New Zealand Datasheet

1 PRODUCT NAME
Brinov™

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Capecitabine 150 mg and 500 mg film-coated tablets.

3 PHARMACEUTICAL FORM
Brinov 150 mg tablets are pink, capsule-shaped, biconvex, film-coated tablets. One side of the tablet is debossed with '150' and the other side of the tablet is plain. Each tablet contains 150 mg of capecitabine.

Brinov 500 mg tablets are pink, capsule-shaped, biconvex, film-coated tablets. Each tablet is plain on both sides. Each tablet contains 500 mg of capecitabine.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

Breast Cancer
Brinov tablets in combination with docetaxel is indicated for the treatment of patients with locally-advanced or metastatic breast cancer after failure of prior anthracycline-containing chemotherapy.

Brinov tablets as monotherapy is indicated for the treatment of patients with locally-advanced or metastatic breast cancer after failure of both a taxane-containing and anthracycline-containing chemotherapy or in whom taxane-containing and anthracycline-containing therapy are not indicated.

Colon Cancer
Brinov tablets as monotherapy or in combination with oxaliplatin is 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
Brinov tablets as monotherapy is indicated for the first-line treatment of patients with metastatic colorectal cancer.

Oesophagogastric Cancer
Brinov tablets in combination with platinum-based chemotherapy is indicated for the first-line treatment of patients with advanced oesophagogastric cancer.

4.2 Dose and method of administration

The capecitabine dose is calculated according to body surface area.

Brinov tablets should be swallowed whole with water within 30 minutes of a meal.

In patients receiving capecitabine in combination with docetaxel, pre-medication to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions should be started prior to intravenous administration of docetaxel.

In patients receiving capecitabine in combination with a platinum agent, pre-medication to retain sufficient hydration and anti-emesis must be initiated prior to intravenous administration of the platinum agent.

Standard Starting Dose
The standard starting dose of capecitabine according to bodyweight is shown in Table 1.

Monotherapy (Metastatic Breast Cancer, Adjuvant Colon Cancer, Metastatic Colorectal Cancer):
In the monotherapy setting, the recommended starting dose of capecitabine is 1,250 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2,500 mg/m^2 total daily dose) for 2 weeks followed by a 1 week rest period, given as 3 week cycles.

In Combination with Docetaxel (Metastatic Breast Cancer):
When used in combination with docetaxel, the suggested initial dose of capecitabine is 1,250 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2,500 mg/m^2 total daily dose) for 2 weeks followed by a 1 week rest period, combined with a 1 hour intravenous infusion of docetaxel 75 mg/m^2 every 3 weeks.

In Combination with Oxaliplatin with or without Bevacizumab (Metastatic Colorectal Cancer):
When used in combination with oxaliplatin with or without bevacizumab, the suggested initial dose of capecitabine is 1,000 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2,000 mg/m^2 total daily dose) for 2 weeks followed by a 1 week rest period, combined with a 30 to 90 minute intravenous infusion of bevacizumab 7.5 mg/m^2 (if using) followed by a 2 hour intravenous infusion of oxaliplatin 130 mg/m^2 on day 1 every 3 weeks. The first dose of capecitabine should be administered on the evening of day 1 and the final dose on the morning of day 15.

In Combination with Oxaliplatin (Adjuvant Colon Cancer):
When used in combination with oxaliplatin, the suggested initial dose of capecitabine is 1,000 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2,000 mg/m^2 total daily dose) for 2 weeks followed by a 1 week rest period, combined with a 2 hour intravenous infusion of oxaliplatin 130 mg/m^2 on day 1, every 3 weeks. The first dose of capecitabine should be administered on the evening of day 1 and the last dose on the morning of day 15. Adjuvant treatment is recommended for a full 24 weeks.

In Combination with Epirubicin/Platinum or Cisplatin (Advanced Oesophagogastric Cancer):
When used in triplet combination with epirubicin and platinum, the suggested initial dose of capecitabine is 625 mg/m^2 administered orally twice daily (morning and evening; equivalent to 1,250 mg/m^2 total daily dose) as a continuous regimen, combined with an intravenous bolus of epirubicin 50 mg/m^2 and either a 2 hour intravenous infusion of cisplatin 60 mg/m^2 or a 2 hour intravenous infusion of oxaliplatin 130 mg/m^2 on day 1 every 3 weeks.

When used in double combination with cisplatin (with or without trastuzumab), the suggested initial dose of capecitabine is 1,000 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2,000 mg/m^2 total daily dose) for 2 weeks followed by a 1 week rest period, combined with a 2 hour intravenous infusion of cisplatin 80 mg/m^2 on day 1 every 3 weeks. The first dose of capecitabine should be administered on the evening of day 1 and the last dose on the morning of day 15.

Combination Oxaliplatin/Cisplatin Premedication:
When oxaliplatin or cisplatin is being administered in combination with capecitabine, patients should be premedicated to achieve antiemesis and hydrated as per the oxaliplatin and cisplatin product information.

Table 1: Standard dose calculations for capecitabine according to body surface area.

	Full dose 1250 mg/m^2 twice a day	Number of tablets per administration (morning and evening) for full dose		Reduced dose 75%	Reduced dose 50%
Body surface area (m^2)	**Dose per administration (mg)**	**150 mg**	**500 mg**	**950 mg/m^2 (twice daily)**	**625 mg/m^2 (twice daily)**
≤ 1.26	1500	0	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	0	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	0	5	1950	1300
2.07 - 2.18	2650	1	5	2000	1300
≥ 2.19	2800	2	5	2150	1450

Table 2: Dose adjustment calculations for capecitabine.

	Full dose 1000 mg/m^2 twice a day	Number of tablets per administration (morning and evening) for full dose		Reduced dose 75%	Reduced dose 50%
Body surface area (m^2)	**Dose per administration (mg)**	**150 mg**	**500 mg**	**750 mg/m^2 (twice daily)**	**500 mg/m^2 (twice daily)**
≤ 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	0	4	1500	1000
2.07 - 2.18	2150	1	4	1600	1050
≥ 2.19	2300	2	4	1750	1100

Dosage Adjustment during Treatment

General:
The dosage of capecitabine may need to be adjusted to manage toxicity, according to the grade of toxicity (see below). If capecitabine is used in combination with another chemotherapeutic drug, the appropriate data sheet for the other agent should be consulted for dosage adjustment recommendations. This advice is applicable to all indications and to all special populations.

Patients should be carefully monitored for toxicities by the treating physician, with symptomatic treatment, dose reductions (Table 2) or treatment interruptions made as required. Doses of capecitabine omitted for toxicity should not be replaced. Once the capecitabine dosage has been reduced, it should not be subsequently increased.

For toxicities that are considered unlikely to become severe or life-threatening by the physician, treatment can be uninterrupted at the same dose without reduction.

Recommended adjustments are based on the 4-point National Cancer Institute of Canada Common Toxicity Criteria (NCIC CTC). Hand–foot syndrome is not included in the NCIC CTC.

Table 3: Relevant adverse events toxicity grades

Clinical Adverse Events Intensity				
Adverse Events	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Life-Threatening (Grade 4)**
Nausea	No substantial effect on food intake	Food intake substantially decreased but patient is able to eat sometimes	Substantial effect on food intake, unable to eat	
Diarrhoea	Increase of one to three stools per day	Increase of four to six stools per day, or nocturnal stools	Increase of seven to nine stools per day or incontinence and malabsorption	Increase of more than ten stools per day or grossly bloody diarrhoea or the requirement for parenteral support
Vomiting	One occurrence in a 24-hour period	Two to five occurrences in a 24-hour period	Six to ten occurrences in a 24-hour period	More than ten occurrences in a 24-hour period or the requirement for parenteral support
Stomatitis	Erythema with no pain	Erythema with pain, oedema, or ulcers but able to eat	Erythema with pain, restricting the ability to eat	
Hand-foot syndrome^{++} (clinical domain)	Tingling, numbness, erythema with no pain, and swelling	Erythema with pain and swelling	Ulceration, moist desquamation, severe pain and blistering	
Hand-food syndrome^{++} (functional domain)	Discomfort which does not interrupt everyday activities	Discomfort which affects everyday activities of daily living	Severe discomfort, unable to work or complete everyday activities	
$^{++}$Criteria as per established protocol.				

Grade 1 toxicity:
The dosage of capecitabine should not be adjusted during the cycle or for the next cycle.

Grade 2 toxicity:
At the first appearance, capecitabine should be interrupted until the toxicity has resolved to Grade 0 or 1 severity. The next dose of capecitabine should be at 100% of the starting dose. At the second appearance, capecitabine should be interrupted until the toxicity has resolved to Grade 0 or 1 severity. The next dose of capecitabine should be at 75% of the starting dose. At the third appearance, capecitabine should be interrupted until the toxicity has resolved to Grade 0 or 1 severity. The next dose of capecitabine should be at 50% of the starting dose. If the event appears at Grade 2 severity four times, capecitabine should be permanently discontinued.

Grade 3 toxicity:
At the first appearance, capecitabine should be interrupted until the toxicity has resolved to Grade 0 or 1 severity. The next dose of capecitabine should be at 75% of the starting dose. At the second appearance, capecitabine should be interrupted until the toxicity has resolved to Grade 0 or 1 severity. The next dose of capecitabine should be at 50% of the starting dose. If the event appears at Grade 3 severity three times, capecitabine should be permanently discontinued.

Grade 4 toxicity:
At the first appearance, capecitabine should be permanently discontinued unless the treating physician believes that it is in the patient's best interest to continue. In which case, capecitabine should be interrupted until the toxicity has resolved to Grade 0 or 1 severity. The next dose of capecitabine should be at 50% of the starting dose. If the event appears at Grade 4 severity for a second time, capecitabine should be permanently discontinued.

Haematological toxicity:
Capecitabine should not be used in patients with baseline neutrophil counts less than 1.5 x 10^9/L and/or thrombocyte counts of less than 100 x 10^9/L. Treatment with capecitabine should be interrupted if Grade 3 or 4 haematological toxicity occurs during a treatment cycle.

Hyperbilirubinaemia:
Treatment with capecitabine should be interrupted if treatment-related elevations in bilirubin of exceeding 3.0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of greater than 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.

General Combination Therapy:
Dose adjustment for toxicity when capecitabine is administered in combination with other treatments should be made according to the above.

If a treatment delay is indicated at the beginning of the treatment cycle for either capecitabine or the other medication(s) used in combination therapy, then the requirements for restarting all drugs should be met before the treatment cycle commences.

If toxicities emerge during a treatment cycle that the treating physician does not consider to be related to capecitabine, then capecitabine treatment should be continued and the dose of the other medication(s) modified corresponding to the appropriate data sheet. If the other agent is permanently discontinued, capecitabine can be resumed if all the requirements for restarting treatment are met.

Dosage Adjustment in Special Populations

Hepatic Impairment due to Liver Metastases:
No starting reduction in capecitabine dosage is required in patients with mild-to-moderate hepatic impairment due to liver metastases; however, careful monitoring is recommended. No data is available to make recommendations in patients with severe hepatic impairment.

Renal Impairment:
No starting reduction in capecitabine dosage is required in patients with mild renal impairment (creatinine clearance of 51–80 mL/min calculated according to Cockroft and Gault equation). In patients with moderate renal impairment (calculated creatinine clearance 30–50 mL/min) scheduled to receive capecitabine at 1,250 mg/m^2 (either as monotherapy or in combination with another agent), the capecitabine dosage should be started at 75% of the starting dose (950 mg/m^2 twice daily). If a patient subsequently develops Grade 2 to 4 toxicity, the capecitabine dosage should be adjusted as described previously. Capecitabine should be discontinued if calculated creatinine clearance is less than 30 ml/min during treatment (see section 4.3).

The dose alteration recommendations for patients with moderate renal impairment relate to both monotherapy and combination use. For the dosage calculations, see Table 1 and Table 2.

Children:
There is no data available to support the use of capecitabine in children.

Elderly:
It is recommended that elderly patients are carefully monitored while receiving capecitabine as patients aged ≥ 65 years experienced more Grade 3 or 4 treatment-related adverse reactions and adverse reactions that led to their discontinuation of capecitabine than younger patients in clinical trials evaluating capecitabine.

No starting reduction in capecitabine dosage is required in elderly patients receiving capecitabine as

monotherapy.

An increased occurrence of Grade 3 and/or 4 treatment related adverse events and serious adverse events was observed when capecitabine was administered in combination with docetaxel in patients who were 60 years old or older.

A starting dose reduction of capecitabine to 75% (950 mg/m^2 twice daily) is recommended in patients aged ≥ 60 years receiving capecitabine in combination with docetaxel.

A starting dose reduction of capecitabine to 800 mg/m^2 twice daily is recommended in patients aged ≥ 65 years receiving capecitabine in combination with irinotecan.

4.3 Contraindications

- Known hypersensitivity to capecitabine or any of the Brinov tablet excipients (see section 6.1).
- Known hypersensitivity to 5-fluorouracil (5-FU) or fluoropyrimidine therapy.
- Severe renal impairment (creatinine clearance < 30 ml/min calculated by Cockroft and Gault equation).
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4).
- During pregnancy or lactation.
- Concomitant treatment with sorivudine or its chemically-related analogues, such as brivudine (see section 4.5).
- Severe neutropenia, thrombocytopenia or leukopenia.
- Severe liver impairment.

If contraindications occur with any of the agents in a combination schedule, that agent must not be used.

4.4 Special warnings and precautions for use

Dose limiting toxicities:
Dose limiting toxicities include abdominal pain, nausea, diarrhoea, hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia) and stomatitis. Most adverse reactions associated with capecitabine are reversible without permanent discontinuation of therapy, although treatment may need to be interrupted or dosages reduced (see section 4.2).

Diarrhoea:
Patients treated with capecitabine may experience diarrhoea, sometimes severe. Careful monitoring is required in patients with severe diarrhoea, with fluid and electrolyte replacement administered if they become dehydrated. Standard anti-diarrhoea treatments, (such as loperamide) may be used. NCIC CTC Grade 2 diarrhoea is defined as an increase of 4–6 stools/day or nocturnal stools, Grade 3 diarrhoea as an increase of 7–9 stools/day or incontinence and malabsorption, and Grade 4 diarrhoea as an increase of ≥ 10 stools/day or grossly bloody diarrhoea or the need for parenteral support. Capecitabine dosage should be adjusted as necessary (see section 4.2).

Dehydration:
Patients with nausea, vomiting, asthenia, anorexia, or diarrhoea may quickly become dehydrated. Capecitabine should be immediately interrupted and dehydration corrected in the event of Grade 2 (or higher) dehydration. Once the patient is rehydrated and any precipitating causes have been corrected or controlled, capecitabine may be restarted. Capecitabine dosage should be adjusted for the precipitating adverse event as necessary (see section 4.2).

Dehydration can result in acute renal failure, particularly in patients who have pre-existing compromised renal function or if capecitabine is given concurrently with known nephrotoxic medicines. Fatal outcome of renal failure has been reported in these circumstances (see section 4.8).

Cardiotoxicity:
Similar to other fluorinated pyrimidines, capecitabine is associated with cardiotoxic adverse events and capecitabine patients have reported; myocardial infarction, angina pectoris (including ventricular fibrillation, torsade de pointes, and bradycardia), arrhythmias/dysrhythmias, cardiomyopathy, cardiac failure, cardiac arrest and electrocardiographic changes (in very rare cases this includes QT prolongation). In patients with a history of significant angina pectoris, arrhythmias and cardiac disease, caution must be exercised. Patients with prior history of coronary artery disease may be at greater risk of capecitabine-associated cardiotoxicity (see section 4.8).

Hypercalcaemia or hypocalcaemia:
During capecitabine treatment there have been reports of hypercalcaemia or hypocalcaemia. In patients with pre-existing hypercalcaemia or hypocalcaemia caution should be taken (see section 4.8).

Peripheral nervous system disease or Central nervous system disease:
In patients with peripheral or central nervous system disease e.g. neuropathy or brain metastases, caution should be taken (see section 4.8).

Electrolyte disturbances or Diabetes mellitus:
In capecitabine patients with electrolyte disturbances or with diabetes mellitus, caution must be taken as these may become more aggravated during treatment.

Ophthalmologic complications:
In patients with a prior history of history or eye disorders, they should be monitored carefully for ophthalmological complications (i.e. corneal disorders or keratitis). Such treatment of eye disorders should be started and treated as clinically appropriate.

Severe skin reactions:
Capecitabine can cause serious skin reactions, for example, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN). Capecitabine must be discontinued permanently in patients who experience a serious skin reaction possibly in relation to their capecitabine treatment (see section 4.8).

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 .

Hand–Foot Syndrome:
Hand–foot syndrome (also known as palmar–plantar erythrodysaesthesia or chemotherapy-induced acral erythema) is a cutaneous toxicity that can be induced by capecitabine. With patients accepting capecitabine monotherapy in the metastatic setting, the time to median onset was seventy-nine days, with a range from eleven to three hundred and sixty days, with a severity range of Grades 1 to 3. For the clinical domain of hand–foot syndrome, numbness, tingling, painless erythema and swelling are considered Grade 1 severity; painful erythema and swelling are considered Grade 2 severity; and moist desquamation, ulceration, blistering and severe pain are considered Grade 3 severity. For the functional domain of hand–foot syndrome, discomfort that does not disrupt normal activities is considered Grade 1 severity; discomfort that impacts activities of daily living is considered Grade 2 severity; and severe discomfort or inability to work or perform activities of daily living are considered Grade 3 severity. Patients experiencing Grade 2 or 3 hand–foot syndrome should have their dosage of capecitabine adjusted as previously described (see section 4.2). The administration of vitamin B6 (pyridoxine) when capecitabine and cisplatin are used in combination is not recommended for the symptomatic or secondary prophylactic treatment of hand–foot syndrome. This is due to published reports that advise that it may reduce the efficacy of cisplatin. In patients that are having capecitabine therapy, there is some evidence that dexpanthenol is effective for hand-foot syndrome prophylaxis.

Renal Impairment:
The incidence of treatment-related Grade 3 and 4 adverse events increased in patients with moderate renal impairment (creatinine clearance 30–50 ml/min) compared with patients with normal renal function. Caution is recommended when administering capecitabine to patients with impaired renal function (see section 4.2).

Hepatic Impairment:
The effects of hepatic impairment or severe hepatic impairment due to causes other than liver metastases on the pharmacokinetics of capecitabine have not been established. Careful monitoring is recommended when administering capecitabine in patients with hepatic impairment (see section 4.2).

Lactase deficiency or glucose-galactose malabsorption:
As Brinov contains lactose as an excipient, patients with rare hereditary problems of galactose intolerance or the glucose-galactose malabsorption or Lapp lactase deficiency should not take this product.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Coumarin-Derivative Anticoagulants:
There have been reports of altered coagulation parameters and/or bleeding in patients administered capecitabine and concomitant coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred between several days and several months of initiating capecitabine and, in several cases, within a month of stopping capecitabine (see section 4.4). In a capecitabine pharmacokinetic clinical interaction study, after a single dose of warfarin 20mg the AUC of S-warfarin increased by 57% with the INR value (International Normalised Ratio [INR] or prothrombin time [PT]) increasing by 91%.

This possible interaction may be due to inhibition of cytochrome P450 2C9 by capecitabine.

Since metabolism of R-warfarin was unaffected, these results suggest, that capecitabine down-regulates isozyme 2C9, with no effect on isozymes 3A4 and 1A2.

Anticoagulant response (International Normalised Ratio [INR] or prothrombin time [PT]) should be monitored closely in patients receiving capecitabine and concomitant oral coumarin-derivative anticoagulation, with the anticoagulant dose adjusted accordingly (see section 4.5).

Phenytoin:
There have been reports of increased phenytoin plasma concentrations in patients administered capecitabine and concomitant phenytoin. This possible interaction may be due to inhibition of cytochrome P450 2C9 by capecitabine. Increased phenytoin plasma concentrations and associated clinical symptoms should be monitored regularly in patients receiving capecitabine and concomitant phenytoin.

Cytochrome P450 2C9 substrates:
With the exception of concomitant warfarin administration, no formal interaction studies between capecitabine and other CYP2C9 substrates have been conducted. Care should be taken if capecitabine is co-administered with these drugs.

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

Folinic Acid:
Folinic acid had no effect on the pharmacokinetics of capecitabine or its metabolites. However, folinic acid has an effect on the pharmacodynamics of capecitabine and its toxicity may be enhanced by folinic acid: the maximum tolerated dose (MTD) of capecitabine alone using the intermittent regimen is 3000 mg/m^2 per day whereas it is only 2000 mg/m^2 per day when capecitabine was combined with folinic acid (30 mg orally twice a day). The enhanced toxicity may be relevant when switching from 5- FU/folinic acid to a capecitabine regimen. This may also be relevant with folic acid supplementation for folate deficiency due

to the similarity between folinic acid and folic acid.

Sorivudine and analogues:
Capecitabine should not be administered concomitantly with sorivudine or its chemically-related analogues (such as brivudine). A clinically significant drug interaction between sorivudine and 5-FU may occur, resulting from the inhibition of DPD by sorivudine and leading to increased and potentially fatal fluoropyrimidine toxicity. Capecitabine should not be initiated until at least four weeks have elapsed after the end of treatment with sorivudine or its chemically-related analogues such as brivudine (see section 4.3).

Allopurinol:
Interactions with allopurinol have been observed for 5-FU; with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with capecitabine should be avoided.

Interferon alpha:
The MTD when capecitabine was used as monotherapy was 3000 mg/m^2 per day compared to the MTD when capecitabine was combined with interferon alpha at 2000 mg/m^2 per day.

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

Bevacizumab:
The pharmacokinetic parameters of capecitabine or its metabolites are not clinically significantly affected by concomitant administration of bevacizumab.

Radiotherapy:
The MTD of capecitabine when combined with radiotherapy for rectal cancer 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 while capecitabine used alone using the intermittent regimen is 3000 mg/m^2 per day.

Interactions with Food
Brinov tablets should be administered within 30 minutes of a meal, given that current safety and efficacy data are based upon administration with food. The rate of capecitabine absorption is decreased with food (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
Pregnancy Category D
Capecitabine should not be used during pregnancy. Women of childbearing potential should be advised to take appropriate contraceptive measures during treatment with capecitabine. If capecitabine is used during pregnancy or the patient becomes pregnant while receiving capecitabine, they should be informed of the potential hazard to the foetus.

Embryolethality and teratogenicity have been observed with capecitabine in reproductive toxicity studies in animals, as expected with a fluoropyrimidine derivative. No studies have been performed with capecitabine in pregnant women; however, it is assumed that capecitabine may cause foetal harm if administered during human pregnancy. Capecitabine should be believed to be a potential human teratogen.

Breast feeding
Capecitabine should not be used during lactation.

In murine studies, capecitabine metabolites were detected in the milk of lactating mice administered capecitabine. It is not known if capecitabine is excreted in human milk.

Fertility
There is no information data on the impact on fertility whilst taking capecitabine. The pivotal studies for capecitabine included males and females (of child bearing potential) only if they used an acceptable form of birth control for the length of the study to avoid pregnancy and for a continuing time after treatment.

Effects on fertility in animal studies were observed (see section 5.3).

4.7 Effects on ability to drive and use machines

For patients taking capecitabine there is a minor to moderate influence on the ability to use machines and drive. Capecitabine may cause nausea, dizziness and fatigue.

4.8 Undesirable effects

Summary of the safety profile:
The overall safety profile of capecitabine was determined from data from over 3,000 patients treated either with capecitabine alone or in combination with other different chemotherapy regimens in multiple indications.

The capecitabine monotherapy safety profile for the metastatic colorectal cancer, adjuvant colon cancer and metastatic breast cancer populations are comparable. See section 5.1 for details of study designs, major studies, and major efficacy results.

The most clinically relevant treatment-related adverse drug reactions and/or (ADRs) commonly reported with capecitabine were gastrointestinal disorders (especially nausea, diarrhoea, abdominal pain, stomatitis, vomiting), hand-foot syndrome (palmar-plantar erythrodysesthesia), fatigue, anorexia, asthenia, cardiotoxicity, thrombosis/embolism and increased renal dysfunction on those with pre-existing compromised renal function.

Tabulated list of adverse reactions:
Adverse drug reactions are listed in Table 4 for capecitabine given as monotherapy and considered by the investigator to be possibly, probably, or remotely related to the administration of capecitabine and in Table 5 considered by the investigator to be possibly, probably, or remotely related to the administration of capecitabine for capecitabine given in combination with different chemotherapy regimens in multiple indications.

The following headings are used to rank the adverse drug reactions by frequency: very common (≥ 1/10 or 10% or greater), common (≥ 1/100 to < 1/10 or 1% or greater and less than 10%), uncommon (≥ 1/1,000 to < 1/100 or 0.1% or greater and less than 1%), rare (≥ 1/10,000 to < 1/1,000 or greater than 0.01% and less than 0.1%), very rare (< 1/10,000 or less than 0.01%). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Capecitabine Monotherapy:
Table 4 lists adverse drug reactions (ADRs) where capecitabine was used alone in monotherapy and was based on over 1,900 patients in a pooled data analysis using safety data from 3 major studies (studies SO14796, M66001 and SO14695). According to the pooled analysis, adverse drug reactions were added according to the overall incidence.

Table 4: Summary of adverse drug reactions (ADRs) reported in patients treated with capecitabine monotherapy

Body System	**Very Common All grades 10% or greater**	**Common All grades 1% or greater and less than 10%**	**Uncommon Severe and/or Life-threatening (grade 3-4) or considered medically relevant 0.1% or greater and less than 1%**	**Rare/Very Rare (Post-Marketing Experience) Less than 0.1%**
General disorders and administration site conditions	Fatigue, Asthenia	Pyrexia, Oedema peripheral, Malaise, Chest pain	Oedema, Chills, Influenza like illness, Rigors, Body temperature increased	
Reproductive system and breast disorders	-	-	Vaginal haemorrhage	
Renal and urinary disorders	-	-	Hydronephrosis, Urinary incontinence, Haematuria, Nocturia, Blood creatinine increased	
Musculoskeletal and connective tissue disorders	-	Pain in extremity, Back pain, Arthralgia	Joint swelling, Bone pain, Facial pain, Musculoskeletal stiffness, Muscular weakness	
Skin and subcutaneous tissue disorders	Palmar-plantar erythro-dysaesthesia syndrome**	Rash, Alopecia, Erythema, Dry skin, Pruritus, Skin hyper-pigmentation, Rash macular, Skin desquamation, Dermatitis, Pigmentation disorder, Nail disorder	Blister, Skin ulcer, Rash, Urticaria, Photosensitivity reaction, Palmar erythema, Swelling face, Purpura, Radiation recall syndrome	Cutaneous lupus erythematosus (rare), Severe skin reactions such as Stevens-Johnson Syndrome and toxic Epidermal Necrolysis (very rare) (see section 4.4.)
Hepatobiliary disorders	-	Hyperbilirubinemia, Liver function test abnormalities	Jaundice	Hepatic failure (rare), Cholestatic hepatitis (rare)
Gastrointestinal disorders	Diarrhoea, Vomiting, Nausea, Stomatitis, Abdominal pain	Gastrointestinal haemorrhage, Constipation, Upper abdominal pain, Dyspepsia, Flatulence, Dry mouth	Intestinal obstruction, Ascites, Enteritis, Gastritis, Dysphagia, Abdominal pain lower, Oesophagitis, Abdominal discomfort, Gastro-oesophageal reflux disease, Colitis, Blood in stool	
Respiratory, thoracic and mediastinal disorders	-	Dyspnoea, Epistaxis, Cough, Rhinorrhoea	Pulmonary embolism, Pneumothorax, Haemoptysis, Asthma, Dyspnoea exertional	
Vascular disorders	-	Thrombophlebitis	Deep vein thrombosis, Hypertension, Petechiae, Hypotension, Hot flush, Peripheral coldness	

Cardiac disorders	-	-	Angina unstable, Angina pectoris, Myocardial ischaemia/infarction, Atrial fibrillation, Arrhythmia, Tachycardia, Sinus tachycardia, Palpitations	Ventricular fibrillation (rare), QT prolongation (rare), Torsade de pointes (rare), Bradycardia (rare), Vasospasm (rare)
Ear and labyrinth disorders	-	-	Vertigo, Ear pain	
Eye disorders	-	Lacrimation increased, Conjunctivitis, Eye irritation	Visual acuity reduced, Diplopia	Lacrimal duct stenosis (rare), Corneal disorders(rare), keratitis (rare), punctate keratitis (rare)
Nervous system disorders	-	Headache, Lethargy Dizziness, Paraesthesia Dysgeusia	Aphasia, Memory impairment, Ataxia, Syncope, Balance disorder, Sensory disorder, Neuropathy peripheral	Toxic leukoencephalopathy (very rare)
Psychiatric disorders	-	Insomnia, Depression	Confusional state, Panic attack, Depressed mood, Libido decreased	
Metabolism and nutrition disorders	Anorexia	Dehydration, Weight decreased	Diabetes, Hypokalaemia, Appetite disorder, Malnutrition, Hypertriglyceridaemia	
Immune system disorders	-	-	Hypersensitivity	
Blood and lymphatic system disorders	-	Neutropenia, Anaemia	Febrile neutropenia, Pancytopenia, Granulocytopenia, Thrombocytopenia, Leukopenia, Haemolytic anaemia, International Normalised Ratio (INR) increased/Prothrombin time prolonged	
Neoplasm benign, malignant and unspecified	-	-	Lipoma	
Infections and infestations	-	Herpes viral infection, Nasopharyngitis, Lower respiratory tract infection	Cellulitis, Tonsillitis, Sepsis, Urinary tract infection, Pharyngitis, Oral candidiasis, Influenza, Gastroenteritis, Fungal infection, Infection, Tooth abscess	

** Based on the post-marketing experience, severe or persistent palmar-plantar erythrodysaesthesia syndrome can eventually lead to loss of fingerprints (see section 4.4)

Capecitabine in Combination Therapy:
Table 5 lists ADRs (adverse drug reactions) associated with the use of capecitabine in combination with different chemotherapy regimens in multiple indications based on safety data from over 3,000 patients. Adverse drug reactions are added to the appropriate frequency grouping (very common or common)

according to the highest incidence seen in any of the major clinical trials and are only added when they were seen in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy (see Table 4). Uncommon adverse drug reactions (ADRs) reported for capecitabine in combination therapy are consistent with the adverse drug reactions (ADRs) reported for capecitabine monotherapy or reported for monotherapy with the combination medicinal product (in literature and/or respective summary of product characteristics).

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

Table 5: Summary of related adverse drug reactions (ADRs) reported in patients treated with capecitabine in combination treatment in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy

Body System	Very common All grades 10% or greater	Common All grades 1% or greater and less than 10%	Rare/Very Rare (Post-Marketing Experience)
Injury, poisoning and procedural complications	-	Contusion	
General disorders and administration site conditions	Pyrexia, Weakness, +Lethargy, Temperature intolerance	Mucosal inflammation, Pain in limb, Pain, Chills, Chest pain, Influenza-like illness, +Fever, Infusion related reaction, Injection site reaction, Infusion site pain, Injection site pain	
Renal and urinary disorder	-	Haematuria, Proteinuria, Creatinine renal clearance decreased, Dysuria	Acute renal failure secondary to dehydration (rare)
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia, Pain in extremity	Pain in jaw, Muscle spasms, Trismus, Muscular weakness	
Skin and subcutaneous tissue disorders	Alopecia, Nail disorder	Hyperhidrosis, Rash erythematous, Urticaria, Night sweats	
Hepatobiliary disorders	-	Hepatic function abnormal	
Gastrointestinal disorders	Constipation, Dyspepsia	Upper gastrointestinal haemorrhage, Mouth ulceration, Gastritis, Abdominal distension, Gastrooesophageal reflux disease, Oral pain, Dysphagia, Rectal haemorrhage, Abdominal pain lower, Oral dysaesthesia, Paraesthesia oral, Hypoaesthesia oral, Abdominal discomfort	
Blood and lymphatic system disorders	+Neutropenia, +Leucopenia, +Anaemia, +Neutropenic fever, Thrombocytopenia	Bone marrow depression, +Febrile Neutropenia	
Respiratory, thoracic and mediastinal system disorders	Sore throat, Dysaesthesia pharynx	Hiccups, Pharyngolaryngeal pain, Dysphonia	

Vascular disorders	Lower limb oedema, Hypertension, +Embolism and thrombosis	Flushing, Hypotension, Hypertensive crisis, Hot flush, Phlebitis	
Cardiac disorders	-	Atrial fibrillation, Cardiac ischaemia/infarction	
Ear and labyrinth disorders	-	Tinnitus, Hypoacusis	
Eye disorders	Lacrimation increased	Visual disorders, Dry eye, Eye pain, Visual impairment, Vision blurred	
Nervous system disorders	Paraesthesia, Dysaesthesia, Peripheral neuropathy, Peripheral sensory neuropathy, Dysgeusia, Headache	Neurotoxicity, Tremor, Neuralgia, Hypersensitivity reaction, Hypoaesthesia	
Psychiatric disorders	-	Sleep disorder, Anxiety	
Metabolism and nutrition disorders	Appetite decreased	Hypokalaemia, Hyponatraemia, Hypomagnesaemia, Hypocalcaemia, Hyperglycaemia	
Immune system disorders	-	Hypersensitivity	
Infections and infestations	-	Herpes zoster, Urinary tract infection, Oral candidiasis, Upper respiratory tract infection, Rhinitis, Influenza, +Infection, Oral herpes	

ADRs are added according to the highest incidence seen in any of the major combination trials.
+ For each term, the frequency count was based on ADRs of all grades.
For terms marked with a "+", the frequency count was based on grade 3-4 ADRs.

Description of selected Adverse Drug Reactions (ADRs)

Hand-foot syndrome (see section 4.4):
For the capecitabine dose on days 1 to 14 every 3 weeks of 1250 mg/m^2, administered twice daily, a frequency of 53% to 60% of all-grades HFS was observed in capecitabine monotherapy trials (comprising studies in treatment of breast cancer, treatment of metastatic colorectal cancer, and adjuvant therapy in colon cancer) and a frequency of 63% was observed in the docetaxel/capecitabine arm for the treatment of metastatic breast cancer. In capecitabine combination therapy, for the capecitabine dose of 1000 mg/m^2 twice daily on days 1 to 14 every 3 weeks, a frequency of 22% to 30% of all-grade HFS was observed.

With data from over 4,700 patients in 14 clinical trials using meta-analysis taking capecitabine as monotherapy or capecitabine in combination in multiple indications (colorectal, colon, breast and gastric cancer) with different chemotherapy regimens showed that all grades of HFS occurred in 2066 (43%) patients after a median time of 239 [95% CI 201, 288] days after starting treatment with capecitabine. The following factors were statistically significantly associated with an increased risk of developing HFS in all studies combined: increasing relative dose intensity in the first six weeks, increasing capecitabine starting dose (gram), increasing duration of study treatment (weeks), decreasing cumulative capecitabine dose (0.1*kg), increasing age (by 10 year increments), female gender, and good ECOG performance status at baseline (0 versus ≥ 1).

Diarrhoea (see section 4.4):
In up to 50% of patients, it has been observed that capecitabine increases the likelihood of diarrhoea.

With data from over 4,700 capecitabine patients in 14 clinical trials using meta-analysis showed that in all

studies combined, the following factors were statistically significantly associated with an increased risk of developing diarrhoea: increasing duration of study treatment (weeks), increasing capecitabine starting dose (gram), female gender and increasing age (by 10 year increments). The following factors were statistically significantly associated with a decreased risk of developing diarrhoea: increasing relative dose intensity in the first six weeks and increasing cumulative capecitabine dose (0.1*kg).

Cardiotoxicity (see section 4.4):
In addition to the adverse reactions described in Tables 4 and 5, the following ADRs with an incidence of less than 0.1% were associated with the use of capecitabine monotherapy based on a pooled analysis from clinical safety data from 7 clinical trials including 949 patients (2 phase III and 5 phase II clinical trials in metastatic breast cancer and metastatic colorectal cancer): cardiac failure, cardiomyopathy, ventricular extrasystoles and sudden death.

Encephalopathy:
In addition to the adverse reactions described in Tables 4 and 5, and based on the above pooled analysis from clinical safety data from 7 clinical trials, encephalopathy was also associated with the use of capecitabine monotherapy with an incidence of less than 0.1%.

Special populations

Elderly patients (see section 4.2):
An analysis of safety data in capecitabine (monotherapy) patients ≥ 60 years of age and an analysis of patients treated with docetaxel plus capecitabine combination therapy showed an increase in the incidence of treatment-related Grade 3 and 4 adverse reactions and treatment-related serious adverse reactions compared to patients < 60 years of age. Patients ≥ 60 years of age treated with docetaxel and capecitabine also had more early withdrawals from treatment due to adverse reactions (ADRs) compared to patients < 60 years of age.

With data from over 4,700 capecitabine patients in 14 clinical trials using meta-analysis showed that in all studies combined, age increase (by 10 year increments) was statistically significantly associated with a decreased risk of developing neutropenia and an increased risk of developing diarrhoea and HFS.

Gender:
With data from over 4,700 capecitabine patients in 14 clinical trials using meta-analysis indicated that female gender was statistically significantly associated with a decreased risk of developing neutropenia and an increased risk of developing diarrhoea and HFS.

Patients with renal impairment (see section 4.2, 4.4, and 5.2):
An analysis of safety data in patients treated with capecitabine monotherapy (colorectal cancer) with baseline renal impairment showed an increase in the incidence of treatment-related Grade 3 and 4 adverse reactions compared to patients with normal renal function (36% in patients without renal impairment n=268, vs. 41% in mild n=257 and 54% in moderate n=59, respectively) (see section 5.2). Patients with moderately impaired renal function show an increased rate of dose reduction (44%) vs. 33% and 32% in patients with no or mild renal impairment and an increase in early withdrawals from treatment (21% withdrawals during the first two cycles) vs. 5% and 8% in patients with no or mild renal impairment.

Reporting of suspected adverse reactions
After approval and launch of the medicine, it is important to report suspected adverse reactions. Reporting of any adverse reactions allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Acute overdose of capecitabine causes symptoms including vomiting, nausea, mucositis, diarrhoea, gastrointestinal irritation and bleeding and bone marrow depression. In the event of overdose, usual therapeutic and supportive medical interventions aimed at alleviating symptoms and preventing their complications should be used.

Please contact the National Poisons Centre on 0800 POISON (0800 764766) for advice on the management of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents. ATC code: L01BC06
Capecitabine is a fluoropyrimidine carbamate, which is non-cytotoxic and which functions as a precursor of 5-fluorouracil (5-FU) which is a cytotoxic moiety that is orally administered.

Through an enzymatic pathway, capecitabine is activated (see section 5.2). Thymidine phosphorylase (ThyPase) is the enzyme responsible for the final conversion to 5-FU. Thymidine phosphorylase while found in normal tissues is also found in tumour tissues, usually at higher levels. Capecitabine demonstrated a synergistic effect in combination with docetaxel in human cancer xenograft models. This may be related to docetaxel upregulating thymidine phosphorylase.

There is evidence that the synthesis of deoxyribonucleic acid (DNA) is interfered through the anabolic pathway for the metabolism of 5-FU being blocked in the methylation reaction of deoxyuridylic acid to thymidylic acid.

The incorporation of 5-FU also leads to inhibition of protein synthesis and inhibition of RNA. Since RNA and DNA are essential for cell growth and division, 5-FU may cause a thymidine deficiency that provokes unbalanced growth and death of a cell. The effects of RNA and DNA deprivation are most marked on those cells which proliferate more rapidly and which metabolise 5-FU at a faster rate.

Clinical Trials

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, 1,987 patients were randomised to treatment with capecitabine (1250 mg/m^2 twice a day for 2 weeks followed by a 1-week rest period and given as 3-week cycles for 24 weeks) or 5-FU and folinic acid (Mayo regimen: 20 mg/m^2 folinic acid 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/folinic acid 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/ folinic acid in DFS and overall survival (OS) showed hazard ratios of 0.88 (95% CI 0.77 - 1.01; p = 0.068) and 0.86 (95% CI 0.74 - 1.01; p = 0.060), respectively. The median follow-up at the time of the analysis was 6.9 years.

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 Dukes Stage C colon cancer supports the use of capecitabine in combination with oxaliplatin (XELOX) for the adjuvant treatment

of patients with colon cancer (N016968). In this trial, 944 patients were randomised to 3 week cycles for 24 weeks with capecitabine (1000 mg/m^2 twice a day for 2 weeks followed by a 7 -day rest period) in combination with oxaliplatin (130 mg/m^2 IV infusion over 2 hours on day 1 every 3 weeks); 942 patients were randomised to bolus 5-FU and folinic acid. 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/folinic acid (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/folinic acid. 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/folinic acid. 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/folinic acid.

Monotherapy - metastatic colorectal cancer:
Data from two identically designed, multicentre, randomised, controlled phase 3 clinical trials support the use of capecitabine for first-line treatment of metastatic colorectal cancer (S014695; S014796). In these trials, 603 patients were randomised to treatment with capecitabine (1250 mg/m^2 twice a day for 2 weeks followed by a 1-week rest period and given as 3-week cycles) and 604 patients were randomised to treatment with 5-FU and folinic acid (Mayo regimen: 20 mg/m^2 folinic acid 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 colorectal cancer:
Data from a multicentre, randomised, controlled phase III clinical study (N016966) support the use of capecitabine in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab for the first-line treatment of metastatic colorectal cancer. The study contained two parts: an initial 2-arm part in which patients were randomised to two different treatment groups, including XELOX or FOLFOX-4, and a subsequent 2 x 2 factorial part with four different treatment groups, including XELOX + placebo (P), FOLFOX-4+P, XELOX+ bevacizumab (XELOX-A), and FOLFOX-4+bevacizumab. The treatment regimens are summarised in the table below.

Table 6: Treatment regimens in Study N016966

	Treatment	**Starting Dose**	**Schedule**
FOLFOX-4 Or	Oxaliplatin Folinic acid	85 mg/m^2 IV 2 hr 200 mg/m^2 IV 2 hr	Oxaliplatin on day 1, every 2 weeks Folinic acid on days 1 and 2, every 2 weeks.
FOLFOX-4 + bevacizumab	5-Fluorouracil	400 mg/ m^2 IV bolus, 600 mg/ m^2 IV 22 hr	5-fluorouracil IV bolus/infusion, each on days 1 and 2, every 2 weeks
	Placebo or bevacizumab	5 mg/kg IV 30 – 90 m	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX Or XELOX + bevacizumab (XELOX-A)	Oxaliplatin Capecitabine	130 mg/m^2 IV 2 hr 1000 mg/m^2 oral twice a day	Oxaliplatin on day 1, every 3 weeks Capecitabine oral twice a day for 2 weeks (followed by 1 week off treatment)
	Placebo or bevacizumab	7.5 mg/kg IV 30-90 min	Day 1, prior to XELOX, every 3 weeks
5-Fluorouracil: IV bolus injection immediately after folinic acid			

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 patient population and the intent-to-treat population (see Table 9 below). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival (OS). A comparison of XELOX-A versus FOLFOX-4 + bevacizumab was a pre-specified exploratory analysis. In this treatment subgroup comparison, XELOX-A was similar compared to FOLFOX-4 + bevacizumab 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 also included in the table below.

Table 7: Key non-inferiority results for the primary analysis and 1-year follow-up data (EPP and ITT populations, Study N016966)

PRIMARY ANALYSIS			
XELOX/XELOX+P/XELOX-A (EPP*: n = 967; ITT: n = 1017)**		**FOLFOX-4/FOLFOX-4+P/FOLFOX-4+Bevacizumab (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: Progression-free 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: Progression-free Survival			
EPP	600	594	1.00 (0.88; 1.13)
ITT	602	596	0.99 (0.88; 1.12)

*EPP=eligible patient population; **ITT=intent-to-treat population

In a randomised, controlled phase III study (CAIRO) for the combination of capecitabine with irinotecan for the first-line treatment of patients with metastatic colorectal cancer, the effect of using capecitabine at a starting dose of 1000 mg/m^2 for 2 weeks every 3 weeks was studied. 820 Patients were randomised to receive either sequential treatment (n=410) or combination treatment (n=410). Sequential treatment consisted of first-line capecitabine (1250 mg/m^2 twice daily for 14 days), second-line irinotecan (350 mg/m^2 on day 1), and third-line combination of capecitabine (1000 mg/m^2 twice daily for 14 days) with oxaliplatin (130 mg/m^2 on day 1). Combination treatment consisted of first-line capecitabine (1000 mg/m^2 twice daily for 14 days) combined with irinotecan (250 mg/m^2 on day 1) (XELIRI) and second-line capecitabine (1000 mg/m^2 twice daily for 14 days) plus oxaliplatin (130 mg/m^2 on day 1). All treatment cycles were administered at intervals of 3 weeks. In first-line treatment the median progression-free survival in the intent-to-treat population was 5.8 months (95% CI 5.1 - 6.2 months) for capecitabine monotherapy and 7.8 months (95% CI 7.0 - 8.3 months; p=0.0002) for XELIRI. However, this was associated with an increased incidence of gastrointestinal toxicity and neutropenia during first-line treatment with XELIRI (26% and 11% for XELIRI and first line capecitabine respectively).

The XELIRI has been compared with 5-FU + irinotecan (FOLFIRI) in three randomised studies in patients with metastatic colorectal cancer. The XELIRI regimens included capecitabine 1000 mg/m^2 twice daily on days 1 to 14 of a three-week cycle combined with irinotecan 250 mg/m^2 on day1. In the largest study (BICC-C), patients were randomised to receive either open label FOLFIRI (n=144), bolus 5-FU (mIFL) (n=145) or XELIRI (n=141) and were additionally randomised to receive either double-blind treatment with celecoxib or placebo. Median PFS was 7.6 months for FOLFIRI, 5.9 months for mIFL (p=0.004) for the comparison with FOLFIRI), and 5.8 months for XELIRI (p=0.015). Median OS was 23.1 months for FOLFIRI, 17.6 months for mIFL (p=0.09), and 18.9 months for XELIRI (p=0.27). Patients treated with XELIRI experienced excessive gastrointestinal toxicity compared with FOLFIRI (diarrhoea 48% and 14% for XELIRI and FOLFIRI respectively).

In the EORTC study patients were randomised to receive either open label FOLFIRI (n=41) or XELIRI (n=44) with additional randomisation to either double-blind treatment with celecoxib or placebo. Median PFS and overall survival (OS) times were shorter for XELIRI versus FOLFIRI (PFS 5.9 versus 9.6 months and OS 14.8 versus 19.9 months), in addition to which excessive rates of diarrhoea were reported in patients receiving the XELIRI regimen (41% XELIRI, 5.1% FOLFIRI).

In the study published by Skof et al, patients were randomised to receive either FOLFIRI or XELIRI. Overall response rate was 49% in the XELIRI and 48% in the FOLFIRI arm (p=0.76). At the end of treatment, 37% of patients in the XELIRI and 26% of patients in the FOLFIRI arm were without evidence of the disease (p=0.56). Toxicity was similar between treatments with the exception of neutropenia reported more commonly in patients treated with FOLFIRI.

Montagnani et al used the results from the above three studies to provide an overall analysis of randomised studies comparing FOLFIRI and XELIRI treatment regimens in the treatment of mCRC. A significant reduction in the risk of progression was associated with FOLFIRI (HR, 0.76; 95% CI, 0.62-0.95; P <0.01), a result partly due to poor tolerance to the XELIRI regimens used.

Data from a randomised clinical study (Souglakos et al, 2012) comparing FOLFIRI + bevacizumab with XELIRI + bevacizumab showed no significant differences in PFS or OS between treatments. Patients were randomised to receive either FOLFIRI plus bevacizumab (Arm-A, n=167) or XELIRI plus bevacizumab (Arm-B, n-166). For Arm B, the XELIRI regimen used capecitabine 1000 mg/m^2 twice daily for 14 days + irinotecan 250 mg/m^2 on day 1. Median progression-free survival (PFS) was 10.0 and 8.9 months; p=0.64, overall survival 25.7 and 27.5 months; p=0.55 and response rates 45.5 and 39.8%; p=0.32 for FOLFIRI-Bev and XELIRI-Bev, respectively. Patients treated with XELIRI + bevacizumab reported a significantly higher incidence of diarrhoea, febrile neutropenia and hand-foot skin reactions than patients treated with FOLFIRI + bevacizumab with significantly increased treatment delays, dose reductions and treatment discontinuations.

Data from a randomised multicentre, controlled phase II study (AIO KRK 0604) supports the use of capecitabine at a starting dose of 800 mg/m^2 for 2 weeks every 3 weeks in combination with irinotecan and bevacizumab for the first-line treatment of patients with metastatic colorectal cancer. 120 patients were randomised to a modified XELIRI regimen with capecitabine 800 mg/m^2 twice daily for two weeks followed by a 7-day rest period), irinotecan (200 mg/m^2 as a 30 minute infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg as a 30 to 90 minute infusion on day 1 every 3 weeks ; 127 patients were randomised to treatment with capecitabine (1000 mg/m^2 twice daily for two weeks followed by a 7-day rest period), oxaliplatin (130 mg/m^2 as a 2 hour infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg as a 30 to 90 minute infusion on day 1 every 3 weeks). Following a mean duration of follow-up for the study population of 26.2 months, treatment responses were as shown below:

Table 8: Key efficacy results for AIO KRK study

	XELOX + bevacizumab (ITT: N=127)	Modified XELIRI+ bevacizumab (ITT: N= 120)	Hazard ratio 95% CI P value
Median overall survival			
ITT 95% CI	24.4 months 19.3 - 30.7	25.5 months 21.0 - 31.0	0.90 0.68 - 1.19 P=0.45
Progression-free Survival after 6 months			
ITT 95% CI	76% 69 - 84%	84% 77 - 90%	-
Median progression free survival			
ITT	10.4 months	12.1 months	0.93

95% CI	9.0 - 12.0	10.8 - 13.2	0.82 - 1.07 P=0.30

Combination therapy - Second-line treatment of colorectal cancer:
Data from a multicentre, randomised, controlled phase III clinical study (N016967) support the use of capecitabine in combination with oxaliplatin for the second-line treatment of metastatic colorectal cancer. In this trial, 627 patients with metastatic colorectal carcinoma who have received prior treatment with irinotecan in combination with a fluoropyrimidine regimen as first-line therapy were 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 bevacizumab). 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 9: Key non-inferiority efficacy results for the primary analysis and 6-month follow- up data of Study N016967 (PPP and ITT populations)

PRIMARY ANALYSIS			
XELOX (PPP*: n = 251; ITT: n = 313)**		**FOLFOX-4 (PPP* n = 252; ITT**: n = 314)**	
Population	**Median Time to Event (Days)**		**HR (95% CI)**
Parameter: Progression-free Survival			
PPP	154	168	1.03 (0.87; 1.24)
ITT	144	146	0.97 (0.83; 1.14)
Parameter: Progression-free Survival			
PPP	388	401	1.07 (0.88; 1.31)
ITT	363	382	1.03 (0.87; 1.23)
ADDITIONAL 6 MONTHS OF FOLLOW-UP			
Population	**Median Time to Event (Days)**		**HR (95% CI)**
Parameter: Progression-free Survival			
PPP	154	166	1.04 (0.87; 1.24)
ITT	143	146	1.03 (0.83; 1.14)
Parameter: Progression-free Survival			
PPP	393	402	1.05 (0.88; 1.27)
ITT	363	382	1.02 (0.86; 1.21)

**PPP=per-protocol population; **ITT=intent-to-treat population

A pooled analysis of the efficacy data from first-line (study N016966; initial 2-arm part) and second line treatment (study N016967) 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; 500patients). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of OS (hazard ratio1.01 [95% CI: 0.87; 1.17]) with a median OS of 468 days (XELOX) versus 478 days (FOLFOX-4).

Advanced gastric cancer:
Data from a multicentre, randomised, controlled phase III clinical trial (ML 17032) in patients with advanced or metastatic gastric cancer supports the use of capecitabine in this setting. In this trial, 160 patients were randomised to treatment with capecitabine (1000 mg/m^2 twice a day for 2 weeks followed by a 7-day rest period) and cisplatin (80 mg/m^2 as a 2-hour infusion every 3 weeks). A total of 156 patients were randomised to treatment with 5-FU (800 mg/m^2 per day, continuous infusion on days 1 to 5 every 3 weeks) and cisplatin (80 mg/m^2 as a 2-hour infusion on day 1, every 3 weeks). The median progression-free survival was 5.6 months (cisplatin + capecitabine) versus 5.0 months (cisplatin + 5-FU). The hazard ratio for duration of survival (overall survival) was similar to the hazard ratio for progression-free survival (hazard ratio 0.85; 95% CI 0.64 - 1.13). The median duration of survival was 10.5 months (cisplatin + capecitabine) versus 9.3 months (cisplatin + 5-FU).

Data from a randomised multicentre, phase III study (REAL-2) comparing capecitabine to 5-FU and oxaliplatin to cisplatin in patients with advanced oesophagogastric cancer supports the use of capecitabine for the first-line treatment of advanced oesophagogastric cancer. In this trial, 1,002 patients were randomised in a 2x2 factorial design to one of the following 4 arms:

- ECF: epirubicin (50 mg/m^2 as a bolus on day 1 every 3 weeks), cisplatin (60 mg/m^2 as a 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 g/m^2 as a 2 hour infusion on day 1 every 3 weeks), and capecitabine (625 mg/m^2 twice a day continuously).
- EOF: epirubicin (50 mg/m^2 as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m^2 given as a 2 hour infusion on day 1 every three weeks), and 5-FU (200 mg/m^2 daily given by continuous infusion via a central line).
- EOX: epirubicin (50 mg/m^2 as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m^2 given as a 2 hour infusion on day 1 every three weeks), and capecitabine (625 mg/m^2 twice a day continuously).

The primary efficacy analyses in the per protocol population demonstrated non-inferiority in OS for capecitabine- vs. 5-FU-based regimens (hazard ratio 0.86, 95% CI: 0.8 to 0.99) and for oxaliplatin- vs. cisplatin-based regimens (hazard ratio 0.92, 95% CI: 0.8 to 1.1). 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.

Oxaliplatin has also been used in combination with capecitabine for the treatment of advanced gastric cancer. Studies with capecitabine solely i.e. monotherapy indicate that capecitabine has activity in advanced gastric cancer.

Colon, colorectal and advanced oesophagogastric cancer: meta-analysis:
A six clinical trial meta-analysis of (studies S014796, S014695, N016966, M66001, M17032, N016967) supports replacing 5-FU in monotherapy combination treatment with capecitabine in gastrointestinal cancer. The pooled analysis includes 3097 patients treated with capecitabine-containing regimens and 3,074 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.

Combination therapy - breast cancer:
Data from one randomised multicentre, controlled phase 3 clinical trial support the use of docetaxel in combination with capecitabine 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 a day for 2 weeks followed by a 1-week rest period) and docetaxel (75 mg/m^2 as a 1 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).

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 a day for 2 weeks followed by 1-week rest period). The overall objective response rates (investigator assessment) were 20% (first trial) and 25% (second trial). The median time to progression was 93 and 98 days. Median survival was 384 and

373 days.

All indications:
With data from over 4,700 patients, a meta-analysis of 14 clinical trials for patients treated with capecitabine in combination with different chemotherapy regimens in multiple indications (gastric, colorectal, breast cancer and colon) or with capecitabine monotherapy showed that patients on capecitabine who developed hand-foot syndrome (HFS) had a longer overall survival compared to patients who did not develop HFS: median overall survival 1100 days (95% CI 1007;1200) vs 691 days (95% CI 638;754) with a hazard ratio of 0.61 (95% CI 0.56; 0.66).

Paediatric population:
The European Medicines Agency (EMA) has waived the obligation to conduct capecitabine studies in all subsets of the paediatric population in adenocarcinoma of the rectum and colon and breast carcinoma and gastric adenocarcinoma (see section 4.2 for paediatric use information).

5.2 Pharmacokinetic properties

Capecitabine pharmacokinetics have been evaluated over a dose range of 502-3514 mg/m^2/day. The parameters of 5'-deoxy-5-fluorouridine (5'-DFUR), 5'-deoxy-5-fluorocytidine (5'-DFCR) and capecitabine, measured on days 1 and 14 were similar. The AUC of 5-FU was 30%-35% higher on day 14. Due to non-linear pharmacokinetics for the active metabolite, capecitabine dose reduction more than dose-proportionally, decreases systemic exposure to 5-FU.

Absorption:
Following oral administration, capecitabine is quickly and extensively absorbed into the intestine and transformed to its main metabolites 5'-DFCR and 5'-DFUR. Taking capecitabine with food decreases the rate of absorption, but with only a small effect on the AUC of 5'-DFUR and the subsequent metabolite 5-FU. When administered after food, the peak plasma concentration (C_{max}) for capecitabine 1,250 mg/m^2 on day 14 of a dosing cycle was 4.47 mcg/mL, with C_{max} concentrations for 5'-DFCR, 5'-DFUR, 5-FU and a-fluoro-β-alanine (FBAL) of 4.47, 3.05, 12.1 and 5.45 mcg/mL, respectively. The times to peak plasma concentrations (T_{max}) were 1.50, 2.00, 2.00, 2.00 and 3.34 h, respectively, with corresponding $AUC_{0-\infty}$, values of 7.75, 7.24, 24.6, 2.03 and 36.3 mcg h/mL, respectively.

Distribution:
In *in vitro* human plasma studies, protein binding for capecitabine, 5'-DFCR, 5'-DFUR and 5-FU were 54%, 10%, 62% and 10%, respectively, mainly to albumin.

Biotransformation:
Hepatic carboxylesterase metabolises capecitabine to 5'-DFCR, which is then converted by cytidine deaminase to 5'-DFUR. Cytidine deaminase is principally located in the liver and tumour tissues. 5'-DFUR then undergoes further catalytic activation occurs by thymidine phosphorylase (ThyPase). The catalytic activation enzymes of ThyPase are found in normal tissues, and in tumour tissues at higher 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 (DPD) dihydropyrimidine dehydrogenase to the much less toxic dihydro-5-fluorouracil (FUH2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-

ureidopropionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA (5-fluoro-ureidopropionic acid) to α-fluoro-β-alanine (FBAL) which is cleared in the urine. (DPD) Dihydropyrimidine dehydrogenase 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 unchanged.

Combination therapy:
Phase I studies evaluating the effect of capecitabine on the pharmacokinetics of either paclitaxel or docetaxel and vice versa showed no effect by capecitabine on the pharmacokinetics of paclitaxel or docetaxel (C_{max} and AUC) and no effect by paclitaxel or docetaxel on the pharmacokinetics of 5'-DFUR.

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

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 27 to 86 year old patients which was a wide range of ages and included 234 (46%) patients greater or equal to 65, the pharmacokinetics of 5-FU and 5'-DFUR was not influenced by age. 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-FU, 5'-DFUR, and 5'-DFCR).

5.3 Preclinical safety data

In repeat-dose toxicity studies, capecitabine given orally by daily administration to mice and cynomolgus monkeys produced toxic effects typical for fluoropyrimidines on the lymphoid, haemopoietic, and gastrointestinal systems. These toxicities were reversible. Skin toxicity, characterised by degenerative/regressive changes, was observed with capecitabine. Capecitabine was devoid of CNS and

hepatic toxicities. Cardiovascular toxicity (e.g. QT-interval prolongation and PR-) was detectable after intravenous administration (100 mg/kg) in cynomolgus monkeys but not after repeated (1379 mg/m^2/day) oral dosing.

A two-year carcinogenicity study on mice 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, degenerative and atrophic changes occurred in reproductive organs of male mice; however, these effects were reversible after a drug-free period (see section 4.6).

In teratogenicity and embryotoxicity studies in mice, dose-related increases in teratogenicity and foetal resorption were observed. In monkeys, embryolethality and abortion 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 (i.e. 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

Croscarmellose sodium, microcrystalline cellulose, hypromellulose, lactose monohydrate, magnesium stearate, titanium dioxide, Macrogol 6000, iron oxide red.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life is 24 months (2 years) from manufacture.

6.4 Special precautions for storage

Store Brinov tablets below 25°C.

Brinov tablets should not be used after the expiry date (EXP) which is stated on the pack.
The expiry date refers to the last day of that month.

6.6 Special precautions for disposal

If your doctor advises you to stop taking Brinov tablets, or they have exceeded their expiry date, request information from your pharmacist on what to do with any product that is left over.

6.5 Nature and contents of container

Brinov tablets 150 mg are available in foil blisters containing 60 tablets.
Brinov tablets 500 mg are available in foil blisters containing 120 tablets.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

REX Medical Ltd
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9 DATE OF FIRST APPROVAL

26 February 2015

10 DATE OF REVISION OF THE TEXT

27 July 2022 v1.10

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.3	Updated information on DPD deficiency.
4.4	Updated information on DPD deficiency.