNL — ≤5 x UNL	reduce by 25% (not below 55 mg/m2)
>5 x UNL (unless bone metastases are present in the absence of any liver disorder)	or>	>5 x UNL	delay dose by a maximum of 2 weeks. If no recovery, discontinue docetaxel.

Once the docetaxel dose is reduced for a given cycle, no further dose reduction is recommended for subsequent cycles unless worsening of the parameters is observed. In case of recovery of liver function tests after previous reduction of the docetaxel dose, the docetaxel dose can be re-escalated to the previous dose level.

Dehydration: Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhea may rapidly become dehydrated. If Grade 2 (or higher) dehydration occur, Capecitabine treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications applied should be those for the precipitating adverse event in accordance with the above guidelines.

Reductions to 75% and 50% of Capecitabine dose

For patients receiving Capecitabine monotherapy or Capecitabine in combination with docetaxel, the following tables show the dosage at 75% and 50%, calculated according to the body surface area:

Table 10: Calculated Capecitabine dose, reduced to 75% of the standard starting dose

Dose level 950 mg/m^2 twice daily		**Number of tablets administered in the morning**		**Number of tablets administered in the evening**	
Body surface area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.26	1150	1	2	1	2
1.27 – 1.38	1300	2	2	2	2
1.39 – 1.52	1450	3	2	3	2
1.53 – 1.66	1500	–	3	–	3
1.67 – 1.78	1650	1	3	1	3
1.79 – 1.92	1800	2	3	2	3
1.93 –2.06	1950	3	3	3	3
2.07 – 2.18	2000	–	4	–	4
≥2.19	2150	1	4	1	4

Calculated Capecitabine dose, reduced to 50% of the standard starting dose

Dose level 625 mg/m^2 twice daily		**Number of tablets administered in the morning**		**Number of tablets administered in the evening**	
Body surface area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.38	800	2	1	2	1
1.39 − 1.52	950	3	1	3	1
1.53 -1.66	1000	–	2	–	2
1.67 -1.78	1000	–	2	–	2
1.79 − 1.92	1150	1	2	1	2
1.93 − 2.06	1300	2	2	2	2
2.07 − 2.18	1300	2	2	2	2
≥2.19	1450	3	2	3	2

Special dosage instructions

Pediatric use
The safety and efficacy of Capecitabine in children and adolescents (<18 years) have not been established.

Geriatric use
For Capecitabine monotherapy, no adjustment of the starting dose is needed. However, severe Grade 3 or 4 treatment-related ADRs were more frequent in patients over 80 years of age compared to younger patients.

When Capecitabine was used in combination with other antineoplastic agents, geriatric patients (≥65 years) experience more Grade 3 and Grade 4 ADRs and ADRs that led to discontinuation, than younger patients. Careful monitoring of elderly patients is advisable.

In combination with docetaxel: an increased incidence of Grade 3 or 4 treatment-related ADRs and treatment-related serious ADRs was observed in patients 60 years of age or more. For patients 60 years of age or more treated with the combination of Capecitabine plus docetaxel, a starting dose reduction of Capecitabine to 75% (950 mg/m^2 twice daily) is recommended. In combination with irinocetan: for patients 65 years of age or more, a starting dose reduction of Capecitabine to 800 mg/m^2 twice daily is recommended.

Renal impairment
In patients with moderate renal impairment (creatinine clearance 30 - 50 mL/min [Cockcroft and Gault]) at baseline, a dose reduction to 75% for a starting dose of 1250 mg/ m^2 is recommended. In patients with mild renal impairment (creatinine clearance 51 - 80 mL/min), no adjustment in starting dose is recommended.

Careful monitoring and prompt treatment interruption is recommended if the patient develops a Grade 2, 3, or 4 ADRs with subsequent dose adjustment as outlined in Table 7 If the calculated creatinine clearance decreases during treatment to a value below 30 mL/min, Capecitabine should be discontinued. The dose adjustment recommendations for patients with moderate renal impairment apply both to monotherapy and combination use.

Hepatic Impairment
In patients with mild to moderate hepatic impairment due to liver metastases, no starting dose adjustment is necessary. However, such patients should be carefully monitored.

Patients with severe hepatic impairment have not been studied.

G. Route of Administration

Oral Route

H. Contraindications

- History of severe and unexpected reactions to fluoropyrimidine therapy,
- Hypersensitivity to capecitabine or to any of the excipients or fluorouracil,
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency.
- During pregnancy and lactation,
- In patients with severe leukopenia, neutropenia, or thrombocytopenia,
- In patients with severe hepatic impairment,
- In patients with severe renal impairment (creatinine clearance below 30 ml/min),
- Recent or concomitant treatment with brivudine.
- If contraindications exist to any of the medicinal products in the combination regimen, that medicinal product should not be used.

I. **Warnings and Precautions**

Dose limiting toxicities
Dose limiting toxicities include diarrhoea, abdominal pain, nausea, stomatitis and hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia). Most adverse reactions are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced.

Diarrhoea.
Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Standard antidiarrhoeal treatments (e.g. loperamide) may be used. NCIC CTC grade 2 diarrhoea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhoea as an increase of 7 to 9 stools/day or incontinence and malabsorption. Grade 4 diarrhoea is an increase of ≥10 stools/day or grossly bloody diarrhoea or the need for parenteral support. Dose reduction should be applied as necessary.

Dehydration.
Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhoea may rapidly become dehydrated. Dehydration may cause acute renal failure, especially in patients with pre-existing compromised renal function or when capecitabine is given concomitantly with known nephrotoxic medicinal products. Acute renal failure secondary to dehydration might be potentially fatal. If grade 2 (or higher) dehydration occurs, capecitabine treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications applied should be applied for the precipitating adverse event as necessary.

Hand-foot syndrome
(also known as hand-foot skin reaction or palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema). Grade 1 hand-foot syndrome is defined as numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt the patient's normal activities.

Grade 2 hand-foot syndrome is painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 hand-foot syndrome is moist desquamation, ulceration, blistering and severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. Persistent or severe hand-foot syndrome (Grade 2 and above) can eventually lead to loss of fingerprints which could impact patient identification. If grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-foot syndrome, subsequent doses of capecitabine should be decreased. When capecitabine and cisplatin are used in combination, the use of vitamin B6 (pyridoxine) is not advised for symptomatic or secondary prophylactic treatment of hand–foot syndrome, because of published reports that it may decrease the efficacy of cisplatin. There is some evidence that dexpanthenol is effective for hand-foot syndrome prophylaxis in patients treated with Capecitabine.

Cardiotoxicity.
Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes (including very rare cases of QT prolongation). These adverse reactions may be more common in patients with a prior history of coronary artery disease. Cardiac arrhythmias (including ventricular fibrillation, torsade de pointes, and bradycardia), angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving capecitabine. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris.

Hypo- or hypercalcaemia. Hypo- or hypercalcaemia has been reported during capecitabine treatment. Caution must be exercised in patients with pre-existing hypo- or hypercalcaemia.

Central or peripheral nervous system disease. Caution must be exercised in patients with central or peripheral nervous system disease, e.g. brain metastasis or neuropathy.

Diabetes mellitus or electrolyte disturbances. Caution must be exercised in patients with diabetes mellitus or electrolyte disturbances, as these may be aggravated during capecitabine treatment.

Coumarin-derivative anticoagulation. In an interaction study with single-dose warfarin administration, there was a significant increase in the mean AUC (+57%) of S-warfarin. These results suggest an interaction, probably due to an inhibition of the cytochrome P450 2C9 isoenzyme system by capecitabine. Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely and the anticoagulant dose adjusted accordingly.

Brivudine. Brivudine must not be administered concomitantly with capecitabine. Fatal cases have been reported following this drug interaction. There must be at least a 4-week waiting period between end of treatment with brivudine and start of capecitabine therapy. Treatment with brivudine can be started 24 hours after the last dose of capecitabine In the event of accidental administration of brivudine to patients being treated with capecitabine, effective measures should be taken to reduce the toxicity of capecitabine. Immediate admission to hospital is recommended. All measures should be initiated to prevent systemic infections and dehydration.

Hepatic impairment. In the absence of safety and efficacy data in patients with hepatic impairment, Capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis. Administration of capecitabine should be interrupted if treatment-related elevations in bilirubin of >3.0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of >2.5 x ULN occur. Treatment with capecitabine monotherapy may be resumed when bilirubin decreases to ≤3.0 x ULN or hepatic aminotransferases decrease to ≤ 2.5 x ULN.

Renal impairment. The incidence of grade 3 or 4 adverse reactions in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) is increased compared to the overall population

Dihydropyrimidine dehydrogenase (DPD) deficiency:
DPD activity is rate limiting in the catabolism of 5-fluorouracil. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidines-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity.

DPD-deficiency related toxicity usually occurs during the first cycle of treatment or after dose increase.

Complete DPD deficiency
Complete DPD deficiency is rare (0.01-0.5% of Caucasians). Patients with complete DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated with Capecitabine.

Partial DPD deficiency
Partial DPD deficiency is estimated to affect 3-9% of the Caucasian population. Patients with partial DPD deficiency are at increased risk of severe and potentially life-threatening toxicity. A reduced starting dose should be considered to limit this toxicity. DPD deficiency should be considered as a parameter to be taken into account in conjunction with other routine measures for dose reduction. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.

Testing for DPD deficiency
Phenotype and/or genotype testing prior to the initiation of treatment with Capecitabine is recommended despite uncertainties regarding optimal pre-treatment testing methodologies. Consideration should be given to applicable clinical guidelines.

Genotypic characterisation of DPD deficiency
Pre-treatment testing for rare mutations of the DPYD gene can identify patients with DPD deficiency.

The four DPYD variants c.1905+1G>A [also known as DPYD*2A], c.1679T>G [DPYD*13], c.2846A>T and c.1236G>A/HapB3 can cause complete absence or reduction of DPD enzymatic activity. Other rare variants may also be associated with an increased risk of severe or life-threatening toxicity.

Certain homozygous and compound heterozygous mutations in the DPYD gene locus (e.g. combinations of the four variants with at least one allele of c.1905+1G>A or c.1679T>G) are known to cause complete or near complete absence of DPD enzymatic activity.

Patients with certain heterozygous DPYD variants (including c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants) have increased risk of severe toxicity when treated with fluoropyrimidines.

The frequency of the heterozygous c.1905+1G>A genotype in the DPYD gene in Caucasian patients is around 1%, 1.1% for c.2846A>T, 2.6-6.3% for c.1236G>A/HapB3 variants and 0.07 to 0.1% for c.1679T>G.

Data on the frequency of the four DPYD variants in other populations than Caucasian is limited. At the present, the four DPYD variants (c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3) are considered virtually absent in populations of African (-American) or Asian origin.

Phenotypic characterisation of DPD deficiency
For phenotypic characterisation of DPD deficiency, the measurement of pre-therapeutic blood levels of the endogenous DPD substrate uracil (U) 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.

Ophthalmologic complications: Patients should be carefully monitored for ophthalmological complications such as keratitis and corneal disorders, especially if they have a prior history of eye disorders. Treatment of eye disorders should be initiated as clinically appropriate.

Severe skin reactions: Capecitabine can induce severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. Capecitabine should be permanently discontinued in patients who experience a severe skin reaction during treatment.

As this medicinal product contains anhydrous lactose as an excipient, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Capecitabine tablets should not be crushed or cut. In case of exposure of either patient or caregiver to crushed or cut Capecitabine tablets adverse drug reactions could occur.

J. Interactions with Other Medications

Interaction studies have only been performed in adults.

Interaction with other medicinal products
Brivudine: a clinically significant interaction between brivudine and fluoropyrimidines (e.g. capecitabine, 5-Fluorouracil, tegafur), resulting from the inhibition of dihydropyrimidine dehydrogenase by brivudine, has been described. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, brivudine must not be administered concomitantly with capecitabine There must be at least a 4-week waiting period between end of treatment with brivudine and start of capecitabine therapy. Treatment with brivudine can be started 24 hours after the last dose of capecitabine.

Cytochrome P-450 2C9 substrates: Other than warfarin, no formal interaction studies between capecitabine and other CYP2C9 substrates have been conducted. Care should be exercised when capecitabine is co-administered with 2C9 substrates (e.g., phenytoin).

Coumarin-derivative anticoagulants: altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These reactions occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. In a clinical pharmacokinetic interaction study, after a single 20 mg dose of warfarin, capecitabine treatment increased the AUC of S-warfarin by 57% with a 91% increase in INR value. Since metabolism of R-warfarin was not affected, these results indicate that capecitabine down-regulates isozyme 2C9, but has no effect on isozymes 1A2 and 3A4. Patients taking coumarin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR) and the anticoagulant dose adjusted accordingly.

Phenytoin
Increased phenytoin plasma concentrations resulting in symptoms of phenytoin intoxication in single cases have been reported during concomitant use of capecitabine with phenytoin. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.

Folinic acid/folic acid
A combination study with capecitabine and folinic acid indicated that folinic acid has no major effect on the pharmacokinetics of capecitabine and its metabolites. However, folinic acid has an effect on the pharmacodynamics of capecitabine and its toxicity may be enhanced by folinic acid: the maximum tolerated dose (MTD) of capecitabine alone using the intermittent regimen is 3000 mg/m^2 per day whereas it is only 2000 mg/m^2 per day when capecitabine was combined with folinic acid (30 mg orally bid). The enhanced toxicity may be relevant when switching from 5- FU/LV to a capecitabine regimen. This may also be relevant with folic acid supplementation for folate deficiency due to the similarity between folinic acid and folic acid.

Antacid: the effect of an aluminium hydroxide and magnesium hydroxide-containing antacid on the pharmacokinetics of capecitabine was investigated. There was a small increase in plasma concentrations of capecitabine and one metabolite (5'-DFCR); there was no effect on the 3 major metabolites (5'-DFUR, 5-FU and FBAL).

Allopurinol: interactions with allopurinol have been observed for 5-FU; with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with capecitabine should be avoided.

Interferon alpha: the MTD of capecitabine was 2000 mg/m^2 per day when combined with interferon alpha-2a (3 MIU/m^2 per day) compared to 3000 mg/m^2 per day when capecitabine was used alone.

Radiotherapy: the MTD of capecitabine alone using the intermittent regimen is 3000 mg/m^2 per day, whereas, when combined with radiotherapy for rectal cancer, the MTD of capecitabine is 2000 mg/m^2 per day using either a continuous schedule or given daily Monday through Friday during a 6-week course of radiotherapy.

Oxaliplatin: no clinically significant differences in exposure to capecitabine or its metabolites, free platinum or total platinum occurred when capecitabine was administered in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab.

Bevacizumab: there was no clinically significant effect of bevacizumab on the pharmacokinetic parameters of capecitabine or its metabolites in the presence of oxaliplatin.

Food interaction

In all clinical trials, patients were instructed to administer capecitabine within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that capecitabine be administered with food. Administration with food decreases the rate of capecitabine absorption.

K. Statement on usage during pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with capecitabine. If the patient becomes pregnant while receiving capecitabine, the potential hazard to the foetus must be explained. An effective method of contraception should be used during treatment and for 6 months after the last dose of capecitabine.

Based on genetic toxicity findings, male patients with female partners of reproductive potential should use effective contraception during treatment and for 3 months following the last dose of capecitabine.

Pregnancy
There are no studies in pregnant women using capecitabine; however, it should be assumed that capecitabine may cause foetal harm if administered to pregnant women. In reproductive toxicity studies in animals, capecitabine administration caused embryolethality and teratogenicity. These findings are expected effects of fluoropyrimidine derivatives. Capecitabine is contraindicated during pregnancy.

Breast-feeding
It is not known whether capecitabine is excreted in human breast milk. No studies have been conducted to assess the impact of capecitabine on milk production or its presence in human breast milk. In lactating mice, considerable amounts of capecitabine and its metabolites were found in milk. As the potential for harm to the nursing infant is unknown, breast-feeding should be discontinued while receiving treatment with capecitabine and for 2 weeks after the final dose.

Fertility
There is no data on Capecitabine and impact on fertility. The Capecitabine pivotal studies included females of childbearing potential and males only if they agreed to use an acceptable method of birth control to avoid pregnancy for the duration of the study and for a reasonable period thereafter.

In animal studies effects on fertility were observed.

L. Adverse Effects/ Undesirable Effects

Summary of the safety profile
The overall safety profile of capecitabine is based on data from over 3000 patients treated with capecitabine as monotherapy or capecitabine in combination with different chemotherapy regimens in multiple indications. The safety profiles of capecitabine monotherapy for the metastatic breast cancer, metastatic colorectal cancer and adjuvant colon cancer populations are comparable The most commonly reported and/or clinically relevant treatment-related adverse drug reactions (ADRs) were gastrointestinal disorders (especially diarrhoea, nausea, vomiting, abdominal pain, stomatitis), hand-foot syndrome (palmar-plantar erythrodysesthesia), fatigue, asthenia, anorexia, cardiotoxicity, increased renal dysfunction on those with preexisting compromised renal function, and thrombosis/embolism.

Tabulated list of adverse reactions
ADRs considered by the investigator to be possibly, probably, or remotely related to the administration of capecitabine are listed in table 11 for capecitabine given as monotherapy and in table 12 for capecitabine given in combination with different chemotherapy regimens in multiple indications. The following headings are used to rank the ADRs by frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Capecitabine Monotherapy:
Table 11 lists ADRs associated with the use of capecitabine monotherapy based on a pooled analysis of safety data from three major studies including over 1900 patients (studies M66001, SO14695, and SO14796). ADRs are added to the appropriate frequency grouping according to the overall incidence from the pooled analysis.

Table 11 Summary of related ADRs reported in patients treated with capecitabine monotherapy

Body System	**Very Common** ***All grades***	**Common** ***All grades***	**Uncommon** ***Severe and/or Life-threatening (grade 3-4) or considered medically relevant***	**Rare/Very Rare (Post-Marketing Experience)**
Infections and infestations	-	Herpes viral infection, Nasopharyngitis, Lower respiratory tract infection	Sepsis, Urinary tract infection, Cellulitis, Tonsillitis, Pharyngitis, Oral candidiasis, Influenza, Gastroenteritis, Fungal infection, Infection, Tooth abscess	
Neoplasm benign, malignant and unspecified	-	-	Lipoma	
Blood and lymphatic system disorders	-	Neutropenia, Anaemia	Febrile neutropenia, Pancytopenia, Granulocytopenia, Thrombocytopenia, Leukopenia, Haemolytic anaemia, International Normalised Ratio (INR) increased/Prothrombin time prolonged	
Immune system disorders	-	-	Hypersensitivity	Angioedema (rare)
Metabolism and nutrition disorders	Anorexia	Dehydration, Weight decreased	Diabetes, Hypokalaemia, Appetite disorder, Malnutrition, Hypertriglyceridaemia,	
Psychiatric disorders	-	Insomnia, Depression	Confusional state, Panic attack, Depressed mood, Libido decreased	
Nervous system disorders	-	Headache, Lethargy Dizziness, Parasthesia Dysgeusia	Aphasia, Memory impairment, Ataxia, Syncope, Balance disorder, Sensory disorder, Neuropathy peripheral	Toxic leukoencephalopathy (very rare)
Eye disorders	-	Lacrimation increased, Conjunctivitis, Eye irritation	Visual acuity reduced, Diplopia	Lacrimal duct stenosis (rare), Corneal disorders(rare), keratitis (rare), punctate keratitis (rare)
Ear and labyrinth disorders	-	-	Vertigo, Ear pain	
Cardiac disorders	-	-	Angina unstable, Angina pectoris, Myocardial ischaemia/infarction, Atrial fibrillation, Arrhythmia, Tachycardia, Sinus tachycardia, Palpitations	Ventricular fibrillation (rare), QT prolongation (rare), Torsade de pointes (rare), Bradycardia (rare), Vasospasm (rare)
Vascular disorders	-	Thrombophlebitis	Deep vein thrombosis, Hypertension, Petechiae, Hypotension, Hot flush, Peripheral coldness	
Respiratory, thoracic and mediastinal disorders	-	Dyspnoea, Epistaxis, Cough, Rhinorrhoea	Pulmonary embolism, Pneumothorax, Haemoptysis, Asthma, Dyspnoea exertional	
Gastrointestinal disorders	Diarrhoea, Vomiting, Nausea, Stomatitis, Abdominal pain	Gastrointestinal haemorrhage, Constipation, Upper abdominal pain, Dyspepsia, Flatulence, Dry mouth	Intestinal obstruction, Ascites, Enteritis, Gastritis, Dysphagia, Abdominal pain lower, Oesophagitis, Abdominal discomfort, Gastrooesophageal reflux disease, Colitis, Blood in stool	
Hepatobiliary disorders	-	Hyperbilirubinemia, Liver function test abnormalities	Jaundice	Hepatic failure (rare), Cholestatic hepatitis (rare)
Skin and subcutaneous tissue disorders	Palmar-plantar erythro-dysaesthesia syndrome**	Rash, Alopecia, Erythema, Dry skin, Pruritus, Skin hyper-pigmentation, Rash macular, Skin desquamation, Dermatitis, Pigmentation disorder, Nail disorder	Blister, Skin ulcer, Rash, Urticaria, Photosensitivity reaction, Palmar erythema, Swelling face, Purpura, Radiation recall syndrome	Cutaneous lupus erythematosus (rare), Severe skin reactions such as Stevens-Johnson Syndrome and toxic Epidermal Necrolysis (very rare)
Muskuloskeletal and connective tissue disorders	-	Pain in extremity, Back pain, Arthralgia	Joint swelling, Bone pain, Facial pain, Musculoskeletal stiffness, Muscular weakness	
Renal and urinary disorders	-	-	Hydronephrosis, Urinary incontinence, Haematuria, Nocturia, Blood creatinine increased	
Reproductive system and breast disorders	-	-	Vaginal haemorrhage	
General disorders and administration site conditions	Fatigue, Asthenia	Pyrexia, Oedema peripheral, Malaise, Chest pain	Oedema, Chills, Influenza like illness, Rigors, Body temperature increased	

** Based on the post-marketing experience, persistent or severe palmar-plantar erythrodysaesthesia syndrome can eventually lead to loss of fingerprints.

Capecitabine in combination therapy:
ADRs associated with the use of capecitabine in combination with different chemotherapy regimens in multiple indications based on safety data from over 3000 patients. ADRs are added to the appropriate frequency grouping (Very common or Common) according to the highest incidence seen in any of the major clinical trials and are only added when they were seen in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy. Uncommon ADRs reported for capecitabine in combination therapy are consistent with the ADRs reported for capecitabine monotherapy or reported for monotherapy with the combination medicinal product (in literature and/or respective summary of product characteristics).

Some of the ADRs are reactions commonly seen with the combination medicinal product (e.g. peripheral sensory neuropathy with docetaxel or oxaliplatin, hypertension seen with bevacizumab); however an exacerbation by capecitabine therapy cannot be excluded.

Table 12 Summary of related ADRs reported in patients treated with capecitabine in combination treatment in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy

Body System	**Very common** ***All grades***	**Common** ***All grades***	**Rare/Very Rare (Post-Marketing Experience)**
Infections and infestations	-	Herpes zoster, Urinary tract infection, Oral candidiasis, Upper respiratory tract infection , Rhinitis, Influenza, +Infection, Oral herpes	
Blood and lymphatic system disorders	Neutropenia, +Leucopenia, +Anaemia, +Neutropenic fever, Thrombocytopenia	Bone marrow depression, +Febrile Neutropenia	
Immune system disorders	-	Hypersensitivity	
Metabolism and nutrition disorders	Appetite decreased	Hypokalaemia, Hyponatraemia, Hypomagnesaemia, Hypocalcaemia, Hyperglycaemia	
Psychiatric disorders	-	Sleep disorder, Anxiety	
Nervous system disorders	Paraesthesia, Dysaesthesia, Peripheral neuropathy, Peripheral sensory neuropathy, Dysgeusia, Headache	Neurotoxicity, Tremor, Neuralgia, Hypersensitivity reaction, Hypoaesthesia	
Eye disorders	Lacrimation increased	Visual disorders, Dry eye, Eye pain, Visual impairment, Vision blurred	
Ear and labyrinth disorders	-	Tinnitus, Hypoacusis	
Cardiac disorders	-	Atrial fibrillation, Cardiac ischaemia/infarction	
Vascular disorders	Lower limb oedema, Hypertension, +Embolism and thrombosis	Flushing, Hypotension, Hypertensive crisis, Hot flush, Phlebitis	
Respiratory, thoracic and mediastinal system disorders	Sore throat, Dysaesthesia pharynx	Hiccups, Pharyngolaryngeal pain, Dysphonia	
Gastrointestinal disorders	Constipation, Dyspepsia	Upper gastrointestinal haemorrhage, Mouth ulceration, Gastritis, Abdominal distension, Gastroesophageal reflux disease, Oral pain, Dysphagia, Rectal haemorrhage, Abdominal pain lower, Oral dysaesthesia, Paraesthesia oral, Hypoaesthesia oral, Abdominal discomfort	
Hepatobiliary disorders	-	Hepatic function abnormal	
Skin and subcutaneous tissue disorders	Alopecia, Nail disorder	Hyperhidrosis, Rash erythematous, Urticaria, Night sweats	
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia, Pain in extremity	Pain in jaw , Muscle spasms, Trismus, Muscular weakness	
Renal and urinary disorder	-	Haematuria, Proteinuria, Creatinine renal clearance decreased, Dysuria	Acute renal failure secondary to dehydration (rare)
General disorders and administration site conditions	Pyrexia, Weakness, +Lethargy, Temperature intolerance	Mucosal inflammation, Pain in limb, Pain, Chills, Chest pain, Influenza-like illness, +Fever, Infusion related reaction, Injection site reaction, Infusion site pain, Injection site pain	
Injury, poisoning and procedural complications	-	Contusion	

+ For each term, the frequency count was based on ADRs of all grades. For terms marked with a "+", the frequency count was based on grade 3-4 ADRs. ADRs are added according to the highest incidence seen in any of the major combination trials.

Description of selected adverse reactions
Hand-foot syndrome
For the capecitabine dose of 1250 mg/m^2 twice daily on days 1 to 14 every 3 weeks, a frequency of 53% to 60% of all-grades HFS was observed in capecitabine monotherapy trials (comprising studies in adjuvant therapy in colon cancer, treatment of metastatic colorectal cancer, and treatment of breast cancer) and a frequency of 63% was observed in the capecitabine/docetaxel arm for the treatment of metastatic breast cancer. For the capecitabine dose of 1000 mg/m^2 twice daily on days 1 to 14 every 3 weeks, a frequency of 22% to 30% of all-grade HFS was observed in capecitabine combination therapy.

A meta-analysis of 14 clinical trials with data from over 4700 patients treated with capecitabine monotherapy or capecitabine in combination with different chemotherapy regimens in multiple indications (colon, colorectal, gastric and breast cancer) showed that HFS (all grades) occurred in 2066 (43%) patients after a median time of 239 [95% CI 201, 288] days after starting treatment with capecitabine. In all studies combined, the following covariates were statistically significantly associated with an increased risk of developing HFS: increasing capecitabine starting dose (gram), decreasing cumulative capecitabine dose (0.1*kg), increasing relative dose intensity in the first six weeks, increasing duration of study treatment (weeks), increasing age (by 10 year increments), female gender, and good ECOG performance status at baseline (0 versus ≥1).

Diarrhoea
Capecitabine can induce the occurrence of diarrhoea, which has been observed in up to 50% of patients.

The results of a meta-analysis of 14 clinical trials with data from over 4700 patients treated with capecitabine showed that in all studies combined, the following covariates were statistically significantly associated with an increased risk of developing diarrhoea: increasing capecitabine starting dose (gram), increasing duration of study treatment (weeks), increasing age (by 10 year increments), and female gender. The following covariates were statistically significantly associated with a decreased risk of developing diarrhoea: increasing cumulative capecitabine dose (0.1*kg) and increasing relative dose intensity in the first six weeks.

Cardiotoxicity
In addition to the ADRs described, the following ADRs with an incidence of less than 0.1% were associated with the use of capecitabine monotherapy based on a pooled analysis from clinical safety data from 7 clinical trials including 949 patients (2 phase III and 5 phase II clinical trials in metastatic colorectal cancer and metastatic breast cancer): cardiomyopathy, cardiac failure, sudden death, and ventricular extrasystoles.

Encephalopathy:
In addition to the ADRs described, and based on the above pooled analysis from clinical safety data from 7 clinical trials, encephalopathy was also associated with the use of capecitabine monotherapy with an incidence of less than 0.1%.

Exposure to crushed or cut capecitabine tablets:
In the instance of exposure to crushed or cut capecitabine tablets, the following adverse drug reactions have been reported: eye irritation, eye swelling, skin rash, headache, paresthesia, diarrhoea, nausea, gastric irritation, and vomiting.

Special populations
Elderly patients
An analysis of safety data in patients ≥60 years of age treated with capecitabine monotherapy and an analysis of patients treated with capecitabine plus docetaxel combination therapy showed an increase in the incidence of treatment-related grade 3 and 4 adverse reactions and treatment-related serious adverse reactions compared to patients <60 years of age. Patients ≥60 years of age treated with capecitabine plus docetaxel also had more early withdrawals from treatment due to adverse reactions compared to patients <60 years of age.

The results of a meta-analysis of 14 clinical trials with data from over 4700 patients treated with capecitabine showed that in all studies combined, increasing age (by 10 year increments) was statistically significantly associated with an increased risk of developing HFS and diarrhoea and with a decreased risk of developing neutropenia.

Gender
The results of a meta-analysis of 14 clinical trials with data from over 4700 patients treated with capecitabine showed that in all studies combined, female gender was statistically significantly associated with an increased risk of developing HFS and diarrhoea and with a decreased risk of developing neutropenia.

Patients with renal impairment
An analysis of safety data in patients treated with capecitabine monotherapy (colorectal cancer) with baseline renal impairment showed an increase in the incidence of treatment-related grade 3 and 4 adverse reactions compared to patients with normal renal function (36% in patients without renal impairment n=268, vs. 41% in mild n=257 and 54% in moderate n=59, respectively) Patients with moderately impaired renal function show an increased rate of dose reduction (44%) vs. 33% and 32% in patients with no or mild renal impairment and an increase in early withdrawals from treatment (21% withdrawals during the first two cycles) vs. 5% and 8% in patients with no or mild renal impairment.

M. Overdose and Treatment

The manifestations of acute overdose include nausea, vomiting, diarrhoea, mucositis, gastrointestinal irritation and bleeding, and bone marrow depression. Medical management of overdose should include customary therapeutic and supportive medical interventions aimed at correcting the presenting clinical manifestations and preventing their possible complications.

N. Effects on ability to drive and use machines

Capecitabine has minor or moderate influence on the ability to drive and use machines. Capecitabine may cause dizziness, fatigue and nausea.

O. Instructions for use.

Capecitabine tablets should be swallowed whole with water within 30 minutes after a meal. Capecitabine tablets should not be crushed or cut. If patients cannot swallow Capecitabine tablets whole and tablets must be crushed or cut, this should be done by a professional trained in the safe handling of cytotoxic drugs.

P. Storage Conditions

Store below 30°C.

Q. Dosage Forms and packaging available

CAPTAB Capecitabine 150 mg Film Coated Tablets is packed as 10 Tablets in Alu-PVC blister, such 3 blisters are packed in a carton along with the leaflet.
CAPTAB Capecitabine 150 mg Film Coated Tablets is packed as 10 Tablets in Alu-PVC blister, such 6 blisters are packed in a carton along with the leaflet.
CAPTAB Capecitabine 500 mg Film Coated Tablets is packed as 10 Tablets in Alu-PVC blister, such 3 blisters are packed in a carton along with the leaflet.

CAPTAB Capecitabine 500 mg Film Coated Tablets is packed as 10 Tablets in Alu-PVC blister, such 12 blisters are packed in a carton along with the leaflet

Shelf Life: 2 years

R. Name and Address of manufacturer/ Product registration holder
Manufactured by:
Shilpa Medicare Limited, Unit-4,
Pharmaceutical Formulations SEZ Plot No's S-20 to S-26, Pharma SEZ, TSIIC, Green Industrial Park, Polepally (V), Jadcherla (M), Mahabubnagar (Dt), 509301 Telangana, India.
Product Registration Holder /Imported by:
Unimed Sdn. Bhd.,
53, Jalan Tembaga SD5/2B, Bandar Sri Damansara,52200 Kuala Lumpur, Malaysia.
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