ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Capecitabine Teva 150 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of capecitabine.

Excipient with known effect:
Each film-coated tablet contains 15.6 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Capecitabine Teva 150 mg are oval biconvex light peach film-coated tablets, 11.5 mm x 5.4 mm with inscription “C” on one side and “150”on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Capecitabine Teva is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes’ stage C) colon cancer (see section 5.1).

Capecitabine Teva is indicated for the treatment of metastatic colorectal cancer (see section 5.1).

Capecitabine Teva is indicated for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen (see section 5.1).

Capecitabine Teva 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. Capecitabine Teva is also indicated 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 Teva should only be prescribed by a qualified physician experienced in the utilisation of antineoplastic 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 single 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). The inclusion of biological medicinal products 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. 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.

Capecitabine Teva 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 Surface Area (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 hyperbilirubinaemia, 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 Teva 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.
- *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.

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

Method of administration
Capecitabine Teva film-coated tablets should be swallowed with water within 30 minutes after a meal.

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,
- In patients with known dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4),
- During pregnancy and lactation,
- In patients with severe leucopenia, neutropenia, or thrombocytopenia,
- In patients with severe hepatic impairment,
- In patients with severe renal impairment (creatinine clearance below 30 ml/min),
- Treatment with sorivudine or its chemically related analogues, such as brivudine (see section 4.5),
- 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 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. 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. 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.

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 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 4.5).

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 section 4.2 and 4.3).

DPD deficiency: Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of DPD activity. A link between decreased levels of DPD and increased, potentially fatal toxic effects of 5-FU therefore cannot be excluded.
Patients with known DPD deficiency should not be treated with capecitabine (see section 4.3). In patients with unrecognised DPD deficiency treated with capecitabine, life-threatening toxicities manifesting as acute overdose may occur (see section 4.9). In the event of grade 2-4 acute toxicity, treatment must be discontinued immediately until observed toxicity resolves. Permanent discontinuation should be considered based on clinical assessment of the onset, duration and severity of the observed toxicities.

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.

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.

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

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 anti-coagulant 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: 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).

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. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine (see section 4.3). There must be at least a 4-week waiting period between end of treatment with sorivudine or its chemically related analogues such as brivudine and start of capecitabine therapy.

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.

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

Breast-feeding
It is not known whether capecitabine is excreted in human breast milk. In lactating mice, considerable amounts of capecitabine and its metabolites were found in milk. Breast-feeding should be discontinued while receiving treatment with capecitabine.

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

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 national reporting system listed in Appendix V.
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 a 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), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and 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*
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, Leucopenia, Haemolytic anaemia, International Normalised Ratio (INR) increased / Prothrombin time prolonged
Immune system disorders	-	-	Hypersensitivity

Body System	Very Common *All grades*	Common *All grades*	Uncommon *Severe and/or Life-threatening (grade 3-4) or considered medically relevant*
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, Paraesthesia, 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	-	Hyperbilirubinaemia , Liver function test abnormalities	Jaundice

Body System	Very Common *All grades*	Common *All grades*	Uncommon *Severe and/or Life-threatening (grade 3-4) or considered medically relevant*
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome	Rash, Alopecia, Erythema, Dry skin, Pruritus, Skin hyperpigmentation, Rash macular, Skin desquamation, Dermatitis, Pigmentation disorder, Nail disorder	Blister, Skin ulcer, Rash, Urticaria, Photosensitivity reaction, Palmar erythema, Swelling face, Purpura, Radiation recall syndrome
Musculoskeletal 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

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 can not 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*
Infections and infestations	-	Herpes zoster, Urinary tract infection, Oral candidiasis,

Body System	Very Common *All grades*	Common *All grades*
		Upper respiratory tract infection, Rhinitis, Influenza, [+]Infection, Oral herpes
Blood and lymphatic system disorders	[+]Neutropenia, [+]Leucopenia, [+]Anaemia, [+]Neutropenic fever, Thrombocytopenia	Bone marrow depression, [+]Febrile Neutropenia
Immune system disorders	-	Hypersensitivity
Metabolism and nutrition disorders	Appetite decreased	Hypokalaemia, Hyponatraemia, Hypomagnesaemia, Hypocalcaemia, Hyperglycaemia
Psychiatric disorders	-	Sleep disorder, Anxiety
Nervous system disorders	Paraesthesia, Dysaesthesia, Peripheral neuropathy, Peripheral sensory neuropathy, Dysgeusia, Headache	Neurotoxicity, Tremor, Neuralgia, Hypersensitivity reaction, Hypoaesthesia
Eye disorders	Lacrimation increased	Visual disorders, Dry eye, Eye pain, Visual impairment, Vision blurred
Ear and labyrinth disorders	-	Tinnitus, Hypoacusis
Cardiac disorders	-	Atrial fibrillation, Cardiac ischaemia/infarction
Vascular disorders	Lower limb oedema, Hypertension, [+]Embolism and thrombosis	Flushing, Hypotension, Hypertensive crisis, Hot flush, Phlebitis
Respiratory, thoracic and mediastinal system disorders	Sore throat, Dysaesthesia pharynx	Hiccups, Pharyngolaryngeal pain, Dysphonia
Gastrointestinal disorders	Constipation, Dyspepsia	Upper gastrointestinal haemorrhage, Mouth ulceration, Gastritis, Abdominal distension, Gastroesophageal reflux disease, Oral pain, Dysphagia, Rectal haemorrhage, Abdominal pain lower, Oral dysaesthesia, Paraesthesia oral, Hypoaesthesia oral, Abdominal discomfort
Hepatobiliary disorders	-	Hepatic function abnormal
Skin and subcutaneous tissue disorders	Alopecia, Nail disorder	Hyperhidrosis, Rash erythematous, Urticaria, Night sweats
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia, Pain in extremity	Pain in jaw , Muscle spasms, Trismus, Muscular weakness
Renal and urinary 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	-	Contusion

Body System	Very Common *All grades*	Common *All grades*
procedural complications		

[+] 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.

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

Table 6 Summary of events reported with capecitabine in the post-marketing setting

Body **System**	***Rare***
Eye disorders	Lacrimal duct stenosis, corneal disorders, keratitis, punctate keratitis
Cardiac disorders	Ventricular fibrillation, QT prolongation, Torsade de pointes, Bradycardia, Vasospasm
Hepatobiliary disorders	Hepatic failure, cholestatic hepatitis
Skin and subcutaneous disorders	Cutaneous lupus erythematosus

Description of selected adverse reactions

Hand-foot syndrome (HFS, 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%.

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 diarrhea 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.

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: cytostatics (antimetabolites), 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 intravenous followed by 425 mg/m^2 intravenous bolus 5-FU, on days 1 to 5, every 28 days for 24 weeks). Capecitabine was at least equivalent to intravenous 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 randomisation, gender, CEA levels at baseline, lymph nodes at baseline, and country. In the all-randomised population, capecitabine was shown to be superior to 5-FU/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 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 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 allrandomised 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 7 for treatment regimens.

Table 7 Treatment Regimens in Study NO16966 (mCRC)

	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	200 mg/m^2 IV 2 hr	Leucovorin on Days 1 and 2, every 2 weeks
	5-Fluorouracil	400 mg/m^2 IV bolus, followed by 600 mg/m^2 IV 22 hr	5-fluorouracil IV bolus/infusion, each on Days 1 and 2, every 2 weeks
	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	1000 mg/m^2 oral twice daily	Capecitabine oral twice daily for 2 weeks (followed by 1 week off-treatment)
	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 8). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival (see table 8). 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 8. However, the on-treatment PFS analysis did not confirm the results of the general PFS and OS analysis: the hazard ratio of XELOX versus FOLFOX-4 was 1.24 with 97.5% CI 1.07-1.44. Although sensitivity analyses show that differences in regimen schedules and timing of tumour assessments impact the ontreatment PFS analysis, a full explanation for this result has not been found.

Table 8 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.

Data from a randomised, controlled phase III study (CAIRO) support the use of 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. 820 Patients were randomized to receive either sequential treatment (n=410) or combination treatment (n=410). Sequential treatment consisted of first-line treatment with 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 treatment of 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.

Data from an interim analysis of a multicentre, randomised, controlled phase II study (AIO KRK 0604) support 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. 115 Patients were randomised to treatment with capecitabine combined with irinotecan (XELIRI) and bevacizumab: 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 118 patients were randomised to treatment with capecitabine combined with oxaliplatin plus bevacizumab: 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). Progression-free survival at 6 months in the intent-to-treat population was 80% (XELIRI plus bevacizumab) versus 74% (XELOX plus bevacizumab). Overall response rate (complete response plus partial response) was 45% (XELOX plus bevacizumab) versus 47% (XELIRI plus bevacizumab).

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 7. 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 intentto-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 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	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 superior 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).

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 C_{max} and 24% lower AUC for capecitabine than Caucasian patients (n=22). Japanese patients had also about 25% lower C_{max} and 34% lower AUC for FBAL than Caucasian patients. The clinical relevance of these differences is unknown. No significant differences occurred in the exposure to other metabolites (5'-DFCR, 5'-DFUR, and 5-FU).

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
Microcrystalline cellulose
Hypromellose
Croscarmellose sodium
Magnesium stearate

Tablet coating:
Macrogol
Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

150 mg film-coated tablets
PVC/PE/PVDC – Aluminium blisters containing 10 film-coated tablets. Each pack contains 60 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.
Computerweg 10
3542DR Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/761/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 April 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Capecitabine Teva 500 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg of capecitabine.

Excipient with known effect:
Each film-coated tablet contains 52.0 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Capecitabine Teva 500 mg are oval biconvex light peach film-coated tablets, 16.0 mm x 8.5 mm with inscription “C” on one side and “500”on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Capecitabine Teva is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes’ stage C) colon cancer (see section 5.1).

Capecitabine Teva is indicated for the treatment of metastatic colorectal cancer (see section 5.1).

Capecitabine Teva is indicated for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen (see section 5.1).

Capecitabine Teva 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. Capecitabine Teva is also indicated 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 Teva should only be prescribed by a qualified physician experienced in the utilisation of antineoplastic 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). The inclusion of biological medicinal products 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. 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.

Capecitabine Teva 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 Surface Area (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 hyperbilirubinaemia, 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.

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 Teva 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.
- *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.

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

Method of administration
Capecitabine Teva film-coated tablets should be swallowed with water within 30 minutes after a meal.

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,
- In patients with known dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4),
- During pregnancy and lactation,
- In patients with severe leucopenia, neutropenia, or thrombocytopenia,
- In patients with severe hepatic impairment,
- In patients with severe renal impairment (creatinine clearance below 30 ml/min),
- Treatment with sorivudine or its chemically related analogues, such as brivudine (see section 4.5),
- 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 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. 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. 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.

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 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 4.5).

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 section 4.2 and 4.3).

DPD deficiency: Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of DPD activity. A link between decreased levels of DPD and increased, potentially fatal toxic effects of 5-FU therefore cannot be excluded.
Patients with known DPD deficiency should not be treated with capecitabine (see section 4.3). In patients with unrecognised DPD deficiency treated with capecitabine, life-threatening toxicities manifesting as acute overdose may occur (see section 4.9). In the event of grade 2-4 acute toxicity, treatment must be discontinued immediately until observed toxicity resolves. Permanent discontinuation should be considered based on clinical assessment of the onset, duration and severity of the observed toxicities.

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.

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.

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:

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 anti-coagulant 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: 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).

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. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine (see section 4.3). There must be at least a 4-week waiting period between end of treatment with sorivudine or its chemically related analogues such as brivudine and start of capecitabine therapy.

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.

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

Breast-feeding
It is not known whether capecitabine is excreted in human breast milk. In lactating mice, considerable amounts of capecitabine and its metabolites were found in milk. Breast-feeding should be discontinued while receiving treatment with capecitabine.

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

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 national reporting system listed in Appendix V.

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), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and 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*
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, Leucopenia, Haemolytic anaemia, International Normalised Ratio (INR) increased / Prothrombin time prolonged
Immune system disorders	-	-	Hypersensitivity
Metabolism and nutrition disorders	Anorexia	Dehydration, Weight decreased	Diabetes, Hypokalaemia, Appetite disorder,

Body System	Very Common *All grades*	Common *All grades*	Uncommon *Severe and/or Life-threatening (grade 3-4) or considered medically relevant*
			Malnutrition, Hypertriglycerid-aemia,
Psychiatric disorders	-	Insomnia, Depression	Confusional state, Panic attack, Depressed mood, Libido decreased
Nervous system disorders	-	Headache, Lethargy Dizziness, Paraesthesia, 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	-	Hyperbilirubinaemia , Liver function test abnormalities	Jaundice

Body System	Very Common *All grades*	Common *All grades*	Uncommon *Severe and/or Life-threatening (grade 3-4) or considered medically relevant*
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome	Rash, Alopecia, Erythema, Dry skin, Pruritus, Skin hyperpigmentation, Rash macular, Skin desquamation, Dermatitis, Pigmentation disorder, Nail disorder	Blister, Skin ulcer, Rash, Urticaria, Photosensitivity reaction, Palmar erythema, Swelling face, Purpura, Radiation recall syndrome
Musculoskeletal 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

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 can not 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*
Infections and infestations	-	Herpes zoster, Urinary tract infection, Oral candidiasis, Upper respiratory tract infection, Rhinitis, Influenza, [+]Infection, Oral herpes
Blood and lymphatic system disorders	[+]Neutropenia, [+]Leucopenia, [+]Anaemia, [+]Neutropenic fever, Thrombocytopenia	Bone marrow depression, [+]Febrile Neutropenia
Immune system disorders	-	Hypersensitivity
Metabolism and nutrition disorders	Appetite decreased	Hypokalaemia, Hyponatraemia, Hypomagnesaemia, Hypocalcaemia, Hyperglycaemia
Psychiatric disorders	-	Sleep disorder, Anxiety
Nervous system disorders	Paraesthesia, Dysaesthesia, Peripheral neuropathy, Peripheral sensory neuropathy, Dysgeusia, Headache	Neurotoxicity, Tremor, Neuralgia, Hypersensitivity reaction, Hypoaesthesia
Eye disorders	Lacrimation increased	Visual disorders, Dry eye, Eye pain, Visual impairment, Vision blurred
Ear and labyrinth disorders	-	Tinnitus, Hypoacusis
Cardiac disorders	-	Atrial fibrillation, Cardiac ischaemia/infarction
Vascular disorders	Lower limb oedema, Hypertension, [+]Embolism and thrombosis	Flushing, Hypotension, Hypertensive crisis, Hot flush, Phlebitis
Respiratory, thoracic and mediastinal system disorders	Sore throat, Dysaesthesia pharynx	Hiccups, Pharyngolaryngeal pain, Dysphonia
Gastrointestinal disorders	Constipation, Dyspepsia	Upper gastrointestinal haemorrhage, Mouth ulceration, Gastritis, Abdominal distension, Gastroesophageal reflux disease, Oral pain, Dysphagia, Rectal haemorrhage, Abdominal pain lower, Oral dysaesthesia, Paraesthesia oral, Hypoaesthesia oral, Abdominal discomfort
Hepatobiliary disorders	-	Hepatic function abnormal
Skin and subcutaneous tissue disorders	Alopecia, Nail disorder	Hyperhidrosis, Rash erythematous, Urticaria, Night sweats
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia, Pain in extremity	Pain in jaw , Muscle spasms, Trismus, Muscular weakness
Renal and urinary disorders	-	Haematuria, Proteinuria, Creatinine renal clearance decreased, Dysuria

Body System	Very Common *All grades*	Common *All grades*
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.

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

Table 6 Summary of events reported with capecitabine in the post-marketing setting

Body System	***Rare***
Eye disorders	Lacrimal duct stenosis, corneal disorders, keratitis, punctate keratitis
Cardiac disorders	Ventricular fibrillation, QT prolongation, Torsade de pointes, Bradycardia, Vasospasm
Hepatobiliary disorders	Hepatic failure, cholestatic hepatitis
Skin and subcutaneous disorders	Cutaneous lupus erythematosus

Description of selected adverse reactions

Hand-foot syndrome (HFS, 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%.

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 diarrhea 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.

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: cytostatics (antimetabolites), 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 intravenous followed by 425 mg/m^2 intravenous bolus 5-FU, on days 1 to 5, every 28 days for 24 weeks). Capecitabine was at least equivalent to intravenous 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 randomisation, gender, CEA levels at baseline, lymph nodes at baseline, and country. In the all-randomised population, capecitabine was shown to be superior to 5-FU/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 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 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 allrandomised 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 7 for treatment regimens.

Table 7 Treatment Regimens in Study NO16966 (mCRC)

	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	200 mg/m^2 IV 2 hr	Leucovorin on Days 1 and 2, every 2 weeks
	5-Fluorouracil	400 mg/m^2 IV bolus, followed by 600 mg/m^2 IV 22 hr	5-fluorouracil IV bolus/infusion, each on Days 1 and 2, every 2 weeks
	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	1000 mg/m^2 oral twice daily	Capecitabine oral twice daily for 2 weeks (followed by 1 week off-treatment)
	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 8). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival (see table 8). 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 8. However, the on-treatment PFS analysis did not confirm the results of the general PFS and OS analysis: the hazard ratio of XELOX versus FOLFOX-4 was 1.24 with 97.5% CI 1.07-1.44. Although sensitivity analyses show that differences in regimen schedules and timing of tumour assessments impact the ontreatment PFS analysis, a full explanation for this result has not been found.

Table 8 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.

Data from a randomised, controlled phase III study (CAIRO) support the use of 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. 820 Patients were randomized to receive either sequential treatment (n=410) or combination treatment (n=410). Sequential treatment consisted of first-line treatment with 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 treatment of 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.

Data from an interim analysis of a multicentre, randomised, controlled phase II study (AIO KRK 0604) support 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. 115 Patients were randomised to treatment with capecitabine combined with irinotecan (XELIRI) and bevacizumab: 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 118 patients were randomised to treatment with capecitabine combined with oxaliplatin plus bevacizumab: 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). Progression-free survival at 6 months in the intent-to-treat population was 80% (XELIRI plus bevacizumab) versus 74% (XELOX plus bevacizumab). Overall response rate (complete response plus partial response) was 45% (XELOX plus bevacizumab) versus 47% (XELIRI plus bevacizumab).

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 7. 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 intentto-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 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	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 superior 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).

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 C_{max} and 24% lower AUC for capecitabine than Caucasian patients (n=22). Japanese patients had also about 25% lower C_{max} and 34% lower AUC for FBAL than Caucasian patients. The clinical relevance of these differences is unknown. No significant differences occurred in the exposure to other metabolites (5'-DFCR, 5'-DFUR, and 5-FU).

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
Microcrystalline cellulose
Hypromellose
Croscarmellose sodium
Magnesium stearate

Tablet coating:
Macrogol
Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C.
Store in the original package in order to protect from moisture.

6.6 Nature and contents of container

500 mg film-coated tablets
PVC/PE/PVDC – Aluminium blisters containing 10 film-coated tablets. Each pack contains 120 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.
Computerweg 10
3542DR Utrecht

The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/761/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 April 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Teva Czech Industries s.r.o.
Ostravska 29, c.p. 305,
74770 Opava-Komarov
Czech Republic

Pharmachemie B.V.
Swensweg 5,
2031 GA Haarlem
The Netherlands

Merckle GmbH
Ludwig Merckle Str. 3
89143 Blaubeuren
Germany

Teva Operations Poland Sp. z.o.o
ul. Mogilska 80,
31-546 Krakow
Poland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2) .

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Capecitabine Teva 150 mg film-coated tablets
capecitabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg capecitabine.

3. LIST OF EXCIPIENTS

Also contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.
Computerweg 10, 3542DR Utrecht,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/761/001

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Capecitabine Teva 150 mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Capecitabine Teva 150 mg film-coated tablets
capecitabine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Capecitabine Teva 500 mg film-coated tablets
capecitabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg capecitabine.

3. LIST OF EXCIPIENTS

Also contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

120 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.
Computerweg 10, 3542DR Utrecht,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/761/002

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Capecitabine Teva 500 mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Capecitabine Teva 500 mg film-coated tablets
capecitabine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Capecitabine Teva 150 mg film-coated tablets
capecitabine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Capecitabine Teva is and what it is used for

Capecitabine Teva belongs to the group of medicines called "cytostatic medicines", which stop the growth of cancer cells. Capecitabine Teva contains capecitabine, which itself is not a cytostatic medicine. Only after being absorbed by the body is it changed into an active anti-cancer medicine (more in tumour tissue than in normal tissue).

Capecitabine Teva is used in the treatment of colon, rectal, gastric, or breast cancers. Furthermore, Capecitabine Teva is used to prevent new occurrence of colon cancer after complete removal of the tumour by surgery.

Capecitabine Teva may be used either alone or in combination with other medicines.

2. What you need to know before you take Capecitabine Teva

Do not take Capecitabine Teva
- if you are allergic to capecitabine or any of the other ingredients of this medicine (listed in section 6). You must inform your doctor if you know that you have an allergy to capecitabine,
- if you previously have had severe reactions to fluoropyrimidine therapy (a group of anticancer medicines such as fluorouracil),
- if you are pregnant or breast-feeding,
- if you have severely low levels of white cells or platelets in the blood (leucopenia, neutropenia or thrombocytopenia),
- if you have severe liver or kidney problems,
- if you have a known deficiency for the enzyme dihydropyrimidine dehydrogenase (DPD), involved in the metabolism of uracil and thymine, or
- if you are being treated now or have been treated in the last 4 weeks with brivudine, sorivudine or similar classes of substance as part of herpes zoster (chickenpox or shingles) therapy.

Warnings and precautions
Talk to your doctor or pharmacist before taking Capecitabine Teva
- if you have liver or kidney diseases
- if you have or had heart problems (for example an irregular heartbeat or pains to the chest jaw and back brought on by physical effort and due to problems with the blood flow to the heart)
- if you have brain diseases (for example. cancer that has spread to the brain, or nerve damage (neuropathy)
- if you have calcium imbalances (seen in blood tests)
- if you have diabetes
- if you have diarrhoea
- if you are, or become dehydrated
- if you have imbalances of ions in your blood (electrolyte imbalances, seen in tests)
- if you have a history of eye problems as you may need extra monitoring of your eyes

DPD deficiency: DPD deficiency is a rare condition present at birth that is not usually associated with health problems unless you receive certain medicines. If you have an unrecognised DPD deficiency and take capecitabine, you may experience severe forms of the side effects listed under section 4 Possible side effects. Contact your doctor immediately if you are concerned about any of the side effects or if you notice any additional side effects not listed in the leaflet (see section 4 Possible side effects.

Children and adolescents
Capecitabine is not indicated in children and adolescents. Do not give capecitabine to children and adolescents.

Other medicines and Capecitabine Teva
Before starting treatment, tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is extremely important, as taking more than one medicine at the same time can strengthen or weaken the effect of the medicines. You need to be particularly careful if you are taking any of the following:
- gout medicines (allopurinol),
- blood-thinning medicines (coumarin, warfarin),
- certain anti-viral medicines (sorivudine and brivudine),
- medicines for seizures or tremors (phenytoin),
- interferon alpha or
- radiotherapy and certain medicines used to treat cancer (folinic acid, oxaliplatin, bevacizumab).

Capecitabine Teva with food, drink and alcohol
You should take Capecitabine Teva no later than 30 minutes after meals.

Pregnancy and breast-feeding
Before starting treatment, you must tell your doctor if you are pregnant, if you think you may be pregnant or if you intend to become pregnant.
You must not take Capecitabine Teva if you are pregnant or think you might be.
You must not breast-feed if you are taking Capecitabine Teva.
Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Capecitabine Teva may make you feel dizzy, nauseous or tired. It is therefore possible that Capecitabine Teva could affect your ability to drive a car or operate machinery.

Capecitabine Teva contains lactose
This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Capecitabine Teva

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Capecitabine should only be prescribed by a doctor experienced in the use of anticancer medicines.

Capecitabine Teva tablets should be **swallowed whole with water, and within 30 minutes of a meal.**

Your doctor will prescribe a dose and treatment regimen that is right for you. The dose of Capecitabine Teva is based on your body surface area. This is calculated from your height and weight. The usual dose for adults is 1250 mg/m^2 of body surface area taken two times daily (morning and evening). Two examples are provided here: A person whose body weight is 64 kg and height is 1.64 m has a body surface area of 1.7 m^2 and should take 4 tablets of 500 mg and 1 tablet of 150 mg two times daily. A person whose body weight is 80 kg and height is 1.80 m has a body surface area of 2.00 m^2 and should take 5 tablets of 500 mg two times daily.

Capecitabine Teva tablets are usually taken for 14 days followed by a 7 day rest period (when no tablets are taken). This 21 day period is one treatment cycle.

In combination with other medicines the usual dose for adults may be less than 1250 mg/m^2 of body surface area, and you may need to take the tablets over a different time period (e.g. every day, with no rest period).

Your doctor will tell you what dose you need to take, when to take it and for how long you need to take it.

Your doctor may want you to take a combination of 150 mg and 500 mg tablets for each dose.
- Take the tablets in the **morning and evening** as prescribed by your doctor.
- Take the tablets within **30 minutes after the end of a meal** (breakfast and dinner).
- It is important that you take all your medicine as prescribed by your doctor.

If you take more Capecitabine Teva than you should
If you take more Capecitabine Teva than you should, contact your doctor as soon as possible before taking the next dose.
You might get the following side effects if you take a lot more capecitabine than you should: feeling or being sick, diarrhoea, inflammation or ulceration of the gut or mouth, pain or bleeding from the intestine or stomach, or bone marrow depression (reduction in certain kinds of blood cells). Tell your doctor immediately if you experience any of these symptoms.

If you forget to take Capecitabine Teva
Do <u>not</u> take the missed dose at all and do <u>not</u> double the next one. Instead, continue your regular dosing schedule and check with your doctor.

If you stop taking Capecitabine Teva
There are no side effects caused by stopping treatment with capecitabine. In case you are using coumarin anticoagulants (containing e.g. phenprocoumon), stopping capecitabine might require that your doctor adjusts your anticoagulant dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

STOP taking Capecitabine Teva immediately and contact your doctor if any of these symptoms occur:

- ***Diarrhoea***: if you have an increase of 4 or more bowel movements compared to your normal bowel movements each day or any diarrhoea at night.
- ***Vomiting***: if you vomit more than once in a 24-hour time period.
- ***Nausea:*** if you lose your appetite, and the amount of food you eat each day is much less than usual.
- ***Stomatitis***: if you have pain, redness, swelling or sores in your mouth.
- ***Hand-and-foot skin-reaction:*** if you have pain, swelling, redness or tingling of hands and/or feet
- ***Fever:*** if you have a temperature of 38°C or higher.
- ***Infection***: if you experience signs of infection caused by bacteria or virus, or other organisms.
- ***Chest pain:*** if you experience pain localised to the centre of the chest, especially if it occurs during exercise.

If caught early, these side effects usually improve within 2 to 3 days after stopping treatment. If these side effects continue, contact your doctor immediately. Your doctor may instruct you to restart treatment at a lower dose.

In addition to the above, when capecitabine is used alone, very common side effects which may affect more than 1 person in 10 are:
- abdominal pain
- rash, dry or itchy skin
- tiredness
- loss of appetite (anorexia)

These side effects can become severe; therefore, it is important that you **always contact your doctor immediately** when you start to experience a side effect. Your doctor may instruct you to decrease the dose and/or temporarily discontinue treatment with Capecitabine Teva. This will help reduce the likelihood that the side effect continues or becomes severe.

Other side effects are:

Common side effects (may affect up to 1 in 10 people) include:
- decreases in the number of white blood cells or red blood cells (seen in tests),
- dehydration, weight loss,
- sleeplessness (insomnia), depression,
- headache, sleepiness, dizziness, abnormal sensation in the skin (numbness or tingling sensation), taste changes,
- eye irritation, increased tears, eye redness (conjunctivitis)
- inflammation of the veins (thrombophlebitis)
- shortness of breath, nose bleeds, cough, runny nose,
- cold sores or other herpes infections,
- infections of the lungs or respiratory system (e.g. pneumonia or bronchitis),
- bleeding from the gut, constipation, pain in upper abdomen, indigestion, excess wind, dry mouth
- skin rash, hair loss (alopecia), skin reddening, dry skin, itching (pruritus), skin discolouration, skin loss, skin inflammation, nail disorder
- pain in the joints, or in the limbs (extremities), chest or back,
- fever, swelling in the limbs, feeling ill
- problems with liver function (seen in blood tests) and increased blood bilirubin (excreted by the liver)

Uncommon side-effects (may affect up to 1 in 100 people) include:
- blood infection, urinary tract infection, infection of the skin, infections in the nose and throat, fungal infections (including those of the mouth), influenza, gastroenteritis, tooth abscess,
- lumps under the skin (lipoma),
- decreases in blood cells including platelets, thinning of blood (seen in tests)
- allergy

- diabetes, decrease in blood potassium, malnutrition, increased blood triglycerides,
- confusional state, panic attacks, depressed mood, decreased libido,
- difficulty speaking, impaired memory, loss of movement coordination, balance disorder, fainting, nerve damage (neuropathy) and problems with sensation
- blurred or double vision,
- vertigo, ear pain.
- irregular heartbeat and palpitations (arrhythmias), chest pain and heart attack (infarction),
- blood clots in the deep veins, high or low blood pressure, hot flushes, cold limbs (extremities), purple spots on the skin
- blood clots in the veins in the lung (pulmonary embolism), collapsed lung, coughing up blood, asthma, shortness of breath on exertion,
- bowel obstruction, collection of fluid in the abdomen, inflammation of the small or large intestine, the stomach or the oesophagus, pain in the lower abdomen, abdominal discomfort, heartburn (reflux of food from the stomach), blood in the stool,
- jaundice (yellowing of skin and eyes)
- skin ulcer and blister, reaction of the skin with sunlight, reddening of palms, swelling or pain of the face
- joint swelling or stiffness, bone pain, muscle weakness or stiffness,
- fluid collection in the kidneys, increased frequency of urination during the night, incontinence, blood in the urine, increase in blood creatinine (sign of kidney dysfunction)
- unusual bleeding from the vagina
- swelling (oedema), chills and rigors

Some of these side effects are more common when capecitabine is used with other medicines for the treatment of cancer. Other side-effects seen in this setting are the following:

Common side-effects (may affect up to 1 in 10 people) include:
- decrease in blood sodium, magnesium or calcium, increase in blood sugar,
- nerve pain,
- ringing or buzzing in the ears (tinnitus), loss of hearing,
- vein inflammation,
- hiccups, change in voice,
- pain or altered/abnormal sensation in the mouth, pain in the jaw,
- sweating, night sweats,
- muscle spasm,
- difficulty in urination, blood or protein in the urine,
- bruising or reaction at the injection site (caused by medicines given by injection at the same time)

Very rare side effects (may affect up to 1 in 10,000 people) include:
- narrowing or blockage of tear duct (lacrimal duct stenosis),
- liver failure,
- inflammation leading to dysfunction or obstruction in bile secretion (cholestatic hepatitis),
- specific changes in the electrocardiogram (QT prolongation),
- certain types of arrhythmia (including ventricular fibrillation, torsade de pointes, and bradycardia).
- eye inflammation causing eye pain and possibly eyesight problems
- inflammation of the skin causing red scaly patches due to an immune system illness

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Capecitabine Teva

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister, after EXP.

Do not store above 30°C.
Store in the original package to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Capecitabine Teva contains

- The active substance is capecitabine. Each film-coated tablet contains 150 mg of capecitabine.
- The other ingredients are:
  - Tablet core: lactose , microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate.
  - Tablet coating: macrogol, hypromellose, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172).

What Capecitabine Teva looks like and contents of the pack

Capecitabine Teva 150 mg are oval biconvex light peach film-coated tablets with inscription “C” on one side and “150” on the other side.

The tablets are available in blisters containing 10 film-coated tablets. Each pack contains 60 tablets.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: Information for the user

Capecitabine Teva 500 mg film-coated tablets
capecitabine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Capecitabine Teva is and what it is used for

Capecitabine Teva belongs to the group of medicines called "cytostatic medicines", which stop the growth of cancer cells. Capecitabine Teva contains capecitabine, which itself is not a cytostatic medicine. Only after being absorbed by the body is it changed into an active anti-cancer medicine (more in tumour tissue than in normal tissue).

Capecitabine Teva is used in the treatment of colon, rectal, gastric, or breast cancers. Furthermore, Capecitabine Teva is used to prevent new occurrence of colon cancer after complete removal of the tumour by surgery.

Capecitabine Teva may be used either alone or in combination with other medicines.

2. What you need to know before you take Capecitabine Teva

Do not take Capecitabine Teva
- if you are allergic to capecitabine or any of the other ingredients of this medicine (listed in section 6). You must inform your doctor if you know that you have an allergy to capecitabine,
- if you previously have had severe reactions to fluoropyrimidine therapy (a group of anticancer medicines such as fluorouracil),
- if you are pregnant or breast-feeding,
- if you have severely low levels of white cells or platelets in the blood (leucopenia, neutropenia or thrombocytopenia),
- if you have severe liver or kidney problems,
- if you have a known deficiency for the enzyme dihydropyrimidine dehydrogenase (DPD), involved in the metabolism of uracil and thymine, or
- if you are being treated now or have been treated in the last 4 weeks with brivudine, sorivudine or similar classes of substance as part of herpes zoster (chickenpox or shingles) therapy.

Warnings and precautions
Talk to your doctor or pharmacist before taking Capecitabine Teva
- if you have liver or kidney diseases
- if you have or had heart problems (for example an irregular heartbeat or pains to the chest jaw and back brought on by physical effort and due to problems with the blood flow to the heart)
- if you have brain diseases (for example. cancer that has spread to the brain, or nerve damage (neuropathy)
- if you have calcium imbalances (seen in blood tests)
- if you have diabetes
- if you have diarrhoea
- if you are, or become dehydrated
- if you have imbalances of ions in your blood (electrolyte imbalances, seen in tests)
- if you have a history of eye problems as you may need extra monitoring of your eyes

DPD deficiency: DPD deficiency is a rare condition present at birth that is not usually associated with health problems unless you receive certain medicines. If you have an unrecognised DPD deficiency and take capecitabine, you may experience severe forms of the side effects listed under section 4 Possible side effects. Contact your doctor immediately if you are concerned about any of the side effects or if you notice any additional side effects not listed in the leaflet (see section 4 Possible side effects.

Children and adolescents
Capecitabine is not indicated in children and adolescents. Do not give capecitabine to children and adolescents.

Other medicines and Capecitabine Teva
Before starting treatment, tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is extremely important, as taking more than one medicine at the same time can strengthen or weaken the effect of the medicines. You need to be particularly careful if you are taking any of the following:
- gout medicines (allopurinol),
- blood-thinning medicines (coumarin, warfarin),
- certain anti-viral medicines (sorivudine and brivudine),
- medicines for seizures or tremors (phenytoin),
- interferon alpha or
- radiotherapy and certain medicines used to treat cancer (folinic acid, oxaliplatin, bevacizumab).

Capecitabine Teva with food,drink and alcohol
You should take Capecitabine Teva no later than 30 minutes after meals.

Pregnancy and breast-feeding
Before starting treatment, you must tell your doctor if you are pregnant, if you think you may be pregnant or if you intend to become pregnant.
You must not take Capecitabine Teva if you are pregnant or think you might be.
You must not breast-feed if you are taking Capecitabine Teva.
Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Capecitabine Teva may make you feel dizzy, nauseous or tired. It is therefore possible that Capecitabine Teva could affect your ability to drive a car or operate machinery.

Capecitabine Teva contains lactose
This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Capecitabine Teva

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Capecitabine should only be prescribed by a doctor experienced in the use of anticancer medicines.

Capecitabine Teva tablets should be **swallowed whole with water, and within 30 minutes of a meal.**

Your doctor will prescribe a dose and treatment regimen that is right for you. The dose of Capecitabine Teva is based on your body surface area. This is calculated from your height and weight. The usual dose for adults is 1250 mg/m^2 of body surface area taken two times daily (morning and evening). Two examples are provided here: A person whose body weight is 64 kg and height is 1.64 m has a body surface area of 1.7 m^2 and should take 4 tablets of 500 mg and 1 tablet of 150 mg two times daily. A person whose body weight is 80 kg and height is 1.80 m has a body surface area of 2.00 m^2 and should take 5 tablets of 500 mg two times daily.

Capecitabine Teva tablets are usually taken for 14 days followed by a 7 day rest period (when no tablets are taken). This 21 day period is one treatment cycle.

In combination with other medicines the usual dose for adults may be less than 1250 mg/m^2 of body surface area, and you may need to take the tablets over a different time period (e.g. every day, with no rest period).

Your doctor will tell you what dose you need to take, when to take it and for how long you need to take it.

Your doctor may want you to take a combination of 150 mg and 500 mg tablets for each dose.
- Take the tablets in the **morning and evening** as prescribed by your doctor.
- Take the tablets within **30 minutes after the end of a meal** (breakfast and dinner).
- It is important that you take all your medicine as prescribed by your doctor.

If you take more Capecitabine Teva than you should
If you take more capecitabine than you should, contact your doctor as soon as possible before taking the next dose.
You might get the following side effects if you take a lot more capecitabine than you should: feeling or being sick, diarrhoea, inflammation or ulceration of the gut or mouth, pain or bleeding from the intestine or stomach, or bone marrow depression (reduction in certain kinds of blood cells). Tell your doctor immediately if you experience any of these symptoms.

If you forget to take Capecitabine Teva
Do <u>not</u> take the missed dose at all and do <u>not</u> double the next one. Instead, continue your regular dosing schedule and check with your doctor.

If you stop taking Capecitabine Teva
There are no side effects caused by stopping treatment with capecitabine. In case you are using coumarin anticoagulants (containing e.g. phenprocoumon), stopping capecitabine might require that your doctor adjusts your anticoagulant dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

STOP taking Capecitabine Teva immediately and contact your doctor if any of these symptoms occur:

- ***Diarrhoea***: if you have an increase of 4 or more bowel movements compared to your normal bowel movements each day or any diarrhoea at night.
- ***Vomiting***: if you vomit more than once in a 24-hour time period.
- ***Nausea:*** if you lose your appetite, and the amount of food you eat each day is much less than usual.
- ***Stomatitis***: if you have pain, redness, swelling or sores in your mouth.
- ***Hand-and-foot skin-reaction:*** if you have pain, swelling, redness or tingling of hands and/or feet
- ***Fever:*** if you have a temperature of 38°C or higher.
- ***Infection***: if you experience signs of infection caused by bacteria or virus, or other organisms.
- ***Chest pain:*** if you experience pain localised to the centre of the chest, especially if it occurs during exercise.

If caught early, these side effects usually improve within 2 to 3 days after stopping treatment. If these side effects continue, contact your doctor immediately. Your doctor may instruct you to restart treatment at a lower dose.

In addition to the above, when capecitabine is used alone, very common side effects which may affect more than 1 person in 10 are:
- abdominal pain
- rash, dry or itchy skin
- tiredness
- loss of appetite (anorexia)

These side effects can become severe; therefore, it is important that you **always contact your doctor immediately** when you start to experience a side effect. Your doctor may instruct you to decrease the dose and/or temporarily discontinue treatment with Capecitabine Teva. This will help reduce the likelihood that the side effect continues or becomes severe.

Other side effects are:

Common side effects (may affect up to 1 in 10 people) include:
- decreases in the number of white blood cells or red blood cells (seen in tests),
- dehydration, weight loss,
- sleeplessness (insomnia), depression,
- headache, sleepiness, dizziness, abnormal sensation in the skin (numbness or tingling sensation), taste changes,
- eye irritation, increased tears, eye redness (conjunctivitis)
- inflammation of the veins (thrombophlebitis)
- shortness of breath, nose bleeds, cough, runny nose,
- cold sores or other herpes infections,
- infections of the lungs or respiratory system (e.g. pneumonia or bronchitis),
- bleeding from the gut, constipation, pain in upper abdomen, indigestion, excess wind, dry mouth
- skin rash, hair loss (alopecia), skin reddening, dry skin, itching (pruritus), skin discolouration, skin loss, skin inflammation, nail disorder
- pain in the joints, or in the limbs (extremities), chest or back,
- fever, swelling in the limbs, feeling ill
- problems with liver function (seen in blood tests) and increased blood bilirubin (excreted by the liver)

Uncommon side-effects (may affect up to 1 in 100 people) include:
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- decreases in blood cells including platelets, thinning of blood (seen in tests)
- allergy

- diabetes, decrease in blood potassium, malnutrition, increased blood triglycerides,
- confusional state, panic attacks, depressed mood, decreased libido,
- difficulty speaking, impaired memory, loss of movement coordination, balance disorder, fainting, nerve damage (neuropathy) and problems with sensation
- blurred or double vision,
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- irregular heartbeat and palpitations (arrhythmias), chest pain and heart attack (infarction),
- blood clots in the deep veins, high or low blood pressure, hot flushes, cold limbs (extremities), purple spots on the skin
- blood clots in the veins in the lung (pulmonary embolism), collapsed lung, coughing up blood, asthma, shortness of breath on exertion,
- bowel obstruction, collection of fluid in the abdomen, inflammation of the small or large intestine, the stomach or the oesophagus, pain in the lower abdomen, abdominal discomfort, heartburn (reflux of food from the stomach), blood in the stool,
- jaundice (yellowing of skin and eyes)
- skin ulcer and blister, reaction of the skin with sunlight, reddening of palms, swelling or pain of the face
- joint swelling or stiffness, bone pain, muscle weakness or stiffness,
- fluid collection in the kidneys, increased frequency of urination during the night, incontinence, blood in the urine, increase in blood creatinine (sign of kidney dysfunction)
- unusual bleeding from the vagina
- swelling (oedema), chills and rigors

Some of these side effects are more common when capecitabine is used with other medicines for the treatment of cancer. Other side-effects seen in this setting are the following:

Common side-effects (may affect up to 1 in 10 people) include:
- decrease in blood sodium, magnesium or calcium, increase in blood sugar,
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- hiccups, change in voice,
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- sweating, night sweats,
- muscle spasm,
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- bruising or reaction at the injection site (caused by medicines given by injection at the same time)

Very rare side effects (may affect up to 1 in 10,000 people) include:
- narrowing or blockage of tear duct (lacrimal duct stenosis),
- liver failure,
- inflammation leading to dysfunction or obstruction in bile secretion (cholestatic hepatitis),
- specific changes in the electrocardiogram (QT prolongation),
- certain types of arrhythmia (including ventricular fibrillation, torsade de pointes, and bradycardia).
- eye inflammation causing eye pain and possibly eyesight problems
- inflammation of the skin causing red scaly patches due to an immune system illness

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If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Capecitabine Teva

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister, after EXP.

Do not store above 30°C.
Store in the original package to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Capecitabine Teva contains

- The active substance is capecitabine. Each film-coated tablet contains 500 mg of capecitabine
- The other ingredients are:
  - Tablet core: lactose , microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate.
  - Tablet coating: macrogol, hypromellose, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172).

What Capecitabine Teva looks like and contents of the pack

Capecitabine Teva 500 mg are oval biconvex light peach film-coated tablets with inscription “C” on one side and “500” on the other side.

The tablets are available in blisters containing 10 film-coated tablets. Each pack contains 120 tablets.

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