New Zealand Datasheet

1 PRODUCT NAME

Capercit tablets

Capecitabine 150 mg and 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablets contains 150 mg or 500 mg of capecitabine.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capercit film-coated tablets 150 mg: light peach colour film–coated tablet of biconvex, oblong shape with '150' debossed on one side and 'RDY' on the other side.

Capercit film-coated tablets 500 mg: peach colour film–coated tablet of biconvex, oblong shape with '500' debossed on one side and 'RDY' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast Cancer

Capercit tablets are indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline containing chemotherapy regimen unless therapy with these and other standard agents are clinically contraindicated.

Capercit tablets in combination with docetaxel are indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy.

Colon Cancer

Capercit tablets are indicated for the adjuvant treatment of patients with Dukes' stage C and high-risk stage B, colon cancer, either as monotherapy or in combination with oxaliplatin.

Colorectal Cancer

Capercit tablets are indicated for the first-line treatment of patients with metastatic colorectal cancer.

Oesophagogastric Cancer

Capercit tablets are indicated for the first-line treatment of patients with advanced oesophagogastric cancer in combination with a platinum-based regimen.

4.2 Dose and method of administration

Standard Dosage

Capercit tablets should be swallowed with water within 30 minutes after the end of a meal.

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

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

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

Combination therapy - Colorectal cancer
In combination with oxaliplatin with or without bevacizumab the recommended starting dose of capecitabine is 1000 mg/m^2 twice daily for 2 weeks followed by a 7 day rest period. The first dose of capecitabine is given on the evening of day 1 and the last dose is given on the morning of day 15.

Given as a 3 week cycle, on day 1 every 3 weeks bevacizumab is administered as a 7.5 mg/kg intravenous infusion over 30 to 90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours.

Combination therapy – colon cancer
In combination with oxaliplatin the recommended starting dose of capecitabine is 1000 mg/m^2 twice daily for 2 weeks followed by a 7 day rest period. The first dose of capecitabine is given on the evening of day 1 and the last dose is given on the morning of day 15. Given as a 3 week cycle, on day 1 oxaliplatin is administered as a 130 mg/m^2 intravenous infusion over 2 hours. Adjuvant treatment is recommended for a total of 24 weeks.

Combination therapy - Oesophagogastric cancer
In triplet combination with epirubicin and cisplatin/oxaliplatin for oesophagogastric cancer, the recommended starting dose of capecitabine is 625 mg/m^2 twice daily as a continuous regimen. Epirubicin is administered as a 50 mg/m^2 intravenous bolus on day 1 of a 3 week cycle. Platinum therapy should consist of either cisplatin administered at a dose of 60 mg/m^2 given as a 2 hour intravenous infusion on day 1 of a 3 week cycle; or oxaliplatin administered at a dose of 130 mg/m^2 given as a 2 hour intravenous infusion on day 1 of a 3 week cycle.

In combination with cisplatin (doublet) with or without trastuzumab for gastric cancer, the recommended starting dose of capecitabine is 1000 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period. The first dose of capecitabine is given on the evening of day 1 and the last dose is given on the morning of day 15. Cisplatin is administered at a dose of 80 mg/m^2 as a 2 hour intravenous infusion on day 1 of a 3-week cycle.

Pre-medication to maintain adequate hydration and anti-emesis should be started prior to oxaliplatin/cisplatin administration for patients receiving capecitabine in combination with one of these agents.

The capecitabine dose is calculated according to body surface area. The following tables show examples of the standard and reduced dose calculations for a starting dose of capecitabine of 1250 mg/m^2 or 1000 mg/m^2.

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 (m2)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤ 1.26	1500	-	3	1150	800
1.27 - 1.38	1650	1	3	1300	800
1.39 - 1.52	1800	2	3	1450	950
1.53 - 1.66	2000	-	4	1500	1000
1.67 - 1.78	2150	1	4	1650	1000
1.79 - 1.92	2300	2	4	1800	1150
1.93 - 2.06	2500	-	5	1950	1300
2.07 - 2.18	2650	1	5	2000	1300
≥ 2.19	2800	2	5	2150	1450

Table 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/m2	**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 (m2)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤ 1.26	1150	1	2	800	600
1.27 - 1.38	1300	2	2	1000	600
1.39 - 1.52	1450	3	2	1100	750
1.53 - 1.66	1600	4	2	1200	800
1.67 - 1.78	1750	5	2	1300	800
1.79 - 1.92	1800	2	3	1400	900
1.93 - 2.06	2000	-	4	1500	1000
2.07 - 2.18	2150	1	4	1600	1050
≥ 2.19	2300	2	4	1750	1100

Dosage Adjustment during Treatment

General

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

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

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

Table 3 - Toxicity grades for some relevant adverse events

Intensity of Clinical Adverse Events*				
Adverse Events	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-threatening (Grade 4)
Diarrhoea	Increase of 1 – 3 stools/day	Increase of 4 - 6 stools/day or nocturnal stools	Increase of 7 – 9 stools/day or incontinence and malabsorption	Increase of ≥10 stools/day or grossly bloody diarrhoea or the need for parenteral support
Nausea	No significant effect on food intake	Food intake significantly decreased but able to eat intermittently	Unable to eat	
Vomiting	1 episode in a 24-hour period	2 - 5 episodes in a 24-hour period	6 - 10 episodes in 24-hour period	> 10 episodes in a 24-hour period or the need for parenteral support
Hand-foot syndrome (clinical domain)	Numbness, tingling, painless erythema, and swelling	Painful erythema and swelling and swelling	Moist desquamation, ulceration, blistering and severe pain ,	
Hand-foot syndrome (functional domain)	Discomfort which which does not disrupt normal activities	Discomfort which affects activities of daily living	Severe discomfort, unable to work or perform activities of daily living	
Stomatitis	Erythema without pain	Painful erythema oedema, or ulcers,	Painful erythema restricting ability to eat	

*The intensity of clinical adverse events was graded on a 4-point scale following the National Cancer Institute of Canada Common Toxicity Criteria (NCIC CTC).
++ Criteria as established by Roche protocol.

Haematology: Patients with baseline neutrophil counts of < 1.5 x 10^9/L and/or thrombocyte counts of < 100 x 10^9/L should not be treated with capecitabine. If unscheduled laboratory assessments during a treatment cycle show Grade 3 or 4 haematologic toxicity, treatment with capecitabine should be interrupted.

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

Table 4: Capecitabine dose reduction schedule

Toxicity 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	Not applicable
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	Not applicable
Grade 4		
1st appearance	Discontinue permanently or If physician deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0-1	50%
2nd appearance	Discontinue permanently	Not applicable

#According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) Common Toxicity Criteria (version 1) or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute (version 3.0). For hand-foot syndrome and hyperbilirubinaemia see Section 4.4.

General combination therapy
Dose modifications for toxicity when capecitabine is used in combination with other therapies should be made according to the table above for capecitabine, and according to the appropriate product information for the other agent(s).

At the beginning of a treatment cycle, if a treatment delay is indicated for either capecitabine or the other agent(s), then administration of all agents should be delayed until the requirements for restarting all medicines are met.

During a treatment cycle for those toxicities considered by the treating physician not to be related to capecitabine [for example, neurotoxicity, ototoxicity, neurosensory toxicity, fluid retention (pleural effusion, pericardial effusion or ascites), bleeding, gastrointestinal perforations, proteinuria, hypertension], then capecitabine should be continued and the dose of the other agent adjusted according to the appropriate product information.

If the other agent(s) have to be discontinued permanently, capecitabine treatment can be resumed when the requirements for restarting capecitabine are met.

This advice is applicable to all indications and to all special populations.

Dosage Adjustments in Special Populations

Hepatic Impairment due to liver metastases: Patients with mild to moderate hepatic impairment due to liver metastases, should be carefully monitored when capecitabine is administered. No starting dose reduction is necessary. Patients with severe hepatic impairment have not been studied.

Renal Impairment: In patients with moderate renal impairment (creatinine clearance 30 — 50 mL/min [Cockroft and Gault]) at baseline, a dose reduction to 75% for a starting dose of 1250 mg/m^2 is recommended. In patients with mild renal impairment (creatinine clearance 51 - 80 mL/min) no adjustment in starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a Grade 2, 3, or 4 adverse event with subsequent dose adjustment as outlined in Table 4 above (see Pharmacokinetics in special populations). If the calculated creatinine clearance decreases during treatment to a value below 30 mL/min, capecitabine should be discontinued. The dose adjustment recommendations for patients with moderate renal impairment apply both to monotherapy and combination use. For dosage calculations, see Tables 1 and 2.

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

Elderly: For capecitabine monotherapy, no adjustment of the starting dose is needed. However, severe Grade 3 or 4 treatment-related adverse reactions were more frequent in patients over 80 years of age compared to younger patients. When capecitabine was used in combination with other agents, elderly patients (≥ 65 years of age) experienced more Grade 3 and Grade 4 adverse drug reactions (Adverse reactions), and Adverse reactions that led to discontinuation, compared to younger patients. Careful monitoring of elderly patients is advisable.

In combination with docetaxel, an increased incidence of Grade 3 or 4 treatment-related adverse events and treatment-related serious adverse events was observed in patients 60 years of age or more. For patients 60 years of age or more treated with the combination of capecitabine plus docetaxel, a starting dose reduction of capecitabine to 75% (950 mg/m^2 twice daily) is recommended. For dosage calculations, see Table 2.

In combination with irinotecan: for patients 65 years of age or more, a starting dose reduction of capecitabine to 800mg/m^2 twice daily is recommended.

4.3 Contraindications

Capercit tablets are contraindicated in patients who have:

- a known hypersensitivity to capecitabine or to any of the excipients contained in the tablets
- a history of severe and unexpected reactions to fluoropyrimidine therapy or with known hypersensitivity to fluorouracil
- severe renal impairment (creatinine clearance below 30 mL/min)
- treatment with sorivudine or its chemically related analogues, such as brivudine
- known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4).

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

4.4 Special warnings and precautions for use

Diarrhoea: Capecitabine can induce diarrhoea, which can sometimes be severe. Patients with severe diarrhoea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. Standard anti-diarrhoea treatments (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. 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 should be applied for the precipitating adverse event as necessary (see Section 4.2).

Dehydration may cause acute renal failure, especially in patients with pre-existing compromised renal function or when capecitabine is given concomitantly with known nephrotoxic agents. Fatal outcome of renal failure has been reported in these situations (see Section 4.8).

Dihydropyrimidine dehydrogenase (DPD) deficiency
Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of DPD activity. Patients with low or absent DPD activity, an enzyme involved in fluorouracil degradation, are at increased risk for severe, life-threatening, or fatal adverse reactions caused by fluorouracil. Patients with certain homozygous or certain compound heterozygous mutations in the DPYD gene locus that cause complete or near complete absence of DPD activity, have the highest risk of life-threatening or fatal toxicity and should not be treated with capecitabine. No dose has been proven safe for patients with complete absence of DPD activity.

For patients with partial DPD deficiency where the benefits of capecitabine are considered to outweigh the risks (taking into account the suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen), these patients must be treated with extreme caution, initially with a substantial dose reduction and frequent subsequent monitoring and dose adjustment according to toxicity.

In patients with unrecognised DPD deficiency treated with capecitabine, life-threatening toxicities manifesting as acute overdose may occur. In the event of Grade 2-4 acute toxicity, treatment must be discontinued immediately. Permanent discontinuation should be considered based on clinical assessment of the onset, duration and severity of the observed toxicities (see Section 4.9).

Cardiotoxicity
The spectrum of cardiotoxicity observed with capecitabine is similar to that of other fluorinated pyrimidines. This includes myocardial infarction, angina, dysrhythmias, cardiac arrest, cardiac failure and electrocardiographic changes. These adverse events may be more common in patients with a prior history of coronary artery disease.

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

Capecitabine can induce hand-foot syndrome (palmar-plantar erythrodysaesthesia or chemotherapy induced acral erythema), which is a cutaneous toxicity. For patients receiving capecitabine monotherapy in the metastatic setting, the median time to onset was 79 days (range from 11 to 360 days), with a severity range of Grades 1 to 3.

Grade 1 is defined by numbness, dysaesthesia/paraesthesia, tingling, or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activity. Grade 2 hand-foot syndrome is defined as painful erythema and swelling of the hands and/or feet that results in discomfort affecting the patient's activities of daily living. Grade 3 hand-foot syndrome is defined as moist desquamation, ulceration, blistering and severe pain of the hands and/or feet that results in severe discomfort that causes the patient to be unable to work or perform activities of daily living.

If Grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to Grade 1. Following Grade 3 hand-foot syndrome, subsequent doses of capecitabine should be decreased (see Dosage and Administration). When capecitabine and cisplatin are used in combination, the use of vitamin B6 (pyroxidine) 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.

Capecitabine can induce hyperbilirubinaemia. 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 may be resumed when bilirubin decreases to ≤ 3.0 x ULN or hepatic aminotransferases decrease to ≤ 2.5 x ULN.

In a medicine 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).

General

Patients treated with capecitabine should be carefully monitored for toxicity. Most adverse events are reversible and do not require permanent discontinuation of therapy, although doses may have to be withheld or reduced (see also Section 4.2).

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

compared to patients less than 60 years of age.

Renal Impairment

Physicians should exercise caution when capecitabine is administered to patients with impaired renal function. As seen with 5-FU the incidence of treatment-related Grade 3 or 4 adverse events was higher in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) (see Section 4.2).

Hepatic Impairment

Patients with hepatic impairment should be carefully monitored when capecitabine is administered. The effect of hepatic impairment not due to liver metastases or severe hepatic impairment on the disposition of capecitabine is not known (see Sections 4.2 and 5.2).

DPD Deficiency:

Rare cases of severe stomatitis, diarrhoea, neutropenia and neurotoxicity have been associated with 5- FU exposure in patients with a deficiency in DPD activity.

Patients who have an absent or low activity of DPD (dihydropyrimidine dehydrogenase is an enzyme involved in the degradation of fluorouracil) are at an increased risk of life-threatening, fatal or severe adverse reaction. DPD-deficiency related toxicity usually occurs during the first cycle of treatment or after dose increase.

It is recommended that DPD status of the patient is determined before therapy through laboratory testing for the detection of total or partial DPD-deficiency, where testing is available. It can also be useful when evaluating patients experiencing capecitabine-related toxicities.

It has been established that patients with specific homozygous or compound heterozygous mutations in the gene locus for DPYD (i.e. c.1236G>A/HapB3, DPYD*2A, c.2846A>T, and c.1679T>G variants) can result in near complete absence or total absence of DPD enzymatic activity (as per laboratory assays) These patients have the highest risk of fatal toxicity or life threatening toxicity – and should NOT be administered capecitabine (section 4.3).

For those patients with a complete absence of DPD (dihydropyrimidine dehydrogenase) activity, no dose has been proven safe.

Patients with specific heterozygous DPYD variants (i.e. c.1236G>A/HapB3, DPYD*2A, c.2846A>T, and c.1679T>G variants) when treated with capecitabine, have an increased risk of severe toxicity.

There is around 1% frequency in Caucasian patients of the heterozygous DPYD*2A genotype in the DPYD gene, 0.07 to 0.1% for c.1679T>G1, 2.6 to 6.3% for c.1236G>A/HapB3 and 1.1% for c.2846A>T variants. Data in populations other than Caucasian, on the frequency of these DPYD variants is limited. Other rare variants cannot be excluded that also may be associated with an increased risk of severe toxicity.

For patients with partial DPD (dihydropyrimidine dehydrogenase) deficiency (with heterozygous DPYD gene mutations) where the benefits of capecitabine are considered to outweigh the risks (taking into account the suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen), these patients must be treated with extreme caution, initially with a substantial dose reduction and frequent subsequent monitoring and dose adjustment according to toxicity. To avoid serious toxicity, a reduction of the starting dose should be considered in these patients. In patients with partial DPD activity (as measured by specific

test), there is not sufficient data for a specific dose to be recommended.

It has been reported that there has been a greater risk of side effects reported with c.1679T>G and DPYD*2A, gene variants due to a greater reduction in enzymatic activity than the other variants. With reduced doses the effects on clinical efficacy are uncertain at this time. Therefore, in the absence of serious toxicity the dose could be increased, while carefully monitoring the patient.

For patients who have had a negative test for the above-mentioned alleles, there is still a risk of adverse events that are severe.

In patients with unrecognised DPD deficiency treated with capecitabine as well as in those patients who test negative for specific DPYD variations, life-threatening toxicities manifesting as acute overdose may occur. In the event of Grade 2 to 4 acute toxicity, treatment must be discontinued immediately. Permanent discontinuation should be considered based on clinical assessment of the onset, duration and severity of the observed toxicities.

4.5 Interaction with other medicines and other forms of interaction

Coumarin Anticoagulants: Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. In a clinical interaction study, after a single 20 mg dose of warfarin, capecitabine treatment increased the AUC of S-warfarin by 57% with a 91% increase in INR value. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolities. Patients taking coumarin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR) and the anticoagulant dose adjusted accordingly.

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

Cytochrome P450 2C9: No formal interaction studies with capecitabine and other medicines known to be metabolised by the cytochrome P450 2C9 isoenzyme have been conducted. Care should be exercised when capecitabine is co-administered with these medicines.

Interaction with Food

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.

Antacid: The effect of an aluminium hydroxide and magnesium hydroxide containing antacid on the pharmacokinetics of capecitabine was investigated in 12 cancer patients. There was a small increase in plasma concentrations of capecitabine and one metabolite (5'DFCR); there was no effect on the 3 major metabolites (5'DFUR, 5-FU and FBAL).

Leucovorin (folinic acid): A phase I study evaluating the effect of leucovorin on the pharmacokinetics of capecitabine was conducted in 22 cancer patients. Leucovorin has no effect on the pharmacokinetics of capecitabine and its metabolites. However, leucovorin has an effect on the pharmacodynamics of capecitabine and its toxicity may be enhanced by leucovorin.

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

Oxaliplatin: No clinically significant differences in exposure to capecitabine or its metabolites, free platinum or total platinum occur when capecitabine and oxaliplatin were administered in combination, with or without bevacizumab.

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

4.6 Fertility, pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

No information available.

4.8 Undesirable effects

Clinical Trials
Adverse reactions considered by the investigator to be possibly, probably, or remotely related to the administration of capecitabine have been obtained from clinical studies conducted with capecitabine monotherapy (in adjuvant therapy of colon cancer, in metastatic colorectal cancer and metastatic breast cancer), and clinical studies conducted with capecitabine in combination with different chemotherapy regimens for

multiple indications. Adverse reactions are added to the appropriate category in the tables below according to the highest incidence from the pooled analysis of seven clinical trials. Within each frequency grouping, Adverse reactions are listed in descending order of seriousness. Frequencies are defined as very common ≥ 1/10, common ≥ 5/100 to <1/10, and uncommon ≥ 1/1000 to < 1/100.

Capecitabine in Monotherapy

Safety data of capecitabine monotherapy were reported for patients who received adjuvanttreatment for colon cancer and for patients who received treatment for metastatic breast cancer or metastatic colorectal cancer. The safety information includes data from a phase III trial in adjuvant colon cancer (995 patients treated with capecitabine and 974 treated with IV 5- FU/leucovorin) and from 4 phase II trials in female patients with breast cancer (*n* = 319) and 3 trials (one phase II and two phase III trials) in male and female patients with colorectal cancer (*n*= 630). The safety profile of capecitabine monotherapy is comparable in patients who received adjuvant treatment for colon cancer and in those who received treatment for metastatic breast cancer or metastatic colorectal cancer. The intensity of Adverse reactions was graded according to the toxicity categories of the NCIC CTC grading system.

Table 5 Summary of Adverse reactions reported in ≥ 5% of patients treated with capecitabine monotherapy

Body System ADR	**Very Common (≥ 10%)**	**Common (≥ 5% - < 10%)**
Metabolism and nutrition disorders	Anorexia (G3/4: 1%)	Dehydration (G3/4: 3%) Appetite decreased (G3/4: < 1%)
Nervous system disorders		Paraesthesia Dysgeusia (G3/4: < 1%) Headache (G3/4: < 1%) Dizziness (excl. vertigo) (G3/4: < 1%)
Eye disorders		Lacrimation increased Conjunctivitis (G3/4: <1%)
Gastrointestinal disorders	Diarrhoea (G3/4: 13%) Vomiting (G3/4: 4%) Nausea (G3/4: 4%) Stomatitis (all)# (G3/4: 4%) Abdominal pain (G3/4: 3%)	Constipation (G3/4: < 1%) Abdominal pain upper (G3/4: < 1%) Dyspepsia (G3/4: < 1%)
Hepatobiliary disorders		Hyperbilirubinemia (G3/4: 1%)
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome (G3/4: 17%) Dermatitis (G3/4: < 1%)	Rash Alopecia Erythema (G3/4: 1%) Dry Skin (G3/4: < 1%)
General disorders and administration site conditions	Fatigue (G3/4: 3%) Lethargy (G3/4: < 1%)	Pyrexia (G3/4: < 1%) Weakness (G3/4: < 1%) Asthenia (G3/4: < 1%)

#stomatitis, mucosal inflammation, mucosal ulceration, mouth ulceration

Skin fissures were reported to be at least remotely related to capecitabine in less than 2% of the patients in seven completed clinical trials (*n* = 949).

The following adverse reactions represent known toxicities with fluoropyrimidine therapy and were reported to be at least remotely related to capecitabine in less than

5% of patients in seven completed clinical trials (*n* = 949).

Gastrointestinal disorders: dry mouth, flatulence, adverse reactions related to inflammation/ulceration of mucous membranes such as oesophagitis, gastritis, duodenitis, colitis, gastrointestinal haemorrhage

Cardiac disorders: lower limb oedema, cardiac chest pain including angina, cardiomyopathy, myocardial ischemia/infarction, cardiac failure, sudden death, tachycardia, atrial arrhythmias including atrial fibrillation, and ventricular extrasystoles

Nervous system disorders: taste disturbance, insomnia, confusion, encephalopathy, and cerebellar signs such as ataxia, dysarthria, impaired balance, abnormal coordination

Blood and lymphatic system disorders: anaemia, bone marrow depression, pancytopenia.

Skin and subcutaneous tissue disorders: pruritus, localised exfoliation, skin hyperpigmentation, nail disorders, photosensitivity reactions, radiation recall syndrome

General disorders and administration site conditions: asthenia, pain in limb, lethargy, chest pain (non-cardiac)

Eye: eye irritation

Respiratory: dyspnoea, cough

Musculoskeletal: back pain, myalgia, arthralgia

Psychiatric disorders: depression

Hepatic failure and cholestatic hepatitis have been reported during clinical trials and post-marketing exposure. A causal relationship with capecitabine has not been established.

Capecitabine in Combination therapy

Table 6 lists adverse reactions associated with the use of capecitabine in combination therapy with different chemotherapy regimens in multiple indications and occurred in addition to those seen with monotherapy and/or at a higher frequency grouping. The safety profile was similar across all indications and combination regimens. These reactions occurred in ≥ 5% of patients treated with capecitabine in combination with other chemotherapies. Adverse drug reactions are added to the appropriate category in the table according to the highest incidence seen in any of the major clinical trials. Some of the adverse reactions are reactions commonly seen with chemotherapy (e.g. peripheral sensory neuropathy with docetaxel or oxaliplatin, hypertension seen with bevacizumab); however, an exacerbation by capecitabine therapy cannot be excluded.

Table 6 Very common and common adverse reactions for capecitabine in combination with different chemotherapies in addition to those seen for capecitabine monotherapy.

Body System Adverse Event Infections and Infestations	**Very Common ≥ 10%**	**Common ≥ 5% to < 10%** Infection+ Oral candidiasis
Infections and Infestations		Infection+ Oral candidiasis
Blood and lymphatic system disorders	Neutropenia + Leukopenia + Febrile neutropenia+ Thromboyctopenia + Anaemia +	
Metabolism and nutrition disorders	Appetite decreased	Hypokalaemia Weight Decreased
Psychiatric disorders		Insomnia
Nervous system disorders	Neuropathy peripheral Peripheral sensory neuropathy Neuropathy Taste disturbance Paraesthesia Dysgeusia Dysaesthesia Headache	Hypoaesthesia
Eye disorders	Lacrimation increased	
Vascular Disorders	Thrombosis/embolism Hypertension Lower limb oedema	
Respiratory	Dysaesthesia pharynx Sore throat	Epistaxis Dysphonia rhinorrhoea Dyspnoea
Gastrointestinal disorders	Constipation Dyspepsia	Dry mouth
Skin and subcutaneous tissue disorders	Alopecia Nail disorder	
Musculoskeletal and connective tissue disorders	Arthragia Myalgia Pain in extremity	Pain in jaw Back Pain
General disorders and administration site conditions	Pyrexia Asthenia Weakness Temperature intolerance	Fever[+] Pain

Frequencies based on all grades except those denoted with[+], which are based on G3/4 Adverse reactions only

Hypersensitivity reactions (2%) and cardiac ischaemia/infarction (3%) have been reported commonly for capecitabine in combination with other chemotherapy but in less than 5% of patients.

Rare or uncommon Adverse reactions reported for capecitabine in combination with other chemotherapy are consistent with the Adverse reactions reported for capecitabine monotherapyy or the combination product monotherapy (refer to the product information document for the combination product).

Laboratory Abnormalities

The following table displays laboratory abnormalities observed in 995 patients (adjuvant colon cancer) and 949 patients (metastatic breast cancer and colon cancer), regardless of relationship to treatment with capecitabine.

Table 7 Laboratory abnormalities[a] : capecitabine monotherapy in adjuvant colon cancer and in metastatic breast and colorectal cancer

Parameter[a]	**Capecitabine 1250 mg/m^2 twice daily intermittent**
	Patients with Grade 3 / 4 abnormality (%)
Increased ALAT (SGPT)	1.6
Increased ASAT (SGOT)	1.1
Increased alkaline phosphatase	3.5
Increased calcium	1.1
Decreased calcium	2.3
Decreased granulocytes	0.3
Decreased hemoglobin	3.1
Decreased lymphocytes	44.4
Decreased neutrophils	3.6
Decreased neutrophils/granulocytes	2.4
Decreased platelets	2.0
Decreased potassium	0.3
Increased serum creatinine	0.5
Decreased sodium	0.4
Increased bilirubin	20
Hyperglycemia	4.4

[a]*Laboratory abnormalities were graded according to the categories of the NCIC CTC GradingSystem.*

Post-marketing experience

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

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

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

Capecitabine is a fluoropyrimidine carbamate derivative that was designed as an orally administered, tumour-activated and tumour-selective cytotoxic agent.

Capecitabine is non-cytotoxic *in vitro*. However, *in-vivo,* it is sequentially coverted to the cytotoxic moiety, fluorouracil (5-FU), which is further metabolised.

Formation of 5-FU is catalysed preferentially at the tumour site by the tumour-associated angiogenic factor thymidine phosphorylase (dThdPase), thereby minimising the exposure of healthy tissues to systemic 5-FU.

The sequential enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations of 5-FU within tumour tissues. Following oral administration of capecitabine to patients with colorectal cancer (n = 8), the ratio of 5-FU concentration in colorectal tumours to adjacent tissues was 3.2 (range, 0.9 to 8.0). The ratio of 5-FU concentration in tumour to plasma was 21.4 (range, 3.9 to 59.9) whereas the ratio in healthy tissues to plasma was 8.9 (range, 3.0 to 25.8). Thymidine phosphorylase activity was four times greater in primary colorectal tumour than in adjacent normal tissue.

Several human tumours, such as breast, gastric, colorectal, cervical and ovarian cancers, have a higher level of thymidine phosphorylase (capable of converting 5'-DFUR [5-deoxy-5-fluorouridine] to 5-FU) than corresponding normal tissues.

Normal and tumour cells metabolise 5-FU to 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor N510~methylenetetrahydrOfolate bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from uracil. Thymidylate is the necessary precursor of thyrnidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

Clinical Trials

Colon and Colorectal Cancer Monotherapy - adjuvant colon cancer

Data from one multicentre, randomised, controlled phase 3 clinical trial in patients with Dukes Stage 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 I-week rest period and given as 3-week cycles for 24 weeks) or 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 for 24 weeks). Capecitabine was at least equivalent to IV 5-FU/LV in disease-free survival (DFS) (p = 0.0001, non-inferiority margin 1 .2). In the all-randomised population, tests for difference of capecitabine vs. 5-FU/LV in DFS and overall survival (OS) showed hazard ratios of 0.88 (95% CI 0.77 — 1.01; p = 0.068) and (95% CI 0.74 — 1.01; p = 0.060), respectively. The median follow up at the time of the analysis was 6.9 years.

Study M66001 did not include patients with Dukes' stage B disease. However, the findings of the study are considered to support the use of capecitabine as adjuvant therapy in patients with high- risk stage B disease, such as those with inadequately sampled nodes, T4 lesions, perforation or poorly differentiated histology.

Combination therapy - adjuvant colon cancer

Data from a multicentre, randomised, controlled phase III 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). 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 7 day rest period) in combination with oxaliplatin (130 mg/m^2 intravenous infusion over 2 hours on day 1 every 3 weeks); 942 patients were randomised to bolus 5-FU and leucovorin. In the primary analysis (ITT population), median observation time was 57 months for DFS and 59 months for OS. XELOX was shown to be significantly superior to 5-FU/LV (HR=0.80, 95% CI=[0.69; 0.93]; p=0.0045). The 3 year DFS rate was 71% for XELOX versus 67% for 5-FU/LV. The analysis for the secondary endpoint of relapse free survival (RFS) supports these results with a HR of 0.78 (95% CI= [0.67; 0.92]; p=0.0024) for XELOX vs. 5- FU/LV. XELOX showed a trend towards superior OS with a HR of 0.87 (95% CI=[0.72; 1.05]; p=0.1486). The 5 year OS rate was 78% for XELOX versus 74% for 5-FU/LV.

Monotherapy - metastatic colorectal cancer

Data from two identically-designed, multicenter, randomised, controlled phase III clinical trials (SO14695; SO14796) conducted in 120 centres internationally, compared capecitabine with 5FU in combination with leucovorin (Mayo regimen) as first-line chemotherapy in patients with advanced and/or 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) and 604 patients were randomised to treatment with 5- FU/leucovorin (Mayo regimen: 20 mg/m^2 leucovorin IV followed by 425 mg/m^2 IV bolus 5-FU, on days 1 to 5, every 28 days).

The overall objective response rates in the all-randomised population (investigator assessment) were 25.7% (capecitabine) vs. 16.7% (Mayo regimen); p < 0.0002. The median time to progression was 140 days (capecitabine) vs. 144 days (Mayo regimen). Median survival was 392 days (capecitabine) vs. 391 days (Mayo regimen).

Combination therapy - first-line treatment of metastatic colorectal cancer

Data from a multicenter, randomised, controlled phase III clinical study (NO16966) support the use of capecitabine in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab (BV) for the first-line treatment of metastastic colorectal cancer. The study contained two parts: an initial 2-arm part in which patients were randomised to two different treatment groups, XELOX or FOLFOX-4, and a subsequent 2x2 factorial part with four different treatment groups, XELOX + placebo (P), FOLFOX-4 + P, XELOX+BV, and FOLFOX-4 + BV. The treatment regimens are summarised in the table below.

Table 8: Treatment regimens in study NO16966

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + BV	Oxaliplatin Leucovorin 5- Fluorouracil	85 mg/m2 IV 2 h 200 mg/m2 IV 2 h 400 mg/m2 IV bolus, 600 mg/ m2 IV 22 h	Oxaliplatin on Day 1, every 2 weeks Leucovorin on Day 1 and 2, every 2 weeks 5-fluorouracil IV bolus/infusion, each on Days 1 and 2 , every 2 weeks
	Placebo or Avastin	5 mg/kg IV 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX + BV	Oxaliplatin Capecitabine	130 mg/m2 IV 2 h 1000 mg/m2 oral bd	Oxaliplatin on Day 1, every 3 weeks Capecitabine oral bd for 2 weeks (followed by 1 week off treatment)
	Placebo or BV	7.5 mg/kg IV 30 - 90 min	ay 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 (PFS) in the eligible per-protocol population (EPP), with progression determined by the study investigators who were not blinded to treatment allocation (see Table 5). The criterion set for concluding non- inferiority was that the upper limit of the 97.5% confidence interval for the hazard ratio for PFS was less than 1.23. The results for OS are similar to those reported for PFS. A comparison of XELOX plus BV versus FOLFOX-4 plus BV was a pre-specified exploratory analysis. In this treatment subgroup comparison, XELOX plus BV was similar compared to FOLFOX-4 plus BV in terms of PFS (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 included in the table below.

Table 9: Key non-inferiority efficacy results for the primary analysis and 1 year follow-up data (EPP population, Study NO16966)

PRIMARY ANALYSIS			
XELOX/XELOX+P/ XELOX-A (EPP#: *n* = 967; ITT; *n=1017*)**		**FOLFOX-4/FOLFOX-4+P/ FOLFOX-4+Avastin (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	1.0 (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. The efficacy in terms of Overall Response Rate (ORR), Progression Free Survival (PFS) and Overall Survival (OS) was similar to that reported in pivotal studies of 5-FU, leucovorin, and irinotecan (FOLFIRI).

Capecitabine at a starting dose of 800 mg/m^2 for 2 weeks every 3 weeks in combination with irinotecan and Avastin (bevacizumab) was studied for the first-line treatment of patients with metastatic colorectal cancer, in a multicentre, randomised, controlled phase II study (AIO KRK0604). One hundred and twenty eight patients were randomised to treatment with capecitabine combined with irinotecan (XELIRI) + Avastin (XELIRI-A): capecitabine (800 mg/m^2 bd for two weeks followed by a 7-day rest period), irinotecan (200 mg/m^2 as a 30 to 90 minute infusion on day 1 every 3 weeks) and Avastin (7.5 mg/kg as a 30 to 90 minute infusion on day 1 every 3 weeks); a total of 127 patients were randomised to treatment with capecitabine combined with oxaliplatin + Avastin (XELOX-A): capecitabine (1000 mg/m2 bd for two weeks followed by a 7-day rest period), oxaliplatin (130 mg/m2 as a 2 hour infusion on day 1 every 3 weeks) and Avastin (7.5 mg/m2 as a 30 to 90 minute infusion on day 1 every 3 weeks). The mean duration of follow-up for the study population was 26.6 months. PFS at 6 months in the intent-to-treat population was 84% (XELIRI-A) versus 76% (XELOX-A). Overall response rate (complete response plus partial response) was 56% (XELIRI-A) versus 53% (XELOX-A).The median overall survival was 25.5 months (XELIRI-A) and 24.4 months (XELOX-A).

Combination therapy - second- line treatment of metastatic colorectal cancer

Data from a multicentre, randomised, controlled phase III clinical study (NOI6967) 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 refer to Table 8 above (without addition of placebo or Avastin). XELOX was demonstrated to be non-inferior to FOLFOX-4 in terms of PFS in the per-protocol population and intent-to-treat population (see table below). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival. The median follow up at the time of the primary analyses in the intent-to-treat population was 2.1 years; data from analyses following an additional 6 months of follow up are also included in the table below.

Table 10: Key non-inferiority efficacy results for the primary analysis and 6-month follow- up data of Study NO16967 (PPP population)

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			
EPP	154	168	1.03 (0.87; 1.24)
ITT	144	146	0.97 (0.83; 1.14)
Parameter: Overall Survival			
EPP	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			
EPP	154	166	1.04 (0.87; 1.24)
ITT	143	146	0.97 (0.83; 1.14)
Parameter: Overall Survival			
EPP	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

A pooled analysis of the efficacy data from first-line (study NO16966; initial 2-arm part) and second line treatment (study NO 16967) further support the non-inferiority results of XELOX versus FOLFOX-4 as obtained in the individual studies: PFS in the per-protocol population (hazard ratio 1.00 [95% CI: 0.88; 1.14]) with a median PFS of 193 days (XELOX; 508 patients) versus 204 days (FOLFOX-4; 500 patients). The results also indicate that XELOX is comparable to FOLFOX-4 in terms of OS (hazard ratio 1.01 [95% CI: 0.87; 1.17]) with a median OS of 468 days (XELOX) versus 478 days (FOLFOX-4).

Combination therapy - oesophagogastric cancer

Two multicentre, randomised, controlled phase III clinical trials were conducted to evaluate the safety and efficacy of capecitabine in patients with previously untreated

advanced or metastatic oesophagogastric.

Data from a multicentre, open-label, randomised, controlled phase III clinical trial (ML17032,) supports the use of capecitabine in this setting. In this trial, 160 patients with previously untreated advanced or metastatic gastric cancer were randomised to treatment with capecitabine (1000 mg/m^2 twice daily for 2 weeks followed by a 1 week rest period) and cisplatin (80 mg/m^2 asa 2 hour IV 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 IV infusion on day 1, every 3 weeks). The primary objective of the study was met, capecitabine in combination with cisplatin was at least equivalent to 5-FU in combination with cisplatin in terms of PFS in the per-protocol analysis. The result for duration of survival (overall survival) was similar to the result for PFS (Table 11).

Table 11: Summary of results for key efficacy parameters (PPP, Study ML17032)

	Median (Months) (95% CI)		
Endpoint Parameter	**Capecitabine/cisplatin n =139**	**5-FU/Cisplatin n = 137**	**Hazard Ratio [95% CI] #**
Progression-Free Survival	5.6 [4.9, 7.3]	5.0 [4.2, 6.3]	0.81 [0.63, 1.04]
Duration of Survival	10.5 [9.3, 11.2]	9.3 [7.4, 10.6]	0.85 [0.64, 1.13]

#Unadjusted treatment effect in Cox proportional model

Data from a randomised multicenter, phase III study comparing capecitabine to 5-FU and oxaliplatin to cisplatin in patients with previously untreated locally advanced or metastatic oesophagogastric cancer supports the use of capecitabine for the first-line treatment of advanced oesophagogastric cancer (REAL-2). In this trial, 1002 patients were randomised in a 2 x 2 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 2 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 2 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 I 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 OS for capecitabine versus 5-FU-based regimens (hazard ratio 0.86, 95% CI: 0.80 to 0.99) and for oxaliplatin versus cisplatin-based regimens (hazard ratio 0.92, 95% CI: 0.80 to 1.10). The median OS was 10.9 months in capecitabine-based regimens and 9.6

months in 5-FU-based regimens. The median OS 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, ML17032) supports capecitabine replacing 5-FU in mono- and combination treatment in gastrointestinal cancer. The pooled analysis includes 3097 patients treated with capecitabine- containing regimens and 3074 patients treated with 5-FU-containing regimens. The hazard ratio for OS was 0.94 (95% CI: 0.89; 1.00, p=0.0489) indicating that capecitabine-containing regimens are comparable to 5-FU containing regimens.

Monotherapy- Breast cancer

Data from two multicentre phase 2 clinical trials support the use of capecitabine monotherapy for treatment of patients with locally advanced or metastatic breast cancer after failure of a taxane and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated. In these trials, a total of 236 patients were treated with capecitabine (1250 mg/m^2 twice daily for 2 weeks followed by a 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.

Combination therapy - Breast cancer

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

5.2 Pharmacokinetic properties

Absorption: After oral administration, capecitabine is rapidly and extensively absorbed, followed by extensive conversion to the metabolites 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-DFUR. Administration with food decreases the rate of capecitabine absorption but has only a minor effect on the AUC of 5'-DFUR and the subsequent metabolite 5-FU. At the dose of 1250 mg/rn2 on day 14 with administration after food intake, the peak plasma concentrations (C_{max} in mcg/mL) for capecitabine, 5-DFCR, 5-DFUR, 5-FU and FBAL were 4.47, 3.05, 12.1, 0.95 and 5.46 respectively. The times to peak plasma concentrations (T_{max} in hours) were 1 .50, 2.00, 2.00, 2.00 and 3.34. The AUC0, values in mcgh/mL were 7.75, 7.24, 24.6, 2.03 and 36.3.

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

Metabolism
Capecitabine is first metabolised by hepatic carboxylesterase to 5-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumour tissues.

Formation of 5-FU occurs preferentially at the tumour site by the tumour-associated angiogenic factor dThdPase, thereby minimising the exposure of healthy body tissues to systemic 5-FU.

The plasma AUC of 5-FU is 6 to 22 times lower than that following an IV bolus of 5-FU (dose of 600 mg/m^2). The metabolites of capecitabine become cytotoxic only after conversion to 5-FU and anabolites of 5-FU (see Section 5.1).

5-FU is further catabolised to the inactive metabolites dihydro-5-fluoruracil (FUH2), 5-fluoro- ureidopropionic acid (FUPA) and a—fluoro-j3-alanine (FBAL) via dihydropyrirnidine dehydrogenase (DPD), which is rate limiting.

Elimination
The elimination half lives (t½, in hours) of capecitabine, 5'-DFCR, 5-DFUR, 5-FU and FBAL were 0.85, 1.11, 0.66, 0.76 and 3.23 respectively. The pharmacokinetics of capecitabine have been evaluated over a dose range of 502 - 3514 mg/rn2/day. The parameters of capecitabine, 5'- DFCR and 5-DFUR measured on days I and 14 were similar. The AUC of 5-FU was 30% - 35% higher on day 14, but did not increase subsequently (day 22). At therapeutic doses, the pharmacokinetics of capecitabine and its metabolites were dose proportional, except for 5-FU.

After oral administration capecitabine metabolites are primarily recovered in the urine. Most (95.5%) of administered capecitabine dose is recovered in urine. 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 medicine.

Combination therapy
Phase I studies evaluating the effect of capecitabine on the pharrnacokinetics 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 (the most important metabolite of capecitabine).

Pharmacokinetics in special populations
A population pharmacokinetic analysis was carried out after capecitabine treatment of 505 patients with colorectal cancer dosed at 1250 mg/m^2 twice daily. Gender, presence or absence of liver metastasis at baseline, Karnofsky Performance Status, total bilirubin, serum albumin, ASAT and ALAT had no statistically significant effect on the pharmacokinetics of 5-DFUR, 5-FU and FBAL.

Patients with hepatic impairment due to liver metastases
No clinically significant effect on the bioactivation and pharmacokinetics of capecitabine was observed in cancer patients with mildly to moderately impaired liver function due to liver metastases (see Section 4.2).

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 capecitabine and 5-FU. Creatinine clearance was found to influence the systemic exposure to 5-DFUR (35% increase in AUC when creatinine clearance decreases by 50%) and to FBAL (114% increase in AUC when creatinine clearance decreases by 50%). FBAL is a metabolite without antiproliferative activity; 5-DFUR is the direct precursor of 5-FU (see Section 4.2).

Elderly
Based on a population pharmacokinetic analysis that included patients with a wide range of ages (27 to 86 years) and included 234 (46%) patients greater than or equal to 65 years, age has no influence on the pharmacokinetics of 5-DFUR and 5-FU. The AUC of FBAL increased with age (20% increase in age results in a 15% increase in the AUC of FBAL). This increase is likely due to a change in renal function (see Sections 4.2 and 5.1).

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

5.3 Preclinical safety data

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Microcrystalline cellulose
Hypromellulose
Lactose
Magnesium stearate
Talc
Titanium dioxide
Iron oxide yellow

6.2 Incompatibilities

No Data available.

6.3 Shelf life

Shelf life is 36 months from date of manufacture.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Capecitabine film coated tablets 150 mg: 60 tablets in foil blisters
Capecitabine film coated tablets 500 mg: 120 tablets in foil blisters

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Dr. Reddy's New Zealand Ltd
82 Totara Crescent
Lower Hutt 5011
WELLINGTON

Tel: 0800 362 733

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