Package Insert

INTACAPE 150 and 500
Capecitabine Tablets USP 150mg and 500 mg

i. Name and Strength of Active Substance(s)

INTACAPE 150: Each film coated tablet contains: Capecitabine Ph.Eur. 150 mg
INTACAPE 500: Each film coated tablet contains: Capecitabine Ph.Eur. 500 mg

ii. Product Description

INTACAPE 150: Light peach coloured, oblong shaped, biconvex, film coated tablets, debossed with '150' on one side and plain on other side.
INTACAPE 500: Peach coloured, oblong shaped, biconvex, film coated tablets, debossed with '500' on one side and plain on other side.

List of excipients
Anhydrous lactose
Microcrystalline cellulose
Croscarmellose sodium
Hypromellose E5
Magnesium stearate
Hypromellose 6 cps
Purified talc
Titanium dioxide
Ferric oxide red
Ferric oxide yellow

iii. Pharmacodynamics/Pharmacokinetics

Pharmacodynamic Properties
Mechanism of Action
Capecitabine is a fluoropyrimidine carbamate derivative that was designed as an orally administered, tumor-activated and tumor-selective cytotoxic agent.
Capecitabine is non-cytotoxic in vitro. However, in vivo, it is sequentially converted to the cytotoxic moiety 5-fluorouracil (5-FU), which is further metabolised.
Formation of 5-FU is catalysed preferentially at the tumor site by the tumor-associated angiogenic factor thymidine phosphorylase (dThdPase), thereby minimising the exposure of healthy tissues to systemic 5-FU.
The sequential enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations of 5-FU within tumor tissues. Following oral administration of capecitabine to patients with colorectal cancer (N=8), the ratio of 5-FU concentration in colorectal tumors vs adjacent tissues was 3.2 (range 0.9 to 8.0). The ratio of 5-FU concentration in tumor vs plasma was 21.4 (range 3.9 to 59.9) whereas the ratio in healthy tissues to plasma was 8.9

(range 3.0 to 25.8). Thymidine phosphorylase activity was 4 times greater in primary colorectal tumor than in adjacent normal tissue.
Several human tumors, such as breast, gastric, colorectal, cervical and ovarian cancers, have a higher level of thymidine phosphorylase (capable of converting 5'-DFUR [5'-deoxy-5-fluorouridine] to 5-FU) than corresponding normal tissues.
Normal cells and tumor cells metabolise 5-FU to 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor N5-10-methylenetetrahydrofolate bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from uracil. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

Clinical / Efficacy Studies
Colon and Colorectal Cancer
Monotherapy in adjuvant colon cancer
Data from one multicenter, randomized, controlled phase 3 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 randomized to treatment with Capecitabine (1250 mg/m^2 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 regimen: 20 mg/m^2 leucovorin i.v. followed by 425 mg/m^2 i.v. bolus 5-FU, on days 1 to 5, every 28 days for 24 weeks). Capecitabine was at least equivalent to i.v. 5-FU/LV in disease-free survival (p=0.0001, non-inferiority margin 1.2). In the all-randomized population, tests for difference of Capecitabine vs 5-FU/LV in disease-free survival and overall survival showed hazard ratios of 0.88 (95% CI 0.77 – 1.01; p = 0. 068) and 0.86 (0.74 – 1.01; p= 0.060), respectively. The median follow up at the time of the analysis was 6.9 years.

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/m^2 twice daily for 2 weeks followed by a 1-week rest period) in combination with oxaliplatin (130 mg/m^2 intravenous infusion over 2-hours on day 1 every 3 weeks); 942 patients were randomized 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 relapse free survival (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 provided 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.
At 7 years median follow up, XELOX maintained a statistically significant superior disease-free survival HR=0.80 (95% CI 0.69, 0.93; p=0.0038), and relapse-free survival HR=0.78

(95% CI 0.67, 0.91; p=0.0015). The OS rate at 7 years was 73% in the XELOX arm and 67% in the 5-FU/LV arm. The additional two years of follow up after the primary analysis show an increase in the difference between survival rates from 3% to 6%.

Monotherapy in metastatic colorectal cancer
Data from two identically designed, multicenter, randomised, controlled, phase 3 clinical trials support the use of Capecitabine for first-line treatment of metastatic colorectal cancer (SO14695; SO14796). In these trials, 603 patients were randomised to treatment with Capecitabine (1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period and given as 3-week cycles) and 604 patients were randomised to treatment with 5-FU and leucovorin (Mayo regimen: 20 mg/m^2 leucovorin i.v. followed by 425 mg/m^2 i.v. 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).

Combination therapy – first-line treatment of colorectal cancer
Data from a multicenter, randomized, controlled phase 3 clinical study (N016966) support the use of Capecitabine in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab (BV) for the first-line treatment of metastastic colorectal cancer. The study contained two parts: an initial 2-arm part in which patients were randomized to two different treatment groups, including XELOX or FOLFOX-4, and a subsequent 2x2 factorial part with four different treatment groups, including XELOX + placebo (P), FOLFOX-4+P, XELOX+BV, and FOLFOX-4+BV. The treatment regimens are summarized in the table below.

Table 1 Treatment regimens in Study NO16966

	Treatment	**Starting Dose**	**Schedule**
FOLFOX-4 or FOLFOX-4 + Bevacizumab	Oxaliplatin	85 mg/m^2 IV 2 hr	Oxaliplatin on Day 1, every 2 weeks Leucovorin on Days 1 and 2, every 2 weeks 5-fluorouracil IV bolus/infusion, each on Days 1 and 2, every 2 weeks
	Leucovorin	200 mg/m^2 IV 2 hr	
	5-Fluorouracil	400 mg/m^2 IV bolus, followed by 600 mg/ m^2 IV 22 hr	
	Placebo or Bevacizumab	5 mg/kg IV 30-90 mins	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX+ Bevacizumab	Oxaliplatin	130 mg/m^2 IV 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/m^2 oral twice daily	
	Placebo or Bevacizumab	7.5 mg/kg IV 30-90 mins	Day 1, prior to XELOX, every 3 weeks
5-Fluorouracil: IV 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 below). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival. 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 the table below.

Table 2 Key non-inferiority results for the primary analysis and 1-year follow-up data (EPP and ITT populations, 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

Combination therapy – Second-line treatment of colorectal cancer

Data from a multicenter, randomized, 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 randomized 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 3). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival. 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 3.

Table 3 Key non-inferiority efficacy results for the primary analysis and 6-month follow-up data of Study NO16967 (PPP and ITT populations)

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	388	401	1.07 (0.88; 1.31)

ITT	363	382	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

A pooled analysis of the efficacy data from first-line (study NO16966; initial 2-arm part) and second-line treatment (study NO16967) further support the non-inferiority results of XELOX versus FOLFOX-4 as obtained in the individual studies: progression-free survival in the per-protocol population (hazard ratio 1.00 [95% CI: 0.88; 1.14]) with a median progression-free survival of 193 days (XELOX; 508 patients) versus 204 days (FOLFOX-4; 500 patients). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival (hazard ratio 1.01 [95% CI: 0.87; 1.17]) with a median overall survival of 468 days (XELOX) versus 478 days (FOLFOX-4).

Combination therapy- Gastric cancer

Data from a multicenter, randomized, controlled phase 3 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 randomized to treatment with Capecitabine (1000 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period) and cisplatin (80 mg/m^2 as a 2-hour infusion every 3 weeks). A total of 156 patients were randomized to treatment with 5-FU (800 mg/m^2 per day, continuous infusion on days 1 to 5 every 3 weeks) and cisplatin (80 mg/m^2 as a 2-hour infusion on day 1, every 3 weeks). The primary objective of the study was met, Capecitabine in combination with cisplatin was at least equivalent to 5-FU in combination with cisplatin in terms of progression-free survival in the per-protocol analysis. The result for duration of survival (overall survival) was similar to the result for progression-free survival (see table below).

Table 4 Summary of results for key efficacy parameters (PPP, Study ML17032)

Parameter	**Median (Months) (95% CI)**		**Hazard Ratio (95% CI)***
	Capecitabine/Cisplatin (N=139)	**5-FU/Cisplatin (N=137)**	
Progression-free survival	5.6 (4.9, 7.3)	5.0 (4.2, 6.3)	0.81 (0.63, 1.04)
Duration of survival	10.5 (9.3, 11.2)	9.3 (7.4, 10.6)	0.85 (0.64, 1.13)

*Unadjusted treatment effect in Cox proportional model.

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/ m^2 as a bolus on day 1 every 3 weeks), cisplatin (60 mg/m^2 as a two hour infusion on day 1 every 3 weeks) and 5-FU (200 mg/m^2 daily given by continuous infusion via a central line).
- ECX: epirubicin (50 mg/m^2 as a bolus on day 1 every 3 weeks), cisplatin (60 mg/m^2 as a two hour infusion on day 1 every 3 weeks), and Capecitabine (625 mg/m^2 twice daily continuously).

- EOF: epirubicin (50 mg/m^2 as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m^2 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/m^2 as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m^2 given as a 2 hour infusion on day 1 every three weeks), and Capecitabine (625 mg/m^2 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. The hazard ratio for overall survival was 0.94 (95% CI: 0.89; 1.00, p=0.0489) with Capecitabine-containing regimens indicating that they are non-inferior to 5-FU-containing regimens.

Combination therapy- breast cancer

Data from one multicenter, randomised, controlled phase 3 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/m^2 twice daily for 2 weeks followed by a 1-week rest period) and docetaxel (75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks). A total of 256 patients were randomised to treatment with docetaxel alone (100 mg/m^2 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 disease progression or death 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- Breast carcinoma

Data from two multicenter phase 2 clinical trials support the use of Capecitabine monotherapy for 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. In these trials, a total of 236 patients were treated with Capecitabine (1250 mg/m^2 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.

Pharmacokinetic Properties

Absorption
After oral administration, capecitabine is rapidly and extensively absorbed, followed by extensive conversion to the metabolites 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-DFUR. Administration with food decreases the rate of capecitabine absorption but has only a minor effect on the areas under the curve (AUC) of 5'-DFUR and the subsequent metabolite 5-FU. At the dose of 1250 mg/m^2 on day 14 with administration after food intake, the peak plasma concentrations (Cmax in μg/ml) for capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 4.47, 3.05, 12.1, 0.95 and 5.46 respectively. The times to peak plasma concentrations (Tmax in hours) were 1.50, 2.00, 2.00, 2.00 and 3.34. The AUC0-∞ values in μg·h/ml were 7.75, 7.24, 24.6, 2.03 and 36.3.

Distribution
Protein binding
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.

Metabolism
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 tumor tissues.
Formation of 5-FU occurs preferentially at the tumor site by the tumor-associated angiogenic factor dThdPase, thereby minimising the exposure of healthy body tissues to systemic 5-FU.
The plasma AUC of 5-FU is 6 to 22 times lower than that following an i.v. bolus of 5-FU (dose of 600 mg/m^2). The metabolites of capecitabine become cytotoxic only after conversion to 5-FU and anabolites of 5-FU (see section 3.1.1, Mechanism of Action).
5-FU is further catabolized to the inactive metabolites dihydro-5-fluorouracil (FUH2), 5-fluoro-ureidopropionic acid (FUPA) and α-fluoro-β-alanine (FBAL) via dihydropyrimidine dehydrogenase (DPD), which is rate limiting.

Elimination
The elimination half-lifes ($t_{1/2}$ 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. The pharmacokinetics of capecitabine have been evaluated over a dose range of 502 - 3514 mg/m^2/day. The parameters of capecitabine, 5'-DFCR and 5'-DFUR measured on days 1 and 14 were similar. The AUC of 5-FU was 30% – 35% higher on day 14 but did not increase subsequently (day 22). At therapeutic doses, the pharmacokinetics of capecitabine and its metabolites were dose proportional, except for 5-FU.
After oral administration, capecitabine metabolites are primarily recovered in the urine. Most (95.5%) of administered capecitabine dose is recovered in urine. Fecal 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 as unchanged drug.

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 (Cmax and AUC) and no effect by docetaxel or paclitaxel on the pharmacokinetics of 5'-DFUR (the most important metabolite of capecitabine).

Pharmacokinetics in Special Populations

A population pharmacokinetic analysis was carried out after Capecitabine treatment of 505 patients with colorectal cancer dosed at 1250 mg/m^2 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
No clinically significant effect on the bioactivation and pharmacokinetics of capecitabine was observed in cancer patients with mildly to moderately impaired liver function due to liver metastases (see section v, Special Dosage Instructions).
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; 5'-DFUR is the direct precursor of 5-FU (see section v, Special Dosage Instructions).

Elderly
Based on a population pharmacokinetic analysis that included patients with a wide range of ages (27 to 86 years) and included 234 (46%) patients greater than or equal to 65 years, 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 (see section v, Special Dosage Instructions and section iii, Pharmacokinetics in Special Populations, subsection Patients with renal impairment).

Race
In a population pharmacokinetic analysis of 455 white patients (90.1%), 22 black patients (4.4%) and 28 patients of other race or ethnicity (5.5%), the pharmacokinetics of Capecitabine in black patients were not different from those in white patients.

iv. Indication

Breast Cancer:

INTACAPE 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. INTACAPE 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.

Colorectal cancer:

INTACAPE is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer.

INTACAPE is indicated for the treatment of metastatic colorectal carcinoma.

Gastric Cancer

INTACAPE is indicated for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen.

v. Recommended Dosage

Standard Dosage

Capecitabine should only be prescribed by a qualified physician experienced in the utilisation of anti-neoplastic agents. Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Treatment should be discontinued if progressive disease or intolerable toxicity is observed. Standard and reduced dose calculations according to body surface area for starting doses of Capecitabine of 1250 mg/m^2 and 1000 mg/m^2 are provided in tables 5 and 6, respectively.

Monotherapy

Colon, colorectal and breast cancer:

The recommended monotherapy starting dose of Capecitabine in the adjuvant treatment of colon cancer, in the treatment of metastatic colorectal cancer or of locally advanced or metastatic breast cancer is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 7-day rest period.

Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

Combination therapy

Breast cancer:

In combination with docetaxel, the recommended starting dose of Capecitabine is 1250 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period, combined with docetaxel at 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks.

Pre-medication with an oral corticosteroid such as dexamethasone according to the docetaxel summary of product characteristics should be started prior to docetaxel administration for patients receiving the Capecitabine plus docetaxel combination.

Colon, colorectal and gastric cancer:

In combination treatment, the recommended starting dose of Capecitabine should be reduced to 1000 mg/m^2 administered twice daily for 2 weeks followed by a 7-day rest period. (see section iii Clinical/ Efficacy studies for further information).

The inclusion of bevacizumab in a combination regimen has no effect on the starting dose of Capecitabine.

Premedication to maintain adequate hydration and anti-emesis according to the cisplatin and oxaliplatin product information should be started prior to cisplatin administration for patients receiving the Capecitabine plus cisplatin or oxaliplatin combination.

Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

Capecitabine dose is calculated according to body surface area. The following tables show examples of the standard and reduced dose calculations (see section “Dosage adjustments during treatment”) for a starting dose of Capecitabine of either 1250 mg/m^2 or 1000 mg/m^2.

Table 5 Standard and reduced dose calculations according to body surface area for a starting dose of capecitabine of 1250 mg/m^2.

	Dose level 1250 mg/m^2 (twice daily)					
	Full dose 1250 mg/m^2	Number of 150 mg tablets, 300 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)			Reduced dose (75%) 950 mg/m^2	Reduced dose (50%) 625 mg/m^2
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	300 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	-	1	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	-	1	4	1800	1150
1.93 - 2.06	2500	-	-	5	1950	1300
2.07 - 2.18	2650	1	-	5	2000	1300
≥ 2.19	2800	-	1	5	2150	1450

Table 6 Standard and reduced dose calculations according to body surface area for a starting dose of capecitabine of 1000 mg/m^2

	Dose level 1000 mg/m^2 (twice daily)					
	Full dose 1000 mg/m^2	Number of 150 mg tablets, 300 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)			Reduced dose (75%) 750 mg/m^2	Reduced dose (50%) 500 mg/m^2
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	300 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤ 1.26	1150	1	-	2	800	600
1.27 - 1.38	1300	-	1	2	1000	600
1.39 - 1.52	1450	1	1	2	1100	750
1.53 - 1.66	1600	-	2	2	1200	800
1.67 - 1.78	1750	1	2	2	1300	800
1.79 - 1.92	1800	-	1	3	1400	900
1.93 - 2.06	2000	-	-	4	1500	1000
2.07 - 2.18	2150	1	-	4	1600	1050
≥ 2.19	2300	-	1	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.
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.

Hematology: Patients with baseline neutrophil counts of <1.5 x 10^9/l and/or thrombocyte counts of <100 x 10^9/l should not be treated with Capecitabine. If unscheduled laboratory assessments during a treatment cycle show grade 3 or 4 hematologic toxicity, treatment with Capecitabine should be interrupted.
If the neutrophil count drops below 1.0 x 10^9/L or if the platelet count drops below 75 x 10^9/L, capecitabine. At recovery, restart capecitabine at full dose.

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

Table 7 Capecitabine dose reduction schedule

Toxicity NCIC grades*	**Dose changes within a treatment cycle**	**Dose adjustment for next cycle/dose (% 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, (see section viii, Warnings and Precautions).

General combination therapy
Dose modifications for toxicity when Capecitabine is used in combination with other therapies should be made according to Table 7 above for Capecitabine and according to the appropriate Prescribing Information for the other agent(s).
At the beginning of a treatment cycle, if a treatment delay is indicated for either Capecitabine or the other agent(s), then administration of all agents should be delayed until the requirements for restarting all drugs are met.
During a treatment cycle for those toxicities considered by the treating physician not to be related to Capecitabine, Capecitabine should be continued and the dose of the other agent adjusted according to the appropriate Prescribing Information.
If the other agent(s) have to be discontinued permanently, Capecitabine treatment can be resumed when the requirements for restarting Capecitabine are met.
This advice is applicable to all indications and to all special populations.

Special Dosage Instructions
Patients with hepatic impairment due to liver metastases

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 (see section iii, Pharmacokinetics in Special Populations and section viii, Warnings and Precautions). Patients with severe hepatic impairment have not been studied.

Patients with renal impairment
In patients with moderate renal impairment (creatinine clearance 30 - 50 ml/min [Cockroft 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 adverse event with subsequent dose adjustment as outlined in Table 7 above (see also section iii Pharmacokinetics in Special Populations). 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. For dosage calculations, see Tables 5 and 6.

Children
The safety and efficacy of Capecitabine in children have not been established.

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

When Capecitabine was used in combination with other agents, elderly patients (≥ 65 years) experienced more grade 3 and grade 4 adverse drug reactions (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 adverse events and treatment-related serious adverse events 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. For dosage calculations, see Table 6.
- In combination with irinotecan: for patients 65 years of age or more, a starting dose reduction of Capecitabine to 800 mg/m^2 twice daily is recommended.

vi. Route of Administration

Oral

vii. Contraindications

Intacape is contraindicated in patients with known hypersensitivity to capecitabine or to any of its components.

Intacape is contraindicated in patients who have a history of severe and unexpected reactions to fluoropyrimidine therapy or with known hypersensitivity to fluorouracil.

As with other fluoropyrimidines, Intacape is contraindicated in patients with known DPD deficiency.

Intacape should not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine (see section ix Interactions with other Medicinal Products and other Forms of Interaction).

Intacape is contraindicated in patients with severe leukopenia, neutropenia or thrombocytopenia.

Intacape is contraindicated in patients with severe hepatic impairment.

Intacape is contraindicated in patients with severe renal impairment (creatinine clearance below 30 ml/min).

If contraindications exist to any of the agents in a combination regimen, that agent should not be used.

viii. Warnings and Precautions

Warnings

Diarrhea: Capecitabine can induce diarrhea, which can sometimes be severe. Patients with severe diarrhea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. Standard anti-diarrhea treatments (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. Dose reduction should be applied as necessary (see section v, Recommended Dosage).

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 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 should be applied for the precipitating adverse event as necessary (see section v, Recommended Dosage).

Dehydration may cause acute renal failure, especially in patients with pre-existing compromised renal function or when capecitabine is given concomitantly with known nephrotoxic agents. Acute renal failure secondary to dehydration is potentially fatal.

Dihydropyrimidine dehydrogenase (DPD) deficiency: Based on postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by Capecitabine (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by Capecitabine.

Withhold or permanently discontinue Capecitabine based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity.

No Capecitabine dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test.

Precautions

Cardiotoxicity: Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes. These adverse reactions may be more common in patients with a prior history of coronary artery disease. Cardiac arrhythmias, 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 (see section xi).

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 (see section xi).

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.

Capecitabine can induce severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN). Capecitabine should be permanently discontinued in patients who experience a severe skin reaction possibly attributable to Capecitabine treatment.

Capecitabine can induce hand–foot syndrome (palmar–plantar erythrodysesthesia or chemotherapy-induced acral erythema), which is a cutaneous toxicity. For patients receiving Capecitabine monotherapy in the metastatic setting, the median time to onset was 79 days (range 11 to 360 days), with a severity range of Grades 1 to 3. Grade 1 hand-foot syndrome is defined by numbness, dysesthesia/paresthesia, tingling or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 is defined as moist desquamation, ulceration, blistering or 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. 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 (see section v, Recommended Dosage). 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.

Capecitabine can induce hyperbilirubinemia. 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.

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.

In a drug 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 (see section ix Interactions with other Medicinal Products and other Forms of Interaction).

General

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

ix. Interactions with Other Medicines and Other Forms of Interaction

Interaction studies have only been performed in adults.

Coumarin 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 events 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 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 anti-coagulant dose adjusted accordingly.

Cytochrome P450 2C9 substrates

No formal drug-drug interaction studies with capecitabine and other drugs known to be metabolized by the cytochrome P450 2C9 isoenzyme have been conducted. Care should be exercised when Capecitabine is co-administered with these drugs.

Phenytoin

Increased phenytoin plasma concentrations have been reported during concomitant use of Capecitabine with phenytoin. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme system by capecitabine (see Coumarin anticoagulants). Patients taking phenytoin concomitantly with Capecitabine should be regularly monitored for increased phenytoin plasma concentrations.

Drug-food interaction

In all clinical trials, patients were instructed to take 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 (see section iii Pharmacokinetics Properties-Absorption).

Antacid

The effect of an aluminium hydroxide and magnesium hydroxide-containing antacid on the pharmacokinetics of Capecitabine was investigated in cancer patients. 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).

Leucovorin (folinic 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: 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).

Sorivudine and analogues

A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase by sorivudine, has been described in the literature. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, Capecitabine should not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine (see section vii, Contraindications). There must be at least a 4-week waiting period between the end of treatment with sorivudine or its chemically related analogues, such as brivudine and start of Capecitabine therapy.

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/m2 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 occur when capecitabine and oxaliplatin were administered in combination, with or without bevacizumab.

Bevacizumab

There was no clinically significant effect of bevacizumab on the pharmacokinetic parameters of capecitabine or its metabolites.

x. Use during Pregnancy/Lactation

Pregnancy

Pregnancy category D

There are no studies in pregnant women using Capecitabine; however, based on the pharmacological and toxicological properties of Capecitabine, it can be assumed that Capecitabine may cause fetal 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 should be considered a potential human teratogen. Capecitabine should not be used during pregnancy. If Capecitabine is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient must be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Capecitabine.

Nursing Mothers

It is not known whether the drug is excreted in human milk. In a study of single oral administration of Capecitabine to lactating mice, a significant amount of capecitabine metabolites was detected in the milk. Nursing should be discontinued during Capecitabine treatment.

Geriatric Use

Among patients with colorectal cancer aged 60 – 79 years receiving Capecitabine monotherapy in the metastatic setting, the incidence of gastrointestinal toxicity was similar to that in the overall population. In patients aged 80 years or older, a larger percentage experienced reversible Grade 3 or 4 gastrointestinal adverse events, such as diarrhea, nausea and vomiting (see section v, Special Dosage Instructions). When Capecitabine was used in combination with other agents elderly patients (≥ 65 years) experienced more grade 3 and grade 4 ADRs and ADRs that led to discontinuation than younger patients. An analysis of safety data in patients equal to or greater than 60 years of age treated with Capecitabine plus docetaxel combination therapy showed an increase in the incidence of treatment-related Grade 3 and 4 adverse events, treatment-related serious adverse events and early withdrawals from treatment due to adverse events compared to patients less than 60 years of age.

Renal Impairment

Physicians should exercise caution when Capecitabine is administered to patients with impaired renal function. As seen with 5-FU the incidence of treatment-related Grade 3 or 4 adverse events was higher in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) (see section v, Special Dosage Instructions).

Hepatic Impairment

Patients with hepatic impairment should be carefully monitored when Capecitabine is administered. The effect of hepatic impairment not due to liver metastases or severe hepatic impairment on the disposition of Capecitabine is not known (see section iii, Pharmacokinetics in Special Populations and section v, Special Dosage Instructions).

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.

xi. Adverse Effects/Undesirable Effects

a. 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. See section iii for details of major studies, including study designs and major efficacy results.

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.

b. Tabulated summary of adverse reactions

ADRs considered by the investigator to be possibly, probably, or remotely related to the administration of Capecitabine are listed in Table 8 for Capecitabine given as a single agent and in Table 9 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, < 1/10) and uncommon (≥ 1/1,000, < 1/100). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Capecitabine Monotherapy:

Table 8 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 8 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***
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
Metabolism and nutrition disorders	Anorexia	Decreased appetite, 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
Eye disorders	-	Lacrimation increased, Conjunctivitis, Eye irritation	Visual acuity reduced, Diplopia
Ear and labyrinth disorders	-	-	Vertigo, Ear pain
Cardiac disorders	-	-	Angina unstable, Angina pectoris, Myocardial ischaemia, Atrial fibrillation, Arrhythmia, Tachycardia, Sinus tachycardia, Palpitations
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
Skin and subcutaneous tissue disorders	Dermatitis, Palmar-plantar erythrodysaesthesia 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
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
Injury, poisoning and procedural complications	-	-	Blister, Overdose

Capecitabine in combination therapy:

Table 9 lists ADRs associated with the use of Capecitabine in combination with different chemotherapy regimens in multiple indications based on safety data from over 1400 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 (see Table 8). Uncommon ADRs reported for Capecitabine in combination therapy are consistent with the ADRs reported for Capecitabine monotherapy or reported for monotherapy with the combination agent (in literature and/or respective summary of product characteristics).

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

Table 9 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***
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	Parasthesia, 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, Parasthesia 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 disorders	-	Haematuria, Proteinuria, Creatinine renal clearance decreased, Dysuria
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.

xii. Post Marketing

The following additional serious adverse reactions have been identified during post-marketing exposure:

System Organ Class	ADR(s)	Frequency
Renal and urinary disorders	Acute renal failure secondary to dehydration *(see section viii Warnings and Precautions)*	Rare
Nervous system disorders	Toxic leukoencephalopathy	Unknown
Hepatobiliary disorders	Hepatic failure, Cholestatic hepatitis	Very rare
Skin and subcutaneous tissue disorders	Cutaneous lupus erythematosus, Severe skin reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (TEN) *(see section viii Warnings and Precautions)*	Very rare
Eye disorders	Lacrimal duct stenosis NOS, Corneal disorders including keratitis	Very rare

xiii. Overdose and Treatment

The manifestations of acute overdose include nausea, vomiting, diarrhea, 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.

xiv. Storage Condition

Do not store above 30 °C.

xv. Dosage Forms or Presentation

Intacape 150 mg film coated tablets: 60 Tablets

Intacape 500 mg flim coated tablets: 120 Tablets

xvi. Name and Address of Product Registrant:

ACCORD HEALTHCARE PRIVATE LIMITED
6 Shenton Way #38-01
OUE Downtown Singapore 068809

xvii. Date of Revision of Package Insert

03.10.2017