SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Capecitabine Dr. Reddy's 500 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg capecitabine.
Excipient with known effect: 50 mg anhydrous lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Peach colour film-coated tablet of biconvex, oblong shape (16.00 mm x 8.50 mm) with '500' debossed on one side and 'RDY' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Capecitabine is indicated for the treatment of:

- for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer (see section 5.1).
- metastatic colorectal cancer (see section 5.1).
- first-line treatment of advanced gastric cancer in combination with a platinum-based regimen (see section 5.1).
- in combination with docetaxel (see section 5.1) 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.
- as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline- containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

4.2 Posology and method of administration

Capecitabine should only be prescribed by a qualified physician experienced in the utilisation of anti-neoplastic medicinal products. Careful monitoring during the first cycle of treatment is recommended for all patients.
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 1 and 2, respectively.

Posology
Recommended posology (see section 5.1):

Monotherapy
Colon, colorectal and breast cancer
Given as monotherapy, the recommended starting dose for 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 14 days 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
Colon, colorectal and gastric cancer
In combination treatment, the recommended starting dose of Capecitabine should be reduced to 800 - 1000 mg/m^2 when administered twice daily for 14 days followed by a 7-day rest period, or to 625 mg/m^2 twice daily when administered continuously (see section 5.1). For combination with irinotecan, the recommended starting dose is 800 mg/m^2 when administered twice daily for 14 days followed by a 7-day rest period combined with irinotecan 200 mg/m^2 on day 1. 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 summary of product characteristics should be started prior to cisplatin administration for patients receiving the Capecitabine plus cisplatin combination.
Premedication with antiemetics according to the oxaliplatin summary of product characteristics is recommended for patients receiving the Capecitabine plus oxaliplatin combination. Adjuvant treatment in patients with stage III colon cancer is recommended for a duration of 6 months.

Breast cancer
In combination with docetaxel, the recommended starting dose of Capecitabine in the treatment of metastatic breast cancer is 1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period, combined with docetaxel at 75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks. Premedication 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.

Capecitabine Dose Calculations
Table 1: 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 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 SurfaceArea (m^2)	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 2: 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 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	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

Posology adjustments during treatment

General

Toxicity due to Capecitabine administration may be managed by symptomatic treatment and/or modification of the 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, e.g. alopecia, altered taste, nail changes, 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. The following are the recommended dose modifications for toxicity:

Table 3: Capecitabine Dose Reduction Schedule (3-weekly Cycle or Continuous Treatment)

Toxicity 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 4.0. For hand-foot syndrome and hyperbilirubinemia, see section 4.4.

Haematology: Patients with baseline neutrophil counts of $<1.5 \times 10^9$/L and/or thrombocyte counts of $<100 \times 10^9$/L should not be treated with Capecitabine. If unscheduled laboratory assessments during a treatment cycle show that the neutrophil count drops below 1.0×10^9/L or that the platelet count drops below 75×10^9/L, treatment with Capecitabine should be interrupted.

Dose modifications for toxicity when Capecitabine is used as a 3 weekly cycle in combination with other medicinal products:
Dose modifications for toxicity when Capecitabine is used as a 3 weekly cycle in combination with other medicinal products should be made according to table 3 above for Capecitabine and according to the appropriate summary of product characteristics for the other medicinal product(s).

At the beginning of a treatment cycle, if a treatment delay is indicated for either Capecitabine or the other medicinal product(s), then administration of all therapy should be delayed until the requirements for restarting all medicinal products 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 medicinal product should be adjusted according to the appropriate Prescribing Information.

If the other medicinal product(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.

Dose modifications for toxicity when Capecitabine is used continuously in combination with other medicinal products: Dose modifications for toxicity when Capecitabine is used continuously in combination with other medicinal products should be made according to table 3 above for Capecitabine and according to the appropriate summary of product characteristics for the other medicinal product(s).

Posology adjustments for special populations:

Hepatic impairment:
Insufficient safety and efficacy data are available in patients with hepatic impairment to provide a dose adjustment recommendation. No information is available on hepatic impairment due to cirrhosis or hepatitis.

Renal impairment:
Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockcroft and Gault] at baseline). The incidence of grade 3 or 4 adverse reactions in patients with moderate renal impairment (creatinine clearance 30-50 mL/min at baseline) is increased compared to the overall population. In patients with moderate renal impairment at baseline, a dose reduction to 75% for a starting dose of 1250 mg/m^2 is recommended. In patients with moderate renal impairment at baseline, no dose reduction is required for a starting dose of 1000 mg/m^2. In patients with mild renal impairment (creatinine clearance 51-80 mL/min at baseline) no adjustment of the starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3 or 4 adverse event during treatment and subsequent dose adjustment as outlined in Table 3 above. If the calculated creatinine clearance decreases during treatment to a value below 30 mL/min, Capecitabine should be discontinued. These dose adjustment recommendations for renal impairment apply both to monotherapy and combination use (see also section “Elderly” below).

Elderly:
During Capecitabine monotherapy, no adjustment of the starting dose is needed. However, grade 3 or 4 treatment-related adverse reactions were more frequent in patients ≥60 years of age compared to younger patients.
When Capecitabine was used in combination with other medicinal products, elderly patients (≥65 years) experienced more grade 3 and grade 4 adverse drug reactions, including those leading to discontinuation, compared to younger patients. Careful monitoring of patients ≥60 years of age is advisable.

- *In combination with docetaxel*: an increased incidence of grade 3 or 4 treatment-related adverse reactions and treatment-related serious adverse reactions were observed in patients 60 years of age or more (see section 5.1). For patients 60

years of age or more , a starting dose reduction of Capecitabine to 75% (950 mg/m^2 twice daily) is recommended. If no toxicity is observed in patients ≥60 years of age treated with a reduced Capecitabine starting dose in combination with docetaxel, the dose of Capecitabine may be cautiously escalated to 1250 mg/m^2 twice daily.

Paediatric population:
There is no relevant use of capecitabine in the paediatric population in the indications colon, colorectal, gastric and breast cancer.

Method of administration
Capecitabine tablets should be swallowed whole with water within 30 minutes after a meal. Capecitabine tablets should not be crushed or cut.

4.3 Contraindications

- History of severe and unexpected reactions to fluoropyrimidine therapy
- Hypersensitivity to capecitabine or to any of the excipients listed in section 6.1 or fluorouracil
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4),
- 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 (see section 4.4 and 4.5 for drug-drug interaction
- If contraindications exist to any of the medicinal products in the combination regimen, that medicinal product should not be used

4.4 Special warnings and precautions for use

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 (see section 4.2).

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 (see section 4.2).

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 (see section 4.8).

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 4.8).

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 4.8).

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 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 4.5).

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 (see section 4.3 and 4.5). 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 (see sections 4.2 and 4.3).

Dihydropyrimidine dehydrogenase (DPD) deficiency.

DPD activity is rate limiting in the catabolism of 5-fluorouracil (see section 5.2). 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 (see section 4.3).

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.
Impaired kidney function can lead to increased blood uracil levels with risk for misdiagnosis of DPD deficiency in patients with moderate renal impairment. Capecitabine is contraindicated in patients with severe renal impairment (see section 4.3).
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. Blood uracil levels should be interpreted with caution in patients with impaired kidney function (see ‘Testing for DPD deficiency’ above).

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.

Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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 (see section 4.8)

4.5 Interaction with other medicinal products and other forms of interaction

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 (see section 4.3 and 4.4). 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 drug-drug 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). See also interaction with coumarin-derivative anticoagulants below, and section 4.4.

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 aluminum 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 (see section 5.2).

4.6 Fertility, 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.

Breastfeeding

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 (see section 5.3)

4.7 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.

4.8 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. See section 5.1 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.

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 4 for Capecitabine given as monotherapy and in Table 5 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) and 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 4 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 4: 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/Prothromb in 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	Lacrimal duct stenosis (rare), Corneal disorders (rare), keratitis (rare), punctate keratitis (rare)
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/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 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	Cutaneous lupus erythematosus (rare), Severe skin reactions such as Stevens-Johnson Syndrome and toxic Epidermal Necrolysis (very rare) (see section 4.4)
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 (see section 4.4)

Capecitabine in combination therapy:

Table 5 lists 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 (see Table 4). 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 5: 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		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 ischemia/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 (see section 4.4):
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 (see section 4.4):
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 diarrhea: 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 diarrhea: increasing cumulative Capecitabine dose (0.1*kg) and increasing relative dose intensity in the first six weeks.

Cardiotoxicity (see section 4.4):
In addition to the ADRs described in Tables 4 and 5, 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 in Tables 4 and 5, 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, diarrhea, nausea, gastric irritation, and vomiting.

Special populations

Elderly patients (see section 4.2):
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

diarrhea and with a decreased risk of developing neutropenia.

Patients with renal impairment (see section 4.2, 4.4, and 5.2):
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) (see section 5.2). 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose
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.

5 PHARMACOLOGICAL PROPERTIES

5.1 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 (see section 5.2). 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 deoxyuridylic 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/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 Clinic regimen: 20 mg/m^2 leucovorin IV followed by 425 mg/m^2 IV 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/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 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/m^2 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/m^2 leucovorin IV followed by 425 mg/m^2 IV 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. See Table 6 for treatment regimens.

Table 6: Treatment Regimens in Study NO16966 (mCRC)

	Treatment	**Starting Dose**	**Schedule**
FOLFOX-4 or FOLFOX-4 + Bevacizumab	Oxaliplatin Leucovorin 5-Fluorouracil	85 mg/m^2 intravenous 2 hr 200 mg/m^2 intravenous 2 hr 400 mg/m^2 intravenous bolus, followed by 600 mg/ m^2 intravenous 22 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
	Placebo or Bevacizumab	5 mg/kg intravenous 30-90 mins	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX+ Bevacizumab	Oxaliplatin Capecitabine	130 mg/m^2 intravenous 2 hr 1000 mg/m^2 oral twice daily	Oxaliplatin on Day 1, every 3 weeks Capecitabine oral twice daily for 2 weeks (followed by 1 week off-treatment)

	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 7). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival (see Table 7). 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 tumor assessments impact the on-treatment PFS analysis, a full explanation for this result has not been found.

Table 7: 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	241	259	1.05 (0.94; 1.18)
ITT	244	259	1.04 (0.93; 1.16)
Parameter: Overall Survival			
EPP	577	549	0.97 (0.84; 1.14)
ITT	581	553	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	242	259	1.02 (0.92; 1.14)
ITT	244	259	1.01 (0.91; 1.12)
Parameter: Overall Survival			
EPP	600	594	1.00 (0.88; 1.13)
ITT	602	596	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/m^2 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 randomized to receive either sequential treatment (n=410) or combination treatment (n=410). Sequential treatment consisted of first-line Capecitabine (1250 mg/m^2 twice

daily for 14 days), second-line irinotecan (350 mg/ m^2 on day 1), and third-line combination of Capecitabine (1000 mg/ m^2 twice daily for 14 days) with oxaliplatin (130 mg/ m^2 on day 1). Combination treatment consisted of first-line Capecitabine (1000 mg/ m^2 twice daily for 14 days) combined with irinotecan (250 mg /m^2 on day 1) (XELIRI) and second-line Capecitabine (1000 mg/m^2 twice daily for 14 days) plus oxaliplatin (130 mg/ m^2 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/m^2 twice daily on days 1 to 14 of a three-week cycle combined with irinotecan 250 mg/m^2 on day 1. 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). Toxcity 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/m^2 twice daily for 14 days +irinotecan 250 mg/m^2 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 an interim analysis of a multicentre, randomised, controlled phase II study (AIO KRK 0604) supports the use of Capecitabine at a starting dose of 800 mg/m^2 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/m^2 twice daily for two weeks followed by a 7-day rest period), irinotecan (200 mg/m^2 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); a total of 127 patients were randomised to treatment with Capecitabine (1000 mg/m^2 twice daily for two weeks followed by a 7-day rest period), oxaliplatin (130 mg/m^2 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 8Key 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 metastastic 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 6. 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 9). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival (see Table 9). 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 9.

Table 9: Key efficacy results for the non-inferiority analysis of Study NO16967

PRIMARY ANALYSI S			
	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	154	168	1.03 (0.87; 1.24)
ITT	144	146	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	154	166	1.04 (0.87; 1.24)
ITT	143	146	0.97 (0.83; 1.14)
Parameter: Overall Survival			
PPP	393	402	1.05 (0.88; 1.27)
ITT	363	382	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/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 randomised 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). 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/ 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/m^2 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. 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/m^2 twice daily for 2 weeks followed by 1-week rest period and docetaxel 75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks). 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 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/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.

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 the reference medicinal product containing Capecitabine in all subsets of the paediatric population in adenocarcinoma of the colon and rectum, gastric adenocarcinoma and breast carcinoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of Capecitabine have been evaluated over a dose range of 502-3514 mg/m^2/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/m^2 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 (FUH2). 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 (see section 4.3 and 4.4).

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 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 (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/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: 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/m^2 Capecitabine twice daily for 14 days, Japanese patients (n=18) had about 36% lower Cmax and 24% lower AUC for Capecitabine than Caucasian patients (n=22). Japanese patients had also about 25% lower Cmax 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).

5.3 Preclinical safety data

In repeat-dose toxicity studies, daily oral administration of Capecitabine to cynomolgus monkeys and mice produced toxic effects on the gastrointestinal, lymphoid and haemopoietic systems, typical for fluoropyrimidines. These toxicities were reversible. Skin toxicity, characterised by degenerative/regressive changes, was observed with Capecitabine. Capecitabine was devoid of hepatic and CNS toxicities. Cardiovascular toxicity (e.g. PR- and QT-interval prolongation) was detectable in cynomolgus monkeys after intravenous administration (100 mg/kg) but not after repeated oral dosing (1379 mg/m^2/day).

A two-year mouse carcinogenicity study produced no evidence of carcinogenicity by Capecitabine.

During standard fertility studies, impairment of fertility was observed in female mice receiving Capecitabine; however, this effect was reversible after a drug-free period. In addition, during a 13-week study, atrophic and degenerative changes occurred in reproductive organs of male mice; however these effects were reversible after a drug-free period (see section 4.6).

In embryotoxicity and teratogenicity studies in mice, dose-related increases in foetal resorption and teratogenicity were observed. In monkeys, abortion and embryolethality were observed at high doses, but there was no evidence of teratogenicity.

Capecitabine was not mutagenic *in vitro* to bacteria (Ames test) or mammalian cells (Chinese hamster V79/HPRT gene mutation assay). However, similar to other nucleoside analogues (ie, 5-FU), Capecitabine was clastogenic in human lymphocytes (*in vitro*) and a positive trend occurred in mouse bone marrow micronucleus tests (*in vivo*).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose anhydrous
Croscarmellose sodium
Cellulose, microcrystalline
Hypromellose (6 cPs)
Magnesium stearate

Tablet coating:
Hypromellose
Talc
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Red iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

Blister (PVC/PE/PVdC-Al/PET/paper or PVC/Aclar-Al/PET/paper.

Pack sizes: 28, 120 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Procedures for safe handling of cytotoxic drugs should be followed

7 MARKETING AUTHORISATION HOLDER

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Cambridge, CB4 0PE,
United Kingdom

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