AUSTRALIAN PRODUCT INFORMATION

XELABINE

(capecitabine) film-coated tablets

1 NAME OF THE MEDICINE

Capecitabine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg capecitabine.

Excipients with known effect: sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

XELABINE 500 mg film-coated tablets: peach coloured, oblong shaped, biconvex, film-coated tablets, debossed with "500" on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Colon Cancer

XELABINE 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

XELABINE is indicated for the treatment of patients with advanced or metastatic colorectal cancer.

Oesophagogastric Cancer

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

Breast Cancer

XELABINE is 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.

XELABINE 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Standard Dosage

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

Monotherapy - Colon, Colorectal and 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; given as 3 week cycles.

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 – Adjuvant 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.

Premedication to maintain adequate anti-emesis according to the oxaliplatin product information should be started prior to oxaliplatin administration for patients receiving the capecitabine plus oxaliplatin combination.

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

150 mg tablet strength available in other brands

Table 2: Standard and Reduced Dose Calculations According to Body Surface Area for a Starting Dose of Capecitabine of 1000 mg/m^2

	Dose Level 1000 mg/m^2 (twice daily)				
	Full Dose 1000 mg/m^2	**Number of 150 mg Tablets# and/or 500 mg Tablets per Administration (each administration to be given morning and evening)**		**Reduced dose (75%) 750 mg/m^2**	**Reduced dose (50%) 500 mg/m^2**
Body Surface Area (m^2)	**Dose per Administration (mg)**	**150 mg**	**500 mg**	**Dose per Administration (mg)**	**Dose per Administration (mg)**
≤ 1.26	1150	1	2	800	600
1.27 – 1.38	1300	2	2	1000	600
1.39 – 1.52	1450	3	2	1100	750
1.53 – 1.66	1600	4	2	1200	800
1.67 – 1.78	1750	5	2	1300	800
1.79 – 1.92	1800	2	3	1400	900
1.93 – 2.06	2000	-	4	1500	1000
2.07 – 2.18	2150	1	4	1600	1050
≥ 2.19	2300	2	4	1750	1100

150 mg tablet strength available in other brands

Duration of Treatment

For metastatic disease capecitabine is intended for long-term administration unless clinically inappropriate. In the adjuvant setting, treatment duration is recommended for 24 weeks.

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.

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 3. 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.

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 3: 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

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 metastatic colorectal and breast cancer clinical trials, patients with renal impairment had a greater incidence of Grade 3 or 4 adverse reactions than other patients, the incidence increasing with the degree of renal impairment from 35% in patients with normal renal function to 55% in patients with moderate renal impairment (creatinine clearance 30 - 50 mL/min). Based on the pharmacokinetic data, a dose reduction to 75% is recommended in moderate renal impairment for both monotherapy and combination use. No initial dose reduction is recommended in patients with mild renal impairment (creatinine clearance 51 - 80 mL/min). Further dose reductions should be made if adverse reactions occur (see Table 3). Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min). Capecitabine is contraindicated in patients with creatinine clearance below 30 mL/min (see Section 4.3 CONTRAINDICATIONS).

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 (ADRs), and ADRs that led to discontinuation, compared to younger patients. Careful monitoring of elderly patients is advisable. For treatment with capecitabine in combination with docetaxel, an increased incidence of Grade 3 or 4 treatment related adverse reactions and treatment-related serious adverse reactions were observed in patients 60 years of age or more. 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 Tables 1 and 2.

4.3 CONTRAINDICATIONS

XELABINE is 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)
- known dihydropyrimidine dehydrogenase (DPD) deficiency
- treatment with sorivudine or its chemically related analogues, such as brivudine

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

General

Patients receiving therapy with capecitabine should be monitored by a physician experienced in the use of cancer chemotherapeutic agents. Patients should be carefully monitored for toxicity.

Most adverse reactions are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Information for Patients

Patients and patients' caregivers should be informed of the expected adverse effects of capecitabine, particularly of nausea, vomiting, diarrhoea and hand-foot syndrome. The frequent oral administration of capecitabine allows patient specific dose adaptations during therapy (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Patients should be encouraged to recognise the common toxicities associated with capecitabine treatment.

Diarrhoea

Patients experiencing Grade 2 diarrhoea (an increase of 4 to 6 stools/day or nocturnal stools) or greater should be instructed to stop taking capecitabine immediately. Standard antidiarrhoeal treatments (e.g. loperamide) are recommended.

Nausea

Patients experiencing Grade 2 nausea (food intake significantly decreased but able to eat intermittently) or greater should be instructed to stop taking capecitabine immediately. Initiation of symptomatic treatment is recommended.

Vomiting

Patients experiencing Grade 2 vomiting (2 to 5 episodes in a 24-hour period) or greater should be instructed to stop taking capecitabine immediately. Initiation of symptomatic treatment is recommended.

Hand-foot Syndrome

Patients experiencing Grade 2 hand-foot syndrome (painful erythema and swelling of the hands and/or feet that results in discomfort affecting the patient's activities of daily living) or greater should be instructed to stop taking capecitabine immediately.

Stomatitis

Patients experiencing Grade 2 stomatitis (painful erythema, oedema or ulcers, but able to eat) or greater should be instructed to stop taking capecitabine immediately. Initiation of symptomatic treatment is recommended.

Diarrhoea

Capecitabine can induce diarrhoea, which can sometimes be severe. In patients receiving capecitabine monotherapy, the median time to first occurrence of Grade 2 to 4 diarrhoea was 31 days, and median duration of Grade 3 or 4 diarrhoea was 4.5 days. Patients with severe diarrhoea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. National Cancer Institute of Canada (NCIC) Grade 2 diarrhoea is defined as an increase of 4 to 6 stools/day or nocturnal stools, Grade 3 diarrhoea as an increase of 7 to 9 stools/day or incontinence and malabsorption, and Grade 4 diarrhoea as an increase of $\geq$ 10 stools/day or grossly bloody diarrhoea or the need for parenteral support. Standard antidiarrhoeal treatments (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. Dose reduction should be applied as necessary.

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 patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications applied should be applied for the precipitating adverse event as necessary (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Post-Marketing Experience).

Hand-foot Syndrome

Capecitabine can induce hand-foot syndrome (palmar-plantar erythrodysaesthesia or chemotherapy induced acral erythema), which is a cutaneous toxicity. Persistent or severe hand-foot syndrome (Grade 2 and above) can lead to loss of fingerprints. 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 Section 4.2 DOSE AND METHOD OF 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.

Cardiac

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 electrocardiograph changes. These adverse reactions may be more common in patients with a prior history of coronary artery disease.

Haematologic

In 949 patients with either advanced or metastatic colorectal cancer or breast cancer who received a dose of capecitabine 1250 mg/m^2 twice daily for 2 weeks followed by a 1 week rest period, 3.6, 2.0 and 3.1% of patients had Grade 3 or 4 neutropenia, thrombocytopenia and decreases in haemoglobin respectively.

In 251 patients with metastatic breast cancer who received a dose of capecitabine in combination with docetaxel, abnormal laboratory values showed 68%, 2.8 % and 9.6% of patients had Grade 3 or 4 neutropenia/granulocytopenia, thrombocytopenia and haemoglobin respectively. The majority of cases did not require medical intervention.

Dihydropyrimidine Dehydrogenase Deficiency

Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhoea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity. DPD-deficiency related toxicity usually occurs during the first cycle of treatment or after dose increase. Fatal outcome has been reported in some cases. Absence of this catabolic enzyme appears to result in prolonged clearance of fluorouracil. Special attention should be given to DPD status before therapy through laboratory testing for the detection of total or partial DPD-deficiency, or when evaluating patients experiencing 5-fluorouracil-related toxicities.

Patients with complete DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated with capecitabine (see Section 4.3 CONTRAINDICATIONS). Patients with partial DPD deficiency are at increased risk of severe and potentially life-threatening toxicity. A reduced starting dose should be considered to limit this toxicity. DPD deficiency should be considered as a parameter to be taken into account in conjunction with other routine measures for dose reduction. Initial dose reduction may impact the efficacy of treatment. Consideration should be given to applicable clinical guidelines.

Hyperbilirubinaemia

Capecitabine can induce hyperbilirubinaemia. Administration of capecitabine should be interrupted if treatment-related elevations in bilirubin of > 3.0 x the upper limit of normal (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 949 patients, grade 3 hyperbilirubinaemia occurred in 133 (14.0%) patients and Grade 4 hyperbilirubinaemia occurred in 35 (3.7%) patients. These reactions were rarely associated with significant elevations in alkaline phosphatase or liver transaminases. The majority of these elevations occurred in patients with progressive hepatic metastases.

In 251 patients with metastatic breast cancer who received combination of capecitabine and docetaxel, Grade 3 hyperbilirubinaemia occurred in 6.8% (n = 17) and Grade 4 hyperbilirubinaemia occurred in 2% (n = 5).

Skin Reactions

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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Post-Marketing Experience).

Use in 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 of severe hepatic impairment on the disposition of capecitabine is not known (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES).

Use in Renal Impairment

In patients with moderate renal impairment (creatinine clearance 30 - 50 mL/min) at baseline, a dose reduction to 75% for starting doses is recommended for both monotherapy and combination use. Careful monitoring and prompt treatment interruption is recommended if the patient develops a Grade 2, 3 or 4 adverse reaction with subsequent dose adjustment as outlined in Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

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 reactions is higher in patients with moderate renal impairment (creatinine clearance 30 - 50 mL) (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Dosage Adjustments in Special Populations). Capecitabine is contraindicated in patients with creatinine clearance below 30 mL/min (see Section 4.3 CONTRAINDICATIONS).

Use in the Elderly

In 949 patients assessed for safety, patients were also assessed for the incidence of Grade 3 and 4 reactions in terms of age groups as illustrated in the table below.

Table 4: Summary of the Occurrence (%) of Treatment Related Grade 3 and 4 Adverse Reactions by Age

Age Group (years)	Number of patients at risk	Grade		Diarrhoea	Nausea	Vomiting	Stomatitis	Hand-Foot Syndrome
		3	4					
Total	949	40.7	3.5	13.2	3.7	3.6	4.1	15.9
< 40	46	30.4	0	4.3	2.2	0	6.5	10.9
40 – 59	369	36.3	1.4	13.0	5.1	3.8	3.8	13.6
60 – 69	295	41.7	5.8	14.6	2.7	3.1	3.7	14.6
70 – 79	218	46.8	4.1	11.9	1.8	4.1	4.6	22.9
80 and over	21	61.9	9.5	28.6	14.3	9.5	4.8	14.3

Among patients with colorectal cancer aged 60 to 79 years receiving capecitabine monotherapy in the metastatic setting, the incidence of Grade 3 and 4 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 adverse reactions. When capecitabine was used in combination with other agents, elderly patients (≥ 65 years of age) experienced more Grade 3 and 4 adverse reactions (ADRs) and ADRs 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 in combination with docetaxel showed an increase in the incidence of treatment-related Grade 3 or 4 adverse reactions, treatment-related serious adverse reactions and early withdrawals from treatment due to adverse reactions compared to patients less than 60 years of age.

Paediatric Use

The safety and effectiveness of capecitabine in persons < 18 years of age has not been established.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Food

The effect of food on the pharmacokinetics of capecitabine was investigated in 11 cancer patients. The rate and extent of absorption of capecitabine is decreased when administered with food. The effect on AUC0-∞ of the 3 main metabolites in plasma (5'DFUR, 5-FU, FBAL) is minor. 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 (220 mg/5 mL) and magnesium hydroxide (195 mg/5 mL) 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.

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 metabolites. 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 and associated clinical symptoms.

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.

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

Effects on Fertility

Impairment of fertility was observed in female mice receiving capecitabine at 760 mg/kg/day (2292 mg/m^2/day) - a disruption in the oestrous cycle occurred with a subsequent failure of mating. A reduction in live litter size, decreased fetal weight and fetal abnormalities were observed in mice dosed at 380 mg/kg/day (1174 mg/m^2/day) before implantation. At the no effect dose of 190 mg/kg/day (587 mg/m^2/day), plasma C_{max} for 5'-DFUR was similar to that observed in humans at the recommended dose, while the AUC value was 4-fold lower than that in humans. The effect of capecitabine on female fertility was reversible after a drug-free period.

In male mice, degenerative changes and a decrease in the number of spermatocytes and spermatids were noted at 760 mg/kg/day (2401 mg/m^2/day). At the no-effect dose of 380 mg/kg/day (1201 mg/m^2/day), plasma C_{max} for 5'-DFUR was slightly greater than that observed in humans at the recommended dose, while the AUC was about half that in humans.

Use in Pregnancy – CATEGORY D

Capecitabine may cause foetal harm when administered to pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with capecitabine.

There are no adequate and well-controlled studies in pregnant women using capecitabine. If the medicine is used during pregnancy, or if the patient becomes pregnant while receiving this medicine, the patient should be advised of the potential hazard to the fetus.

Studies Conducted in Animals

Mice

Capecitabine and/or its metabolites have been shown to cross the placenta in mice. Capecitabine was shown to be teratogenic and embryolethal when administered orally to mice during organogenesis at a dose of 198 mg/kg/day (676 mg/m^2/day). Teratogenic findings included cleft palate, anophthalmia, microphthalmia, oligodactyly, polydactyly, syndactyly, kinky tail and dilatation of cerebral ventricles. The non-teratogenic dose level in mice was 50 mg/kg/day (approximately 170 mg/m^2/day). Systemic exposure to 5'-DFUR at the 50 mg/kg/day dose level was not assessed in any studies; however, this dose level is estimated to be about 20 times lower than that in patients dosed at 2510 mg/m^2/day, based on plasma AUC values.

Capecitabine administered to mice dams for the period following organogenesis through to weaning at doses up to 400 mg/kg/day (1428 mg/m^2/day) was not associated with any adverse effects on the dams or offspring. In separate studies, this dose produced 5'-DFUR C_{max} and AUC values about 1.4 and 0.43 times, respectively, of the corresponding values in patients administered 2510 mg/m^2/day.

Monkeys

Capecitabine was embryolethal when administered to dams during organogenesis at a dose of 90 mg/kg/day equivalent to 1095 mg/m^2/day. However, no teratogenic effects were observed in those fetuses that did survive at that dose level. The no-effect dose was 45 mg/kg/day (560 mg/m^2/day), which produced a plasma 5'-DFUR AUC value that was about one third of the corresponding value in patients at the recommended dose.

Use in Lactation

It is not known whether capecitabine and its metabolites are 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. No effects were observed on the offspring of lactating mice dosed orally with capecitabine at 400 mg/kg/day (1428 mg/m^2/day). However, plasma AUC for 5'-DFUR at this dose was lower than that in patients receiving the recommended dose of the medicine. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving capecitabine therapy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

Adverse drug reactions (ADRs) 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. ADRs 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, ADRs 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 adjuvant treatment 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 ADRs was graded according to the toxicity categories of the NCIC CTC grading system.

Table 5: Summary of ADRs 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 skin 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

** Based on the post-marketing experience, persistent or severe palmar-plantar erythrodysaesthesia syndrome can eventually lead to loss of fingerprints (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

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 ADRs 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, oral pain, ADRs 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, cardiac arrest, sudden death, tachycardia, atrial arrhythmias including atrial fibrillation, and ventricular extrasystoles

Nervous System Disorders: insomnia, hypoesthesia, hyperesthesia, confusion, encephalopathy, and cerebellar signs such as ataxia, dysarthria, impaired balance, abnormal coordination, vertigo

Infections and Infestations: ADRs related to bone marrow depression, immune system compromise, and/or disruption of mucous membranes, such as local and fatal systemic infections (including bacterial, viral, fungal etiologies) and sepsis

Blood and Lymphatic System Disorders: anaemia, bone marrow depression, pancytopenia.

Skin and Subcutaneous Tissue Disorders: pruritus, localised exfoliation, skin hyperpigmentation, nail disorders, pigmentation disorders, skin fissures, exfoliative dermatitis, pruritic rash, skin discolouration, photosensitivity reactions, radiation recall syndrome

General Disorders and Administration Site Conditions: pain in limb, chest pain, rigors, malaise

Eye: conjunctivitis, eye irritation

Respiratory: dyspnoea, cough, epistaxis

Musculoskeletal: back pain, myalgia, arthralgia

Metabolic: decreased weight

Psychiatric Disorders: depression

Jaundice, 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 ADRs 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) or, with bevacizumab (e.g. hypertension); however, an exacerbation by capecitabine therapy cannot be excluded.

Table 6: Very Common and Common ADRs for Capecitabine in Combination with Different Chemotherapies in Addition to those Seen for Capecitabine Monotherapy

Body System **Adverse Event**	**Very Common** **≥ 10%**	**Common** **≥ 5% to < 10%**
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

Body System Adverse Event	Very Common ≥ 10%	Common ≥ 5% to < 10%
Psychiatric disorders		Insomnia
Nervous system disorders	Neuropathy peripheral Peripheral sensory neuropathy Taste disturbance Neuropathy Paraesthesia Dysgeusia Dysaesthesia Headache	Hypoaesthesia
Eye disorders	Lacrimation increased	
Vascular Disorders	Thrombosis/embolism Hypertension Lower limb oedema	
Respiratory	Dysaesthesia pharynx Sore throat	Epistaxis Dysphonia Rhinorrhea Dyspnoea
Gastrointestinal disorders	Constipation Dyspepsia	Dry mouth
Skin and subcutaneous tissue disorders	Alopecia Nail disorder	
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia Pain in extremity	Pain in jaw Back Pain
General disorders and administration site disorders	Pyrexia Asthenia Weakness Temperature intolerance	Fever+ Pain

+ Frequencies based on all grades except those denoted with +, which are based on G3/4 ADRs 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 ADRs reported for capecitabine in combination with other chemotherapy are consistent with the ADRs reported for capecitabine monotherapy 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 haemoglobin	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

Parameter[a]	Capecitabine 1250 mg/m^2 twice daily intermittent
	Patients with Grade 3 / 4 abnormality (%)
Decreased sodium	0.4
Increased bilirubin	20
Hyperglycemia	4.4

[a]Laboratory abnormalities were graded according to the categories of the NCIC CTC Grading System.

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 including fatal outcome (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Rare
Nervous system disorders	Toxic leukoencephalopathy	Unknown
Metabolism and nutrition disorders	Hypertriglyceridaemia	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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Very rare
Eye disorders	Lacrimal duct stenosis NOS, Corneal disorders including keratitis	Very rare

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

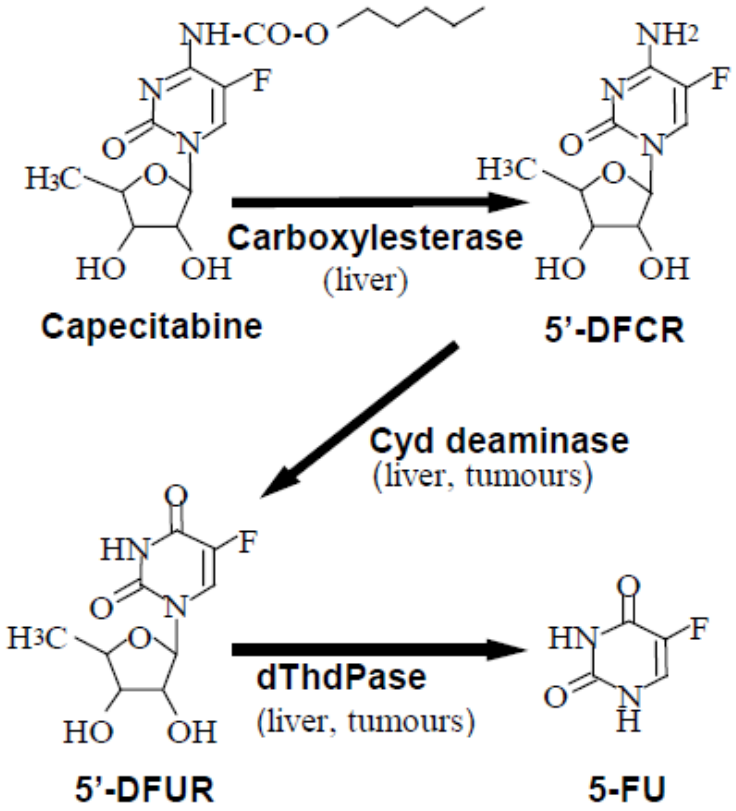
Capecitabine itself is non-cytotoxic; however, it is selectively activated to the cytotoxic moiety, fluorouracil (5-FU), by thymidine phosphorylase in tumours.

Bioactivation

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

Capecitabine is absorbed unchanged from the gastrointestinal tract, metabolised primarily in the liver by the 60 kDa carboxylesterase to 5'-deoxy-5-fluorocytidine (5'-DFCR), which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumour tissue. Further metabolism of 5'-DFUR to the pharmacologically active agent 5-FU occurs mainly at the site of the tumour by the tumour-associated angiogenic factor thymidine phosphorylase (dThdPase), which has levels considerably higher in tumour tissues compared to normal tissues. Several human tumours such as breast, gastric, colorectal, cervical and ovarian cancers have a higher level of thymidine phosphorylase than normal tissues. This minimises the exposure of healthy tissues to systemic 5-FU. Catabolism of 5-FU by dihydropyrimidine dehydrogenase (DPD) leads to formation of dihydro-5-fluorouracil (FUH_2), followed by ring cleavage with dihydropyrimidinase (DHP) to 5-fluoro-ureido-propionic acid (FUPA) and finally to α-fluoro-β-alanine (FBAL) by the enzyme β-ureido-propionase (BUP).

Figure 1: Metabolic Pathway of capecitabine to 5-FU



Mechanism of Action

Both 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 N^{5-10} methylenetetrahydrofolate bind covalently to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding prevents formation of thymidylate from uracil, the necessary precursor of thymidine triphosphate that is required for DNA synthesis. A deficiency of thymidine triphosphate can inhibit cell division. The second mechanism results from the incorporation of FUTP into RNA in place of UTP, thereby preventing the correct nuclear processing of ribosomal RNA and messenger RNA. These effects are most marked on rapidly proliferating cells, such as tumour cells, which utilise 5-FU at a higher rate.

Clinical Trials

Colon and Colorectal Cancer

Monotherapy - Adjuvant Colon Cancer

Data from an open-label, multicentre, randomised, phase III clinical trial investigated the efficacy and safety of capecitabine for the adjuvant treatment in patients who underwent surgery for Dukes' stage C colon cancer (XACT: study M66001). In this trial, 1987 patients were randomised to treatment with capecitabine (1250 mg/m^2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 week cycles for 24 weeks) or 5-FU and leucovorin (Mayo regimen: 20 mg/m^2 leucovorin intravenous (IV) followed by 425 mg/m^2 IV bolus 5-FU, on days 1 to 5, every 28 days for 24 weeks).

The major efficacy parameters assessed were disease free survival (DFS, primary endpoint) and overall survival (OS). The median follow-up at the time of the analysis was 6.9 years. Capecitabine was shown to be at least equivalent to 5-FU/leucovorin in DFS and OS.

Table 8: Adjuvant colon cancer efficacy results monotherapy[1]

Endpoint Parameter	Number of patients (%) without an Event[2]		Hazard Ratio[3] [95% CI]	p-value[4]
	Capecitabine *n* = 1004	5-FU/leucovorin *n* = 983		
Disease Free Survival	65.3	61.3	0.88 [0.77, 1.01]	0.068
Overall Survival	80.1	76.9	0.86 [0.74, 1.01]	0.060

1 All-randomised population
2 For disease free survival event = death, relapse or new occurrence of colon cancer (NOCC); for relapse free survival event = death related to treatment or to disease progression, relapse or NOCC; for overall survival event = death (all causes)
3 Hazard Ratio capecitabine vs. 5-FU/leucovorin. Non-inferiority criterion: 95% CI upper bound ≤1.25
4 Wald chi-square test

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

A phase II open label, multicentre, randomised clinical trial was conducted to explore the efficacy and safety of three different treatment regimens in patients with advanced and/or metastatic colorectal cancer. These were continuous therapy with capecitabine (1331 mg/m^2/day, n= 39) over 12 weeks; intermittent therapy with capecitabine (1250 mg/m^2 twice daily, n = 34) 2 weeks treatment followed by a 1 week rest period, given as 3 week cycles over 12 weeks and intermittent therapy with capecitabine in combination with oral leucovorin (capecitabine 1657 mg/m^2/day; leucovorin 60 mg/day, n = 35). The objective response rate was 22% in the continuous arm, 25% in the intermittent arm and 24% in the combination arm.

Data from two identically-designed, multicentre, randomised, controlled phase III clinical trials (SO14695; SO14796) conducted in 120 centres internationally, compared capecitabine with 5-FU 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 at a daily dose of 1250 mg/m^2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 week cycles over 30 weeks. A total of 604 patients were randomised to treatment with 5-FU/leucovorin (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 mean duration of treatment was 139 days for capecitabine treated patients and 140 days for 5-FU/leucovorin treated patients.

The major efficacy endpoints assessed were time to disease progression (primary endpoint), objective response rate and OS. The objective response rate included partial and complete responses. The results from the two phase III trials were similar; the pooled efficacy data from both trials are given in the table below.

Table 9: Adjuvant Colon Cancer Efficacy Results Monotherapy[1]

Endpoint Parameter	**Capecitabine n = 603**	**5-FU/leucovorin n = 604**	**Difference [95% CI]**
Time to Disease Progression median (range)	140 days (131-161)	144 days (134-164)	HR[2] 1.00 [0.89; 1.12]
Response Rate	25.7%	16.7%	9% [4.3 – 13.5%]
Overall Survival median	392 days	391 days	HR 0.96 [0.85; 1.08]

1 All-randomised population

2 Hazard Ratio capecitabine / 5-FU leucovorin. Non-inferiority criterion: 95% CI upper bound ≤ 1.20

Capecitabine was equivalent to 5-FU/leucovorin in time to disease progression, equivalent in overall survival and superior in objective response rate.

Combination Therapy - First-line Treatment of Metastatic Colorectal Cancer

Data from a multicentre, randomised, controlled phase III clinical study (NO16966) support the use of capecitabine in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab (BV) 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, 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 10: 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	Day 1, prior to XELOX, every 3 weeks

5-Fluorouracil: IV bolus injection immediately after leucovorin

Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4-containing arms in the overall comparison was demonstrated in terms of progression-free survival (PFS) in the eligible per-protocol population (EPP), with progression determined by the study investigators who were not blinded to treatment allocation (see Table 11). 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 Table 11.

Table 11: 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+BV (EPP[#]: *n* = 967)		**FOLFOX-4/FOLFOX-4+P FOLFOX-4+BV (EPP[#]: *n* = 937)**	
Population	**Median Time to Event (Days)**		**HR (97.5% CI)**
Parameter: Progression-free Survival			
EPP (95% CI)	241 (229; 254)	259 (245; 268)	1.05 (0.94; 1.18)
Parameter: Overall Survival			
EPP (95% CI)	577 (535; 615)	549 (528; 576)	0.97 (0.84; 1.14)
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)
Parameter: Overall Survival			
EPP	600	594	1.00 (0.88; 1.13)

[#]EPP = eligible patient population

Study NO16966 also demonstrated superiority of the bevacizumab-containing arms over placebo-containing arms.

Combination Therapy - Second-line Treatment of Metastatic Colorectal Cancer

Data from a multicentre, randomised, controlled phase III clinical study (NO16967) support the use of capecitabine in combination with oxaliplatin for the second-line treatment of metastatic colorectal cancer. In this trial, 627 patients with metastatic colorectal cancer 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. The treatment regimens used in study NO16967 are summarised in the table below.

Table 12: Treatment Regimens in Study NO16967

	Treatment	**Starting Dose**	**Schedule**
FOLFOX-4	Oxaliplatin Leucovorin 5-Fluorouracil	85 mg/m^2 IV 2 h 200 mg/m^2 IV 2 h 400 mg/m^2 IV bolus, 600 mg/m^2 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
XELOX	Oxaliplatin Capecitabine	130 mg/m^2 IV 2 h 1000 mg/m^2 oral bd	Oxaliplatin on Day 1, every 3 weeks Capecitabine oral bd for 2 weeks (followed by 1 week off treatment)

5-Fluorouracil: IV bolus injection immediately after leucovorin

XELOX was demonstrated to be non-inferior to FOLFOX-4 in terms of PFS in the per-protocol population (see Table 13). The criterion set for concluding non-inferiority was the upper limit of the 95% confidence interval for the hazard ratio for PFS was less than 1.30. The results for overall survival were similar to those for PFS. The median follow up at the time of primary analyses in the intent-to-treat population was 2.1 years; data from analyses following an additional 6 months of follow up are also included in Table 13.

Table 13: 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)		**FOLFOX-4 (PPP[#]: *n* = 252)**	
Population	**Median Time to Event (Days)**		**HR (95% CI)**
Parameter: Progression-free Survival			
PPP (95% CI)	154 (140; 175)	168 (145; 182)	1.03 (0.87; 1.24)
Parameter: Overall Survival			
PPP (95% CI)	388 (339; 432)	401 (371; 440)	1.07 (0.88; 1.31)
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)
Parameter: Overall Survival			
PPP	393	402	1.05 (0.88; 1.27)

[#]PPP = per-protocol 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 (1000mg/m^2 twice daily for 2 weeks followed by a 1 week rest period) and cisplatin (80 mg/m^2 as a 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). Patients received treatment for at least 6 weeks (2 cycles) and were treated until disease progression or unacceptable toxicity.

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. Duration of survival (overall survival) with the combination of capecitabine and cisplatin was also at least equivalent to that of 5-FU and cisplatin.

Table 14: Summary of Results for Key Efficacy Parameters (PPP, Study ML17032)

Endpoint Parameter	Capecitabine/cisplatin *n* = 139	5-FU/Cisplatin *n* = 137	Hazard Ratio [95% CI]#
Progression-Free Survival median (months) [95% CI]	5.6 [4.9, 7.3]	5.0 [4.2, 6.3]	0.81 [0.63, 1.04]
Duration of Survival median (months) [95% CI]	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:

Table 15: Treatment Regimens in the REAL-2 Study

Treatment	Starting Dose	Schedule
Epirubicin (E) Cisplatin (C) 5-Fluorouracil (F)	50 mg/m^2 IV bolus 60 mg/m^2 2 hour IV infusion 200 mg/m^2 continuous infusion via a central line	Day 1, every 3 weeks Day 1, every 3 weeks Daily
Epirubicin (E) Cisplatin (C) Capecitabine (X)	50 mg/m^2 IV bolus 60 mg/m^2 2 hour IV infusion 625 mg/m^2 bd orally	Day 1, every 3 weeks Day 1, every 3 weeks Twice daily
Epirubicin (E) Oxaliplatin (O) 5-Fluorouracil (F)	50 mg/m^2 IV bolus 130 mg/m^2 2 hour IV infusion 200 mg/m^2 continuous infusion via a central line	Day 1, every 3 weeks Day 1, every 3 weeks Daily
Epirubicin (E) Oxaliplatin (O) Capecitabine (X)	50 mg/m^2 IV bolus 130 mg/m^2 2 hour IV infusion 625 mg/m^2 bd orally	Day 1, every 3 weeks Day 1, every 3 weeks Twice daily

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.

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) with capecitabine-containing regimens indicating that they are comparable to 5-FU containing regimens.

Monotherapy - Breast Cancer

Two phase II open label, multicentre trials were conducted to evaluate the efficacy and safety of capecitabine in patients with locally advanced and/or metastatic breast cancer who had been previously treated with taxanes. Capecitabine was administered at a dose of 1250 mg/m^2 twice daily for 2 weeks treatment followed by a 1 week rest period, given as 3 week cycles.

In the first trial, 162 female outpatients were selected from an investigator's current practice or from referred patients. This heavily pre-treated patient population was refractory to previous paclitaxel therapy (77% resistant, 23% failed). Additionally, most patients were resistant (41%) or had failed (26%) previous anthracycline therapy and 82% had been exposed to 5-FU.

In the second trial, 74 patients were treated; all but three had received prior treatment with taxanes (paclitaxel and/or docetaxel). In addition, over 95% had previously been treated with an anthracycline-based chemotherapy.

Table 16: Breast Cancer Monotherapy Efficacy Results[1]

Endpoint Parameter	**Capecitabine with paclitaxel *n* = 162**	**Capecitabine with paclitaxel/docetaxel *n* = 74**
Response Rate (95% CI)	20% (13.6 - 27.8)	24.6% (15.05 – 36.49)
Duration of Response median (range)	241 days (97 – 324)	253 days (213 – 301)
Time to Disease Progression median (95% CI)	93 days (84 – 106)	98 days (71 – 130)
Survival median	384 days	373 days

1 Intent to Treat population

A prospectively defined clinical benefit response score (pain, analgesic consumption and Karnofsky Performance Status) was used to assess the effect of treatment on tumour-associated morbidity. The overall clinical benefit response was positive in 29 patients (20%) in the first trial and 8 patients (15%) in the second trial, 45 patients (31%) and 22 patients (41%), respectively, remained stable.

Of the 51 patients with baseline pain ≥ 20 mm on the visual analogue scale in the first trial, 24 patients (47%) had a positive response in pain intensity (greater than or equal to 50% decrease lasting for at least 4 weeks), similar analysis in the second trial showed 7/27 patients (26%) had a positive pain response.

Combination Therapy - Breast Cancer

The dose of capecitabine used in the phase III clinical trial in combination with docetaxel was based on the results of a phase I trial, where a range of doses of docetaxel given every 3 weeks in combination with an intermittent regimen of capecitabine (2 weeks treatment followed by a 1 week rest period) were evaluated. The combination dose regimen was selected based on the tolerability profile of docetaxel 75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks in combination with 1250 mg/m^2 twice daily for 2 weeks of capecitabine administered every 3 weeks for at least 6 weeks. The approved dose of 100 mg/m^2 of docetaxel administered every 3 weeks was the control arm of the phase III study.

Capecitabine in combination with docetaxel was assessed in an open label, multicentre, randomised trial. A total of 511 patients with locally advanced and/or metastatic breast cancer resistant to, or recurring after an anthracycline containing therapy, or relapsing during or recurring within two years of completing an anthracycline containing adjuvant therapy were enrolled. In this trial, 255 patients were randomised to receive capecitabine in combination with docetaxel and 256 patients received docetaxel alone.

Capecitabine in combination with docetaxel resulted in statistically significant improvements in time to disease progression, overall survival and objective response rate compared to monotherapy with docetaxel as shown in Table 17 and Figures 2 and 3. Health related quality of life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC-QLQ; C30 version 2, including Breast Cancer Module BR23). HRQoL was similar in the two treatment groups.

Table 17: Breast Cancer Combination Treatment Efficacy Results[1]

Endpoint Parameter	**Capecitabine/docetaxel *n* = 255**	**docetaxel *n* = 256**	**Difference**	***p*-value**
Time to Disease Progression median [95% CI]	186 days [165, 198]	128 days [105, 136]	HR[2] = 0.643 [0.563, 0.770]	0.0001
Survival median [95% CI]	442 days [374, 492]	352 days [298, 362]	HR = 0.753 [0.603, 0.940]	0.0126

Response Rate [95% CI]	41.6% [35.5, 47.9]	29.7% [24.2, 35.7]	11.9% [3.4, 20.0]	0.0058

[1] All-randomised population. Investigator assessment.
[2] Hazard Ratio

Figure 2: Kaplan-Meier Estimates for Time to Disease Progression Capecitabine and Docetaxel vs. Docetaxel

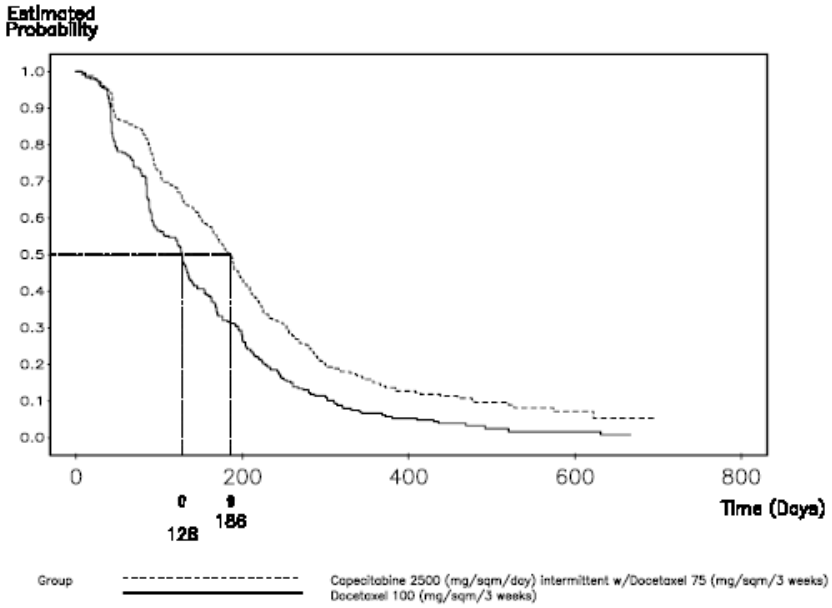
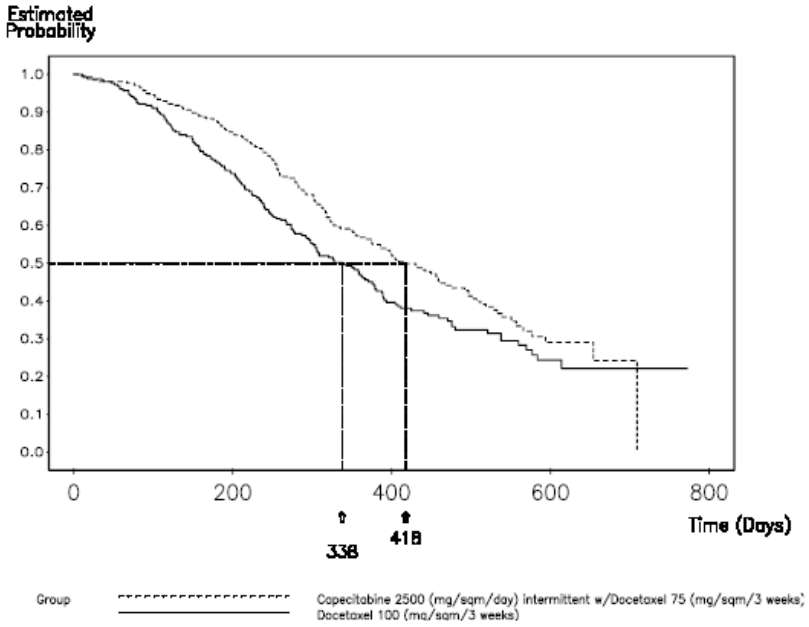


Figure 3: Kaplan-Meier Estimates of Survival Capecitabine and Docetaxel vs. Docetaxel



5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics in Tumours and Adjacent Healthy Tissue

A pharmacokinetic study in 19 colorectal patients was conducted investigating the tumour selectivity of capecitabine comparing 5-FU concentrations in tumour, healthy tissue and plasma. Following oral administration of capecitabine (1250 mg/m^2 twice daily, 5 to 7 days before surgery), concentrations of 5-FU were significantly greater in primary tumour than in adjacent healthy tissue (geometric mean ratio 2.5; 95% CI: [1.5 to 4.1]) and plasma (geometric mean ratio 14).

Thymidine phosphorylase activity was four times greater in primary tumour tissue (colon) than in normal tissue.

Human Pharmacokinetics

The pharmacokinetics of capecitabine and its metabolites have been evaluated in 11 studies in a total of 213 cancer patients at a dosage range of 502 to 3514 mg/m^2/day. In the dose range of 250 to 1250 mg/m^2 as a single dose, the pharmacokinetics of capecitabine and its metabolites were dose proportional, except for 5-FU. Area under the curve (AUC) of 5-FU was 30% higher on day 14, but did not increase subsequently (day 22). A summary of key data for a dose of 1255 mg/m^2 twice daily is presented below:

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 of 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. The absorption of capecitabine is confirmed since 95.5% of an orally administered dose is recovered in urine.

Distribution

In vitro human plasma studies have determined that capecitabine, 5'-DFCR, 5'-DFUR and 5-FU are 54%, 10%, 62% and 10% protein bound respectively, 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. 5-FU is further catabolised to the inactive metabolites dihydro-5-fluorouracil (FUH_2), 5-fluoro-ureidopropionic acid (FUPA) and α-fluoro-β-alanine (FBAL) via dihydropyrimidine dehydrogenase (DPD), which is rate limiting.

Excretion

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 the urine as unchanged drug.

Pharmacokinetic Parameters

Table 18 shows the time course of pharmacokinetic parameters for capecitabine and 5-FU in plasma at steady-state (day 14) following administration of the recommended dose (1250 mg/m^2 twice daily) in 8 cancer patients. The peak of plasma concentrations of intact drug and 5-FU are reached within 1.5 and 2 hours, respectively (median times), and the concentrations decline with half-lives of 0.85 and 0.76 hours, respectively.

Table 18: Pharmacokinetic Parameters Estimated on Day 14 After Administration of Capecitabine (1250 mg/m^2 twice daily) in 8 Cancer Patients

Parameter	Capecitabine	5-FU
C_{max} (µg/mL)	3.99	0.709
t_{max} (h)	1.50 (0.78 – 2.17)[#]	2.00 (1.28 – 4.08)
AUC_{0-t} (µg.h/mL)	7.29	1.62
$AUC_{0-\infty}$ (µg.h/mL)	7.40	1.63
$T_{1/2}$ (h)	0.85	0.76

[#] Median values (min-max) are reported for t_{max}

Combination Therapy

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

Pharmacokinetics in Special Populations

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for recommendations regarding the use of capecitabine in (i) the elderly; (ii) patients with hepatic impairment and (iii) patients with renal impairment.

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, AST/ALT had no statistically significant effect on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL.

Elderly

A population pharmacokinetic analysis which included patients with a wide range of ages (27 to 86 years) and included 234 (46%) patients greater or equal to 65 years of age, found 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.

Race

Based on the 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 black patients were not different compared to white patients. For the other minority groups the numbers were too small to draw a conclusion. Limited available data suggest that there are no clinically significant differences in capecitabine pharmacokinetics between Caucasians and Oriental subjects.

Hepatic Impairment

Capecitabine has been evaluated in patients with mild to moderate hepatic impairment due to liver metastases as defined by a composite score including bilirubin, AST/ALT and alkaline phosphatase. C_{max} of capecitabine, 5'-DFUR and 5-FU were increased by 49%, 33% and 28%, respectively. $AUC_{0-\infty}$ of capecitabine 5'-DFUR and 5-FU were increased by 48%, 20% and 15%, respectively. Conversely, Cmax and AUC of 5'-DFCR decreased by 29% and 35%, respectively. Therefore, bioactivation of capecitabine is not affected.

Renal Impairment

A pharmacokinetic study in cancer patients with mild to severe renal impairment showed that renal impairment significantly increased systemic 5'-DFUR exposure.

5'-DFUR is the direct precursor of 5-FU and is considered an indicator of tissue exposure to 5- FU. A 50% reduction in creatinine clearance increased 5'-DFUR AUC by 35%, 95% CI: [12, 64], on the first day of capecitabine treatment. Exposure to another metabolite, FBAL increased 114%, 95% CI: [73, 165], when creatinine clearance was decreased by 50%. This was expected since most of the capecitabine dose is recovered as FBAL in urine. FBAL does not have anti-tumour activity.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Capecitabine was not mutagenic or clastogenic in the following models: in vitro Ames test (bacterial) and V79/HPRT (mammalian) gene mutation assays and *in vivo* mouse micronucleus test. However, consistent with the known chromosome-damaging potential of nucleoside analogs, capecitabine was clastogenic *in vitro* in human peripheral blood lymphocytes in the absence of S9 metabolic activation.

Carcinogenicity

In a two year carcinogenicity study in mice, there was no evidence for a carcinogenicity potential of capecitabine at dietary doses up to 90 mg/kg/day (270 mg/m^2/day). In terms of plasma AUC values, systemic exposure to capecitabine and 5'-DFUR at the highest dose was at least 10 times lower than that in humans at the recommended dose.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, hypromellose, and magnesium stearate. The peach or light peach film coating contains hypromellose, purified talc, titanium dioxide and iron oxide yellow, iron oxide red and purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in a dry place.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: blister packs (either Al/Al or PVC/PVdC/Al)

Pack sizes: 30, 60, 120

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

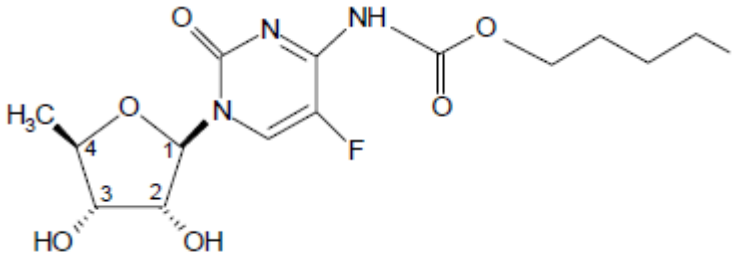
AUST R 213045 – XELABINE capecitabine 500 mg film-coated tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Chemical name: 5'-deoxy-5-fluoro-N-[(pentyloxy)carbonyl]- cytidine

Molecular formula: $C_{15}H_{22}FN_3O_6$

Molecular weight: 359.35

Capecitabine is an oral, antineoplastic agent belonging to the fluoropyrimidine carbamate class. It was rationally designed as an orally administered precursor of 5'-deoxy-5-fluorouridine (5'-DFUR), which is selectively activated to the cytotoxic moiety, fluorouracil, in tumours. Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20°C.

CAS Number

154361-50-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

03/07/2014

10 DATE OF REVISION

05/05/2025

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial change throughout document
2, 3, 6.5	Minor editorial changes to remove 150 mg strength

4.2	Update to Table 1: Standard and Reduced Dose Calculations According to Body Surface Area for a Starting Dose of Capecitabine of 1250 mg/m2 Update to Table 2: Standard and Reduced Dose Calculations According to Body Surface Area for a Starting Dose of Capecitabine of 1000 mg/m2

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