1. NAME OF THE MEDICINAL PRODUCT

Xeloda®500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

500 mg capecitabine

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Xeloda is indicated for first line monotherapy of metastatic colorectal cancer (see section 5.1).

Xeloda 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. Xeloda 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

Xeloda should only be prescribed by a qualified physician experienced in the utilisation of anti-neoplastic agents.

Recommended posology:

The recommended dose 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 seven day rest period. Xeloda tablets should be swallowed with water within 30 minutes after a meal. Treatment should be discontinued if progressive disease or intolerable toxicity is observed. In combination with docetaxel, the recommended dose of Xeloda is 1250 mg/m^2 twice daily for 2 weeks followed by 1-week 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 Xeloda plus docetaxel combination.

Table 1: Xeloda dose calculation according to body surface area, standard starting dose

Dose level 1250 mg/m^2 (twice daily)		Number of tablets administered in the morning		Number of tablets administered in the evening	
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.26	1500	-	3	-	3
1.27 - 1.38	1650	1	3	1	3
1.39 - 1.52	1800	2	3	2	3
1.53 - 1.66	2000	-	4	-	4
1.67 - 1.78	2150	1	4	1	4
1.79 - 1.92	2300	2	4	2	4
1.93 - 2.06	2500	-	5	-	5
2.07 - 2.18	2650	1	5	1	5
≥2.19	2800	2	5	2	5

Table 2: Calculated Xeloda dose, reduced to 75% of the standard starting dose

Dose level 950 mg/m2 (twice daily)		Number of tablets administered in the morning		Number of tablets administered in the evening	
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.26	1150	1	2	1	2
1.27 - 1.38	1300	2	2	2	2
1.39 - 1.52	1450	3	2	3	2
1.53 - 1.66	1500	-	3	-	3
1.67 - 1.78	1650	1	3	1	3
1.79 - 1.92	1800	2	3	2	3
1.93 - 2.06	1950	3	3	3	3
2.07 - 2.18	2000	-	4	-	4
≥2.19	2150	1	4	1	4

Table 3: Calculated Xeloda dose, reduced to 50% of the standard starting dose

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

Posology adjustments during treatment:

Toxicity due to Xeloda 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. Patients taking Xeloda should be informed of the need to interrupt treatment immediately if moderate or worse toxicity occurs Doses of Xeloda omitted for toxicity are not replaced or restored, instead the patient should resume the planned treatment cycle. The following are the recommended dose modifications for toxicity:

Table 4: Xeloda Monotherapy Dose Reduction Schedule

Toxicity NCIC grades*	During a course of therapy	Dose adjustment for next cycle (% of starting dose)
• *Grade 1*	Maintain dose level	Maintain dose level
• *Grade 2*		
-1st appearance	Interrupt until resolved to grade 0-1	100%
-2nd appearance	Interrupt until resolved to grade 0-1	75%
-3rd appearance	Interrupt until resolved to grade 0-1	50%
-4th appearance	Discontinue treatment permanently	
• *Grade 3*		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance	Interrupt until resolved to grade 0-1	50%
-3rd appearance	Discontinue treatment permanently	
• *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%

*National Cancer Institute of Canada (NCIC) Common Toxicity Criteria (version 1) were used except for hand-foot syndrome

The following are the recommended dose modifications for toxicity <u>when Xeloda and docetaxel are used in combination:</u>

Table 5: Xeloda (X) in Combination with Docetaxel (Taxotere®, T) Dose Reduction Schedule for Non-Haematological Toxicities (for dose modifications due to haematological toxicities, see section on haematological toxicity after the table)

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

1. National Cancer Institute of Canada Common Toxicity Criteria (NCIC CTC), version 1.0 revised December 1994

Specific dose adjustment in combination with docetaxel:

Xeloda and/or docetaxel dose modifications should be made according to the general dose modification scheme above, if nothing else is stated regarding specific dose adjustments. For those toxicities considered 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. At the beginning of a treatment cycle, if either a docetaxel or a Xeloda treatment delay is indicated, both docetaxel and Xeloda administration should be delayed until the requirements for restarting both drugs are met. For further information about docetaxel see also the summary of product characteristics for docetaxel (Taxotere®).

Haematology: Xeloda treatment may continue throughout a grade 3 neutropenic episode. However, the patient should be closely monitored and administration of Xeloda should be interrupted if any grade 2 clinical event (eg diarrhoea, stomatitis, fever) coincides with the grade 3 neutropenic episode. If grade

4 neutropenia occurs treatment with Xeloda should be interrupted until recovery to grade 0-1. Treatment should only be re-administered when the neutrophil count is ≥1.5 x 10^9/l (grade 0-1).

Docetaxel dosage should be reduced from 75 mg/m^2 to 55 mg/m^2 in patients with neutropenia <0.5 x 10^9/l (grade 4) for more than 1 week, or febrile (>38°C) neutropenia. Docetaxel should be discontinued if grade 4 neutropenia or febrile neutropenia occurs at a dose of 55 mg/m^2 docetaxel, docetaxel. Patients with baseline neutrophil counts of <1.5 x 10^9/l and/or thrombocyte counts of <100 x 10^9/l should not be treated with the Xeloda/docetaxel combination.

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

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

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

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

ASAT and/or ALAT values	Alkaline phosphatase values	Docetaxel Dose modification
≤1.5 x ULN	AND ≤5 x ULN	no dose modification
>1.5 x ULN - ≤2.5 x ULN	AND ≤2.5 x ULN	no dose modification
>2.5 x ULN - ≤5 x ULN	AND ≤2.5 x ULN	reduce by 25% (not below 55 mg/m^2)
>1.5 x ULN - ≤5 x ULN	AND >2.5 x ULN - ≤5 x ULN	reduce by 25% (not below 55 mg/m^2)
>5 x ULN	OR >5 x ULN (unless bone metastasis are present in the absence of any liver disorder)	delay dose by a maximum of 2 weeks. If no recovery, discontinue docetaxel.

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

Diarrhoea: Follow the general dose modification scheme above (see also section 4.4).

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, Xeloda treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications applied should be those for the precipitating adverse event in accordance with the above guidelines.

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:. Xeloda is contraindicated in patients with severe renal impairment (creatinine clearance below 30 ml/min [Cockroft and Gault] at baseline). The incidence of grade 3 or 4 adverse events 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% of starting dose is recommended. 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 the table above. These dose adjustment recommendations for renal impairment apply both to monotherapy and combination use (see also section "Elderly" below).

Children (under 18 years): the safety and efficacy of Xeloda in children has not been studied.

Elderly: no adjustment of the starting dose is needed during Xeloda monotherapy. However, grade 3 or 4 treatment-related adverse events were more frequent in patients ≥60 years of age 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 events and treatment-related serious adverse events were observed in patients 60 years of age or more (see section 5.1). For patients 60 years of age or more treated with the combination of Xeloda plus docetaxel, a starting dose reduction of Xeloda 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 Xeloda starting dose in combination with docetaxel, the dose of Xeloda may be cautiously escalated to 1250 mg/m^2 twice daily.

4.3 Contraindications

History of severe and unexpected reactions to fluoropyrimidine therapy,
Known hypersensitivity to capecitabine, fluorouracil or any of the excipients,
In patients with known dihydropyrimidine dehydrogenase (DPD) deficiency,
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.
Contraindications for docetaxel also apply to the Xeloda plus docetaxel combination.

4.4 Special warnings and special 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 events are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced.

Diarrhoea. Xeloda can induce the occurrence of diarrhoea, which has been observed in 50% of patients. 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. If grade 2, 3 or 4 diarrhoea occurs, administration of Xeloda should be immediately interrupted until the diarrhoea resolves or decreases in intensity to grade 1. Following grade 3 or 4

diarrhoea, subsequent doses of Xeloda should be decreased or treatment discontinued permanently (grade 4).

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 Xeloda should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-foot syndrome, subsequent doses of Xeloda should be decreased.

Cardiotoxicity. Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes. These adverse events may be more common in patients with a prior history of coronary artery disease. Cardiac arrhythmias, angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving Xeloda. 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 Xeloda 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 Xeloda 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 Xeloda 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, Xeloda use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis. Administration of Xeloda 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 Xeloda monotherapy may be resumed when bilirubin decreases to ≤ 3.0 x ULN or hepatic aminotransferases decrease to ≤ 2.5 x ULN. For combination treatment with Xeloda and docetaxel, see also section 4.2.

Renal impairment. The incidence of grade 3 or 4 adverse events 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).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with other medicinal products:

Coumarin-derivative anticoagulants: altered coagulation parameters and/or bleeding have been reported in patients taking Xeloda concomitantly with coumarin-derivative anticoagulants such as

warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating Xeloda therapy and, in a few cases, within one month after stopping Xeloda. In a clinical pharmacokinetic interaction study, after a single 20 mg dose of warfarin, Xeloda 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 Xeloda 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 Xeloda with phenytoin. Patients taking phenytoin concomitantly with Xeloda should be regularly monitored for increased phenytoin plasma concentrations.

Folinic acid: a combination study with Xeloda and folinic acid indicated that folinic acid has no major effect on the pharmacokinetics of Xeloda and its metabolites. However, folinic acid has an effect on the pharmacodynamics of Xeloda: the maximum tolerated dose (MTD) of Xeloda alone using the intermittent regimen is 3000 mg/m^2 per day whereas it is only 2000 mg/ m^2 per day when Xeloda 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, Xeloda must not be administered with sorivudine or its chemically related analogues, such as brivudine (see section 4.3).

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 Xeloda should be avoided.

Interaction with cytochrome P-450: For potential interactions with isozymes 1A2, 2C9 and 3A4, see interactions with coumarin-derivative anticoagulation.

Interferon alpha: the MTD of Xeloda 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 Xeloda was used alone.

Radiotherapy: the MTD of Xeloda alone using the intermittent regimen is 3000 mg/m^2 per day, whereas, when combined with radiotherapy for rectal cancer, the MTD of Xeloda 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.

Food Interaction: In all clinical trials, patients were instructed to administer Xeloda within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that Xeloda be administered with food. Administration with food decreases the rate of capecitabine absorption (see section 5.2).

4.6 Pregnancy and lactation

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

potential should be advised to avoid becoming pregnant while receiving treatment with Xeloda. If the patient becomes pregnant while receiving Xeloda, the potential hazard to the foetus must be explained.

It is not known whether Xeloda 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 Xeloda.

4.7 Effects on ability to drive and use machines

Xeloda may cause dizziness, fatigue and nausea. These effects may impair the ability to drive and use machines.

4.8 Undesirable effects

The adverse reactions considered to be possibly, probably, or remotely related to the administration of Xeloda have been obtained from clinical studies conducted with Xeloda monotherapy (in adjuvant therapy of colon cancer, in metastatic colorectal cancer and metastatic breast cancer) and Xeloda in combination with docetaxel in metastatic breast cancer after failure of cytotoxic chemotherapy. The most commonly reported treatment-related adverse events were gastrointestinal disorders (especially diarrhoea, nausea, vomiting, abdominal pain, stomatitis), fatigue and hand-foot syndrome (palmar-plantar erythrodysesthesia).

Safety data of Xeloda monotherapy in adjuvant treatment for colon cancer (995 patients) and metastatic colorectal cancer (596 patients) were reported in three phase III trials (Table 6). The most frequently reported treatment-related adverse reactions in these trials were gastrointestinal disorders, especially diarrhoea, nausea, vomiting, stomatitis, and hand-foot syndrome (palmar-plantar erythrodysesthesia). The safety profile of Xeloda monotherapy for the breast cancer and colorectal cancer populations is comparable.

The following headings are used to rank the undesirable effects by frequency: Very common (>1/10), common (>1/100, < 1/10) and uncommon (>1/1,000, < 1/100).

Table 6: Summary of related adverse events reported in patients treated with Xeloda monotherapy in adjuvant treatment for colon cancer and metastatic colorectal cancer (total of 1591 patients)

Body System Adverse Event	Very Common	Common
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome (57%)	Rash (7%), alopecia (6%), erythema (6%), dry skin (5%), pruritus (2%), skin hyper-pigmentation (2%), rash macular (1%); skin desquamation (1%), dermatitis (1%), pigmentation disorder (1%), nail disorder (1%)
Gastrointestinal disorders	Diarrhoea (47%), nausea (35%), stomatitis (23%), vomiting (18%), abdominal pain (11%)	Constipation (6%), upper abdominal pain (6%), dyspepsia (5%), flatulence (3%), dry mouth (3%), loose stools (2%),
General disorders and administration site conditions	Fatigue (16%), asthenia (10%)	Pyrexia (6%), lethargy (6%), oedema peripheral (3%), malaise (1%)
Metabolism and nutrition disorders	Anorexia (10%),	Dehydration (3%), decreased appetite (2%)
Nervous System Disorders	(none)	Dysgeusia (5%), dizziness (5%), headache (4%), parasthesia (3 %), lethargy (1%)
Eye disorders	(none)	Lacrimation increased (5%), conjunctivitis (4%), eye irritation (1%)
Hepatobiliary Disorders	(none)	Hyperbilirubinemia/blood bilirubin/blood bilirubin increased (3%)
Respiratory, thoracic and mediastinal disorders	(none)	Dyspnoea (3%), epistaxis (2%), cough (1%), rhinorrhea (1%)
Muskuloskeletal and connective tissue disorders	(none)	Pain in extremity (3%), back pain (2%), arthralgia (2%)
Investigations		Weight decreased (2%)
Blood and lymphatic system disorders	(none)	Neutropenia (2%), anaemia (2%)
Psychiatric disorders	(none)	Insomnia (2%), depression (1%)
Infections and infestations	(none)	Herpes simplex (1%), nasopharyngitis (1%)

Skin and subcutaneous tissue disorders (uncommon): Rash pruritic, skin discolouration, photosensitivity reaction, rash erythematous, dermatitis exfoliative, exanthema, onychorrhexis, hyperhidrosis, hypotrichosis, eczema, skin fissures, swelling face, onycholysis, palmar erythema, night sweats, skin ulcer, nail discolouration, nail ridging, rash generalized, rash maculo-papular, rash papular, penile ulceration, plantar erythema, skin lesion, actinic keratosis, localised exfoliation,nail dystrophy, pruritus generalised, rash vesicular, nail pigmentation, onychomadesis, urticaria, hyperkeratosis, purpura, rash scaly, skin inflammation

Gastrointestinal disorders(uncommon): Oral pain, gastritis, dysphagia, dry lip, lip ulceration, abdominal pain lower, abdominal distension, oesophagitis, chapped lips, lip pain, rectal haemorrhage, abdominal discomfort, gastrooesophageal reflux disease, cheilitis, haemorrhoids, aphthous stomatitis, proctalgia, colitis, glossodynia, proctitis, salivary hypersecretion, frequent bowel movements, gingival pain, intestinal obstruction, pruritus ani, Eructation, gastrointestinal haemorrhage, lip blister, small intestinal obstruction, aptyalism, enteritis, stomach discomfort, epigastric discomfort, abdominal tenderness, hypoaesthesia oral, rectal discharge, tongue ulceration, anal fissure, enterocolitis, haematochezia, melaena, ascites, bowel sounds abnormal, diarrhoea haemorrhagic, haematemesis

General disorders and administration site conditions (uncommon): Chills, influenza like illness, non-cardiac chest pain, chest pain, pain, rigors, ill-defined disorder, thirst, chest discomfort, oedema, feeling cold, feeling hot, facial pain, pitting oedema, tenderness

Metabolism and nutrition disorders (uncommon): Hypokalemia, cachexia, appetite disorder, diabetes mellitus inadequate control, hypertriglyceridaemia, malnutrition, diabetes mellitus, hypoalbuminaemia

Nervous System Disorders (uncommon): Hypoaesthesia, paresthesia oral, ageusia, disturbance in attention, syncope, hyperaesthesia, burning sensation, balance disorder, somnolence, amnesia, memory impairment, dysaethesia, ataxia, parosmia, tremor, neuropathy peripheral, dizziness postural, aphasia, peripheral sensory neuropathy

Eye disorders (uncommon): Eye pain, vision blurred, keratoconjunctivitis sicca, dry eye, eye pruritus, visual acuity reduced, eye discharge, eye redness, diplopia, conjunctival haemorrhage, eyelid pain

Respiratory, thoracic and mediastinal disorders (uncommon): Pharyngolaryngeal pain, hiccups, dyspnoea exertional, rhinitis, nasal passage irritation, dry throat, nasal ulcer, pulmonary embolism, hoarseness, haemoptysis, productive cough, wheezing, asthma, nasal discomfort, postnasal drip, throat irritation, pneumothorax

Muskuloskeletal and connective tissue disorders (uncommon): Myalgia, joint swelling, muscle cramp, bone pain, flank pain, facial pain, neck pain, musculoskeletal stiffness, muscular weakness

Blood and lymphatic system disorders (uncommon): Febrile neutropenia, leucopenia, thrombocytopenia, granulocytopenia, haemolytic anaemia, pancytopenia
Very common: lymphocytopenia (51.3–58.2%,grade 3/4 2.1–5.1%), anemia (2–41.4%, grade 3/4 1%, in combination with cisplatin or oxaliplatin with or without epirubicin 17–79%, grade 3/4 3–10.5%), thrombocytopenia (5–21.1%, grade 3/4 0.5–5.2%), neutropenia (1–30.3%, grade 3/4 <1–6%, in combination with docetaxel: 80.8%, grade 3/4: 62.9%, in combination with cisplatin with or without epirubicin: 33–85.6%, grade 3/4 16–51.1%), febrile neutropenia (mainly in combination with docetaxel and cisplatin with or without epirubicin: <1–16 %, grade 3/4 6.7%), leukopenia (3–14%, grade 3/4 3%). Common: granulocytopenia. Uncommon: pancytopenia, bone marrow depression.

Investigations (uncommon): Alanine aminotransferase increased, weight increased, hepatic enzyme increased, body temperature increased, aspartate aminotransferase increased, blood potassium decreased, haemoglobin decreased, liver function test abnormal, blood alkaline phosphatase increased, blood in stool, gamma-glutamyltransferase increased, international normalised ratio increased, blood creatinine increased

Psychiatric disorders (uncommon): Anxiety, nervousness, confusional state, depressed mood, irritability, restlessness, mood altered, sleep disorder, anger, libido deceased, nightmare, panic attack

Hepatobiliary disorders (uncommon): Hepatic steatosis, hepatomegaly, jaundice, hepatic pain

Infections and infestations (uncommon): Oral candidiasis, urinary tract infection, upper respiratory tract infection, lower respiratory tract infection, localized infection, cystitis, pneumonia, pharyngitis, vaginal candidiasis, candidiasis, influenza, nail infection, bronchitis, gastroenteritis, sepsis, folliculitis, rhinitis, vaginitis, wound infection, fungal skin infection, paronychia, fungal infection, herpes virus infection, herpes zoster, infection, tooth abscess, cellulitis, onychomycosis, tonsillitis

Vascular disorders (uncommon): Flushing, phlebitis, deep vein thrombosis, hypertension, hypotension, thrombophlebitis, hot flush, orthostatic hypotension, petechiae, thrombophlebitis superficial, peripheral coldness, phlebothrombosis, venous thrombosis limb

Cardiac disorders (uncommon): Angina pectoris, palpitations, artrial fibrillation, arrhythmia, tachycardia, sinus tachycardia, angina unstable, myocardial ischemia

Injury, poisoning and procedural complications (uncommon): Blister, contusion, sunburn, overdose, stoma site reaction

Reproductive system and breast disorders (uncommon): Balanitis, vaginal haemorrhage, vaginal burning sensation, genital erythema, genital pruritus male, phimosis

Renal and urinary disorders (uncommon): Dysuria, pollakiuria, haematuria, chromaturia, urinary incontinence, hydronephrosis, nocturia

Ear and labyrinth disorders (uncommon): Vertigo, ear pain

Immune system disorders (uncommon): Hypersensitivity

Neoplasm benign, malignant and unspecified (uncommon): Lipoma

Table 7: Laboratory abnormalities reported in patients treated with Xeloda monotherapy in adjuvant treatment for colon cancer and metastatic colorectal cancer (total 1591 patients)

	Patients with grade 1 to 4 abnormality (%)	**Patients with grade 3/4 (%)**	**Patients with grade 4 (%)**
Decreased haemoglobin	73.3	1.4	0.4
Decreased neutrophils/granulocytes	25.4	2.4	1.6
Decreased platelets	18.8	1.0	0.6
Decreased lymphocytes	83.5	21.9	4.0
Decreased sodium	26.0	0.6	0.1
Decreased potassium	24.3	0.6	0.1
Increased calcium	6.4	0.9	0.8
Decreased calcium	16.7	1.8	1.5
Increased bilirubin	49.4	21.06	2.6
Increased alkaline phosphatase	44.3	1.3	0.1
Increased ALAT (SGPT)	29.9	1.2	0.1
Increased ASAT (SGOT)	33.9	0.8	0.1

Xeloda and docetaxel in combination: The most frequent treatment-related undesirable effects (≥5%) reported in a phase III trial in breast cancer patients failing anthracycline treatment are presented in Table 8. Treatment-related undesirable effects reported in the comparator arm of this trial, using the standard dose of docetaxel, are also presented. Rare or uncommon undesirable effects, as described in the section on Xeloda monotherapy, can be expected for combination therapy as well. These are not listed in the following table.

Table 8: Summary of adverse events reported in patient treated with Xeloda in combination with docetaxel for metastatic breast cancer after failure of cytotoxic chemotherapy

Adverse Event	**Xeloda 1250 mg/m^2/bid with Docetaxel 75 mg/m^2/3 weeks (n=251)**		**Docetaxel 100 mg/m^2/ 3 weeks (n=255)**	
Body System/Adverse Event	**Total %**	**Grade 3 / 4 %**	**Total %**	**Grade 3 / 4 %**
Gastrointestinal				
Stomatitis	67	18	42	5
Diarrhoea	64	14	45	5
Nausea	43	6	35	2
Vomiting	33	4	22	1
Constipation	14	1	12	-
Abdominal pain	14	2	9	1
Dyspepsia	12	-	5	<1
Abdominal pain upper	9	-	6	1
Dry mouth	5	-	4	-
Skin and Subcutaneous				
Hand-foot Syndrome	63	24	7	1
Alopecia	41	6	42	7
Nail disorder	14	2	15	-
Dermatitis	8	-	9	1
Rash Erythematous	8	<1	4	-
Nail Discolouration	6	-	4	<1
Onycholysis	5	1	5	1
General				
Asthenia	23	3	22	5
Pyrexia	21	1	29	<1
Fatigue	21	4	25	5
Weakness	13	1	9	2
Pain in limb	9	<1	8	<1
Lethargy	6	-	5	1
Pain	6	-	2	-
Blood & lymphatic system				
Neutropenic fever	16	16	21	21
Neurological				
Taste disturbance	15	<1	14	<1
Paresthesia	11	<1	15	1
Dizziness	9	-	6	<1
Headache	7	<1	8	1
Peripheral Neuropathy	5	-	10	1
Metabolism				
Anorexia	12	1	10	1
Appetite Decreased	10	-	4	-
Dehydration	8	2	5	1
Weight Decreased	6	-	4	-
Eye				
Lacrimation increased	12	-	5	-

Adverse Event	**Xeloda 1250 mg/m^2/bid with Docetaxel 75 mg/m^2/3 weeks (n=251)**		**Docetaxel 100 mg/m^2/ 3 weeks (n=255)**	
Body System/Adverse Event	**Total %**	**Grade 3 / 4 %**	**Total %**	**Grade 3 / 4 %**
Musculoskeletal				
Myalgia	14	2	24	2
Arthralgia	11	1	18	2
Back pain	7	1	6	1
Cardiovascular				
Lower limb oedema	14	1	12	1
Respiratory				
Sore throat	11	2	7	<1
Dyspnoea	7	1	9	<1
Cough	6	<1	9	-
Epistaxis	5	<1	5	-
Infection				
Oral candidiasis	6	<1	7	<1

Table 9: Laboratory abnormalities: Xeloda in combination with docetaxel in metastatic breast cancer after failure of cytotoxic chemotherapy

Adverse Event	**Xeloda 1250 mg/m^2/bid with Docetaxel 75 mg/m^2/3 weeks (n=251)**	**Docetaxel 100 mg/m^2/ 3 weeks (n=255)**
Laboratory Abnormalities (according to NCIC/CTC)	**Grade 3 / 4 %**	**Grade 3 / 4 %**
Lymphopenia	89	84
Leukocytopenia	61	75
Neutropenia	63	72
Anemia	10	6
Thrombocytopenia	3	3
Hyperbilirubinemia	9	3

Post-Marketing Experience

The following additional serious adverse events have been identified during post-marketing exposure:
- Very rare: lacrimal duct stenosis

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: cytostatic (antimetabolite), ATC code: L01B C

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.

Adjuvant Therapy with Xeloda in colon cancer
Data from one multicenter, randomized, controlled phase 3 clinical trial in patients with stage III (Dukes' C) colon cancer supports the use of Xeloda for the adjuvant treatment of patients with colon cancer (XACT Study). In this trial, 1987 patients were randomized to treatment with Xeloda (1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period and given as 3-week cycles for 24 weeks) or 5-FU and leucovorin (Mayo Clinic regimen: 20 mg/m^2 leucovorin IV followed by 425 mg/m^2 IV bolus 5-FU, on days 1 to 5, every 28 days for 24 weeks). Xeloda was at least equivalent to IV 5-FU/LV in disease-free survival in per protocol population (hazard ratio 0.89; 95% CI 0.76-1.04). In the all-randomized population, tests for difference of Xeloda vs 5-FU/LV in disease-free and overall survival showed hazard ratios of 0.87 (95% CI 0.75 – 1.00; p = 0.053) and 0.84 (95% CI 0.69 – 1.01; p = 0.071), respectively. Relapse-free survival, censoring patients at the time of last tumour assessment in case of death unrelated to disease progression or unrelated to treatment (for disease-free survival these death cases were considered as events), was statistically different in favour of Xeloda comparing to 5-FU/LV [HR 0.86 (95% CI 0.74 – 0.99; p = 0.041)]. The median follow up at the time of the analysis was 3.8 years.

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

Combination therapy with Xeloda and docetaxel in locally advanced or metastatic breast cancer
Data from one multicenter, randomised, controlled phase 3 clinical trial support the use of Xeloda 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 Xeloda (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 Xeloda + docetaxel combination arm (p=0.0126). Median survival was 442 days (Xeloda + docetaxel) vs. 352 days (docetaxel alone). The overall objective response rates in the all-randomised population (investigator assessment) were 41.6% (Xeloda + docetaxel) vs. 29.7% (docetaxel alone); p = 0.0058. Time to progressive disease was superior in the Xeloda + docetaxel combination arm (p<0.0001). The median time to progression was 186 days (Xeloda + docetaxel) vs. 128 days (docetaxel alone).

Monotherapy with Xeloda after failure of taxanes, anthracycline containing chemotherapy, and for whom anthracycline therapy is not indicated
Data from two multicenter phase 2 clinical trials support the use of Xeloda 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 Xeloda (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.

An analysis of safety data in patients treated with Xeloda monotherapy (colorectal cancer) with baseline renal impairment showed an increase in the incidence of treatment-related grade 3 and 4 adverse events 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.

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

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.

Protein binding: *in vitro* human plasma studies have determined that capecitabine, 5'-DFCR, 5'-DFUR and 5-FU are 54%, 10%, 62% and 10% protein bound, mainly to albumin.

Metabolism: capecitabine is first metabolised by hepatic carboxylesterase to 5'-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumour tissues. Further catalytic activation of 5'-DFUR then occurs by thymidine phosphorylase (ThyPase). The enzymes involved in the catalytic activation are found in tumour tissues but also in normal tissues, albeit usually at lower levels. The sequential enzymatic biotransformation of capecitabine to 5-FU

leads to higher concentrations within tumour tissues. In the case of colorectal tumours, 5-FU generation appears to be in large part localised in tumour stromal cells. Following oral administration of capecitabine to patients with colorectal cancer, the ratio of 5-FU concentration in colorectal tumours to adjacent tissues was 3.2 (ranged from 0.9 to 8.0). The ratio of 5-FU concentration in tumour to plasma was 21.4 (ranged from 3.9 to 59.9, n=8) whereas the ratio in healthy tissues to plasma was 8.9 (ranged from 3.0 to 25.8, n=8). Thymidine phosphorylase activity was measured and found to be 4 times greater in primary colorectal tumour than in adjacent normal tissue. According to immunohistochemical studies, thymidine phosphorylase appears to be in large part localised in tumour stromal cells.

5-FU is further catabolised by the enzyme dihydropyrimidine dehydrogenase (DPD) to the much less toxic dihydro-5-fluorouracil (FUH_2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureidopropionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β-alanine (FBAL) which is cleared in the urine. Dihydropyrimidine dehydrogenase (DPD) activity is the rate limiting step. Deficiency of DPD may lead to increased toxicity of capecitabine (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 Xeloda on the pharmacokinetics of either docetaxel or paclitaxel and vice versa showed no effect by Xeloda 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 Xeloda 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.

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: anhydrous lactose, croscarmellose sodium, hypromellose, microcrystalline cellulose, magnesium stearate.

Tablet coating: titanium dioxide (E171), hypromellose , yellow and red iron oxide (E172), talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Nature: PVC/PE/PVDC blisters

Content: 120 film-coated tablets (12 blisters of 10 tablets)

7. MARKETING AUTHORISATION HOLDER

F. Hoffmann-La Roche Ltd
124 Grenzacherstrasse Basel,
CH-4070 Switzerland