AUSTRALIAN PRODUCT INFORMATION – CAPECITABINE-DRLA (CAPECITABINE) TABLETS

1 NAME OF THE MEDICINE

Capecitabine

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

Capecitabine tablets are supplied as biconvex oblong film-coated tablets for oral administration. Each light peach coloured tablet contains 150 mg capecitabine and each peach coloured tablet contains 500 mg capecitabine.

Excipients with known effect: lactose. For the full list of excipients, see Section 6.1 List of excipients.

150 mg: Light peach film-coated tablet of biconvex, oblong shape with the marking "150" on one side and "RDY" on other side.

500 mg: Peach, film-coated tablet of biconvex, oblong shape with the marking "500" on one side and "RDY" on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

Colorectal Cancer
Capecitabine-DRLA tablets are indicated for the treatment of patients with advanced or metastatic colorectal cancer.

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

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

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

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, 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

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

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 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 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

Capecitabine-DRLA tablets are contraindicated in patients who have:

- a known hypersensitivity to capecitabine or to any of the excipients contained in the tablets
- a history of severe and unexpected reactions to fluoropyrimidine therapy or with known hypersensitivity to fluorouracil
- severe renal impairment (creatinine clearance below 30 mL/min)
- 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

Identified precautions

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 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 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 anti- diarrhoeal 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 ≥10 stools/day or grossly bloody diarrhoea or the need for parenteral support. Standard anti-diarrhoeal 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 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 4.8 ADVERSE EFFECTS).

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 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 1 250 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

Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhoea, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity. A link between decreased levels of DPD and increased potentially fatal toxic effects of 5-FU therefore cannot be excluded.

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 aminotransfereases 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 Necrosis (TEN). Capecitabine should be permanently discontinued in patients who experience a severe skin reaction possibly attributable to capecitabine treatment (see 4.8 ADVERSE 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 5.2 PHARMACOKINETIC PROPERTIES and 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 4.2 DOSE AND METHOD OF ADMINISTRATION section.

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 *Dose Adjustment in Special Populations*). Capecitabine is contraindicated in patients with creatinine clearance below 30 mL/min (see 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 60-79 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 $AUC_{0-\infty}$ 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) andmagnesium 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 metabolities. Patients taking coumarin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR) and the anticoagulant dose adjusted accordingly.

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

Capecitabine may cause foetal harm when administered to pregnant women. Women of child bearing 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 foetus.

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 Cmax 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 tissue disorders	Palmar-plantar erythrodysaesthesia syndrome** (G3/4: 17%) Dermatitis (G3/4: < 1%)	Rash, Alopecia Erythema (G3/4: 1%) Dry Skin (G3/4: < 1%)
General disorders and administration site conditions	Fatigue (G3/4: 3%) Lethargy (G3/4: < 1%)	Pyrexia (G3/4: < 1%) Weakness (G3/4: < 1%) Asthenia (G3/4: < 1%)

[#] stomatitis, mucosal inflammation, mucosal ulceration, mouth ulceration

** Based on the post-marketing experience, persistent or severe palmar-plantar erythrodysaesthesia syndrome can eventually lead to loss of fingerprints.

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, hypertension seen with bevacizumab); 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
Psychiatric disorders		Insomnia
Nervous system disorders	Neuropathy peripheral Peripheral sensory neuropathy Neuropathy Taste disturbance Paraesthesia Dysgeusia Dysaesthesia Headache	Hypoaesthesia
Eye disorders	Lacrimation increased	
Vascular Disorders	Thrombosis/embolism Hypertension Lower limb oedema	
Respiratory	Dysaesthesia pharynx Sore throat	Epistaxis Dysphonia Rhinorrhoea Dyspnoea
Gastrointestinal disorders	Constipation Dyspepsia	Dry mouth
Skin and subcutaneous tissue disorders	Alopecia Nail disorder	
Musculoskeletal and connective tissue disorders	Arthragia Myalgia Pain in extremity	Pain in jaw Back Pain

General disorders and administration site conditions	Pyrexia Asthenia Weakness Temperature intolerance	Fever [+] Pain

[+] *Frequencies based on all grades except those denoted with [+], which are based on G3/4 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 monotherapyy or the combination product monotherapy (refer to the product information document for the combination product).

Laboratory Abnormalities

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

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

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

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

POST-MARKETINGEXPERIENCE

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 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 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

Mechanism of action

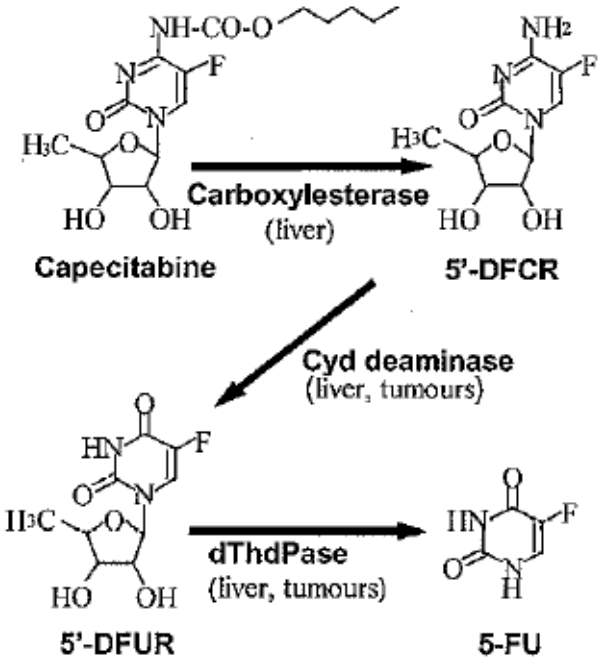
Capecitabine itself is non-cytotoxic; however, it is selectively activated to the cytotoxic moiety, fluorouracil (5-FU), by thymidine phosphorylase in tumours.

Bioactivation

Capecitabine is a fluoropyrimidine carbamate derivative that was designed as an orally administered, tumour-activated and tumour-selective cytotoxic agent. Capecitabine is non-cytotoxic *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 (FUH2), 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, multicenter, 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, multicenter, 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: Metastatic colorectal cancer pooled trials 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, investigator assessment
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 multicenter, randomised, controlled phase III clinical study (NO16966) support the use of capecitabine in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab (BV) for the first-line treatment of metastastic colorectal cancer. The study contained two parts: an initial 2-arm part in which patients were randomised to two different treatment groups, XELOX or FOLFOX-4, and a subsequent 2x2 factorial part with four different treatment groups, XELOX + placebo (P), FOLFOX-4 + P, XELOX+BV, and FOLFOX-4 + BV. The treatment regimens are summarised in the table below.

Table 10: Treatment regimens in study NO16966

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + BV	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
	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/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)
	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 5). The criterion set for concluding non- inferiority was that the upper limit of the 97.5% confidence interval for the hazard ratio for PFS was less than 1.23. The results for OS are similar to those reported for PFS. A comparison of XELOX plus BV versus FOLFOX-4 plus BV was a pre-specified exploratory analysis. In this treatment subgroup comparison, XELOX plus BV was similar compared to FOLFOX-4 plus BV in terms of PFS (hazard ratio 1.01 [97.5% CI 0.84, 1.22]). The median follow up at the time of the primary analyses in the intent-to-treat population was 1.5 years; data from analyses following an additional 1 year of follow up are included in 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 multicenter, randomised, controlled phase III clinical study (NO16967) support the use of capecitabine in combination with oxaliplatin for the second-line treatment of metastastic colorectal cancer. In this trial, 627 patients with metastatic colorectal 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 (1000 mg/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)	50 mg/m^2 IV bolus	Day 1, every 3 weeks
Cisplatin (C)	60 mg/m^2 2 hour IV infusion	Day 1, every 3 weeks
5-Fluorouracil (F)	200 mg/m^2 continuous infusion via a central line	Daily
Epirubicin (E)	50 mg/m^2 IV bolus	Day 1, every 3 weeks
Cisplatin (C)	60 mg/m^2 2 hour IV infusion	Day 1, every 3 weeks
Capecitabine (X)	625 mg/m^2 bd orally	Twice daily
Epirubicin (E)	50 mg/m^2 IV bolus	Day 1, every 3 weeks
Oxaliplatin (O)	130 mg/m^2 2 hour IV infusion	Day 1, every 3 weeks
5-Fluorouracil (F)	200 mg/m^2 continuous infusion via a central line	Daily
Epirubicin (E)	50 mg/m^2 IV bolus	Day 1, every 3 weeks
Oxaliplatin (O)	130 mg/m^2 2 hour IV infusion	Day 1, every 3 weeks
Capecitabine (X)	625 mg/m^2 bd orally	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) indicating that capecitabine-containing regimens are comparable to 5-FU containing regimens.

Monotherapy - Breast cancer

Two phase II open label, multicenter 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, multicenter, 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 11 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]	 352days [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

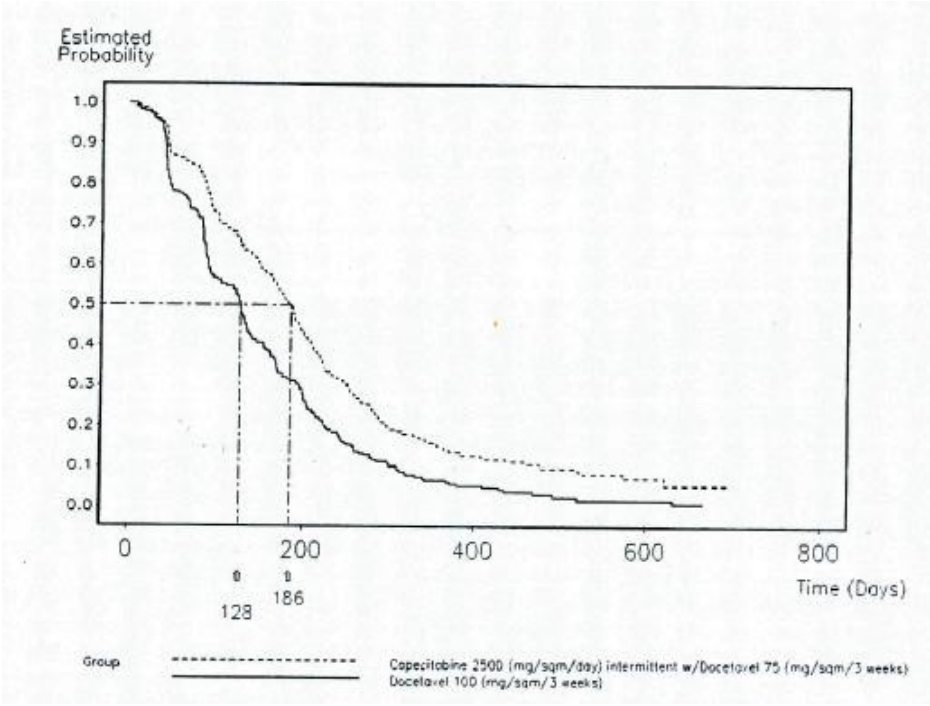
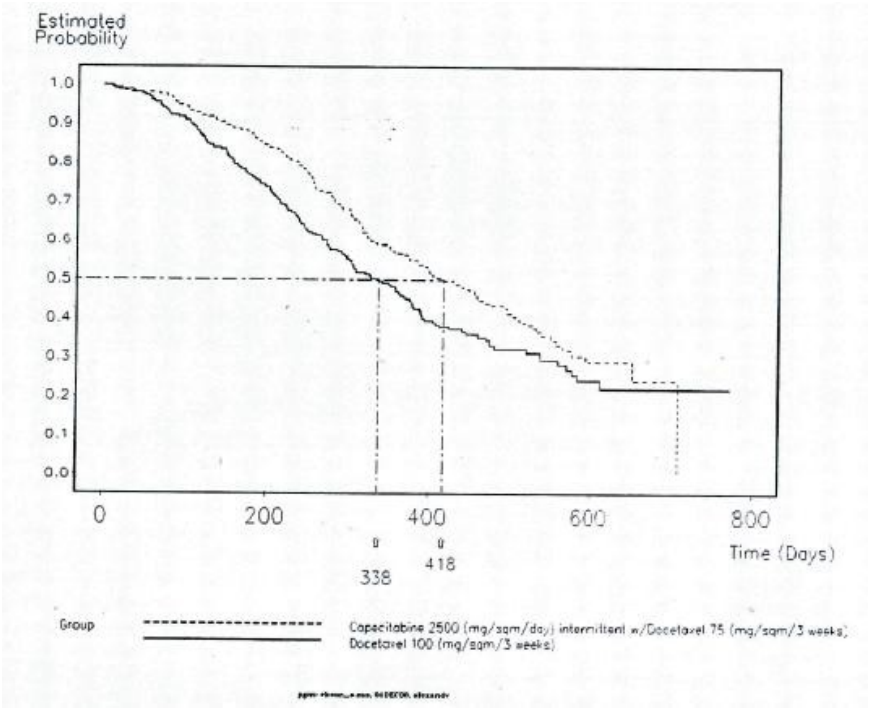


Figure 3. Kaplan-Meier Estimates of Survival Capecitabine and Docetaxel vs. Docetaxel



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 (FUH2), 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 also 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.2 DOSE AND METHOD OF ADMINISTRATION 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, C_{max} 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 inactive ingredients in capecitabine tablets are anhydrous lactose, croscarmellose sodium, hypromellose, microcrystalline cellulose and magnesium stearate. The peach or light peach film coating contains hypromellose, purified talc, titanium dioxide and iron oxide yellow (CI77492) and iron oxide red (CI77491).

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

Capecitabine-DRLA tablets should be stored below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister packs of 60 or 120.

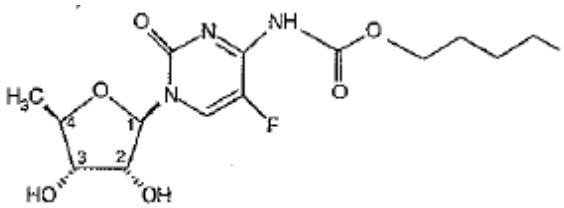
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name for capecitabine is 5'-deoxy-5-fluoro-N-[(pentyloxy)carbonyl]-cytidine.



Molecular formula: $C_{15}H_{22}FN_3O_6$
Molecular weight: 359.35.

CAS number

154361-50-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Dr. Reddy's Laboratories (Australia) Pty Ltd
Level 9, 492 St Kilda Road
Melbourne, VIC, 3004

9 DATE OF FIRST APPROVAL

24 June 2013

10 DATE OF REVISION

25 September 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Dehydration may cause acute renal failure with fatal outcome. Persistent or severe hand-foot syndrome (Grade 2 and above) can lead to loss of fingerprints. Skin reactions: Capecitabine can induce severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN).
4.8	Change of reported frequencies for asthenia, taste disturbance, lethargy Update of post-marketing experience.

CAPECITABINE-DRLA

Film-Coated Tablets
pronounced cap-eh-SITE-ah-bean

contains the active ingredient capecitabine

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about Capecitabine-DRLA tablets.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you taking this medicine against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your doctor or pharmacist.

Keep this leaflet with the medicine.

You may need to read it again.

What this medicine is used for

Capecitabine-DRLA contains the active ingredient capecitabine.

Capecitabine-DRLA belongs to a group of medicines called anti-neoplastic agents. Within this group, Capecitabine-DRLA belongs to a class of medicines called fluoropyrimidine analogues.

Capecitabine-DRLA is used to treat cancer of the bowel and rectum (colorectal), breast and stomach and food pipe (oesophagus). It may be prescribed alone or in combination with other medicines used to treat cancer, such as chemotherapy medicines.

The medicine contained in Capecitabine-DRLA tablets, capecitabine, is converted by the liver and cancer cells to another medicine called 5-fluorouracil (also called 5-FU).

It is 5-FU that acts to kill or stop the growth of cancer cells.

Your doctor may have prescribed Capecitabine-DRLA for another purpose.

Ask your doctor if you have any questions why Capecitabine-DRLA has been prescribed for you.

This medicine is available only with a doctor's prescription.

Capecitabine-DRLA is not addictive.

Before you take this medicine

When you must not take it

Do not take Capecitabine-DRLA if:

1. **you have had an allergy to**

- **Capecitabine or any of the ingredients listed at the end of this leaflet**
- **5-fluorouracil (also called 5-FU), a medicine used to treat cancer**
- **Other fluoropyrimidine medicines**

Some of the symptoms of an allergic reaction may include:

- shortness of breath
- wheezing or difficulty in breathing
- swelling of the face, lips, tongue or other parts of the body
- rash, itching, hives on the skin

2. **if you have severe kidney disease**
3. **if you have known dihydropyrimidine dehydrogenase (DPD) deficiency**
4. **you are taking a medicine containing sorivudine or brivudine**

Taking sorivudine or brivudine at the same time as Capecitabine-DRLA is potentially fatal.

5. **the package is torn or shows signs of tampering**
6. **the expiry date (EXP) printed on the pack has passed**

If you take this medicine after the expiry date has passed, it may not work as well.

If you are not sure if you should be taking Capecitabine-DRLA, talk to your doctor.

Use in children

Do not give this medicine to children.

Safety and effectiveness in persons less than 18 years of age have not been established.

Before you start to take it

Tell your doctor or pharmacist if you have allergies to:

- **any of the ingredients listed at the end of this leaflet**

- **any other medicines**
- **any other substances, such as foods, preservatives or dyes.**

Tell your doctor if:

1. **you are pregnant or plan to become pregnant**

   Capecitabine-DRLA may be harmful to an unborn baby when taken by a pregnant woman. It is not recommended that you take Capecitabine-DRLA while you are pregnant. Additionally, if you are a woman, you should use effective contraception to avoid becoming pregnant while you are taking Capecitabine-DRLA.

2. **you are breast-feeding or plan to breast-feed**

   It is not known whether Capecitabine-DRLA and 5-FU pass into breast milk. You doctor will discuss the risks and benefits of you taking Capecitabine-DRLA if you are breast-feeding.

3. **you have any other health problems, especially the following:**
   - **heart disease**
   - **liver disease**
   - **kidney disease**
4. **you are dehydrated**

   - some signs and symptoms of dehydration include:
     - dry skin
     - dark coloured urine
     - thirst
     - weakness or fatigue
     - loss of appetite
5. **you plan to have surgery.**

If you have not told your doctor about any of the above, tell them before you start taking Capecitabine-DRLA.

Taking other medicines

Tell your doctor if you are taking any other medicines including any that you have bought without a prescription from a pharmacy, supermarket or healthfood shop.

Some medicines may interfere with Capecitabine-DRLA. These medicines include:

- warfarin (Coumadin®, Marevan®), a medicine used to thin the blood
- phenytoin (Dilantin®), a medicine used to treat epilepsy and heart irregularities
- leucovorin, also called folinic acid, a medicine used to treat folic acid deficient anaemias
- antacids, medicines used to treat heart burn or indigestion

These medicines may be affected by Capecitabine-DRLA, or may affect how well Capecitabine-DRLA works. You may need to use different amounts of your medicines, or take different medicines. Your doctor will advise you.

Your doctor or pharmacist has more information on medicines to be careful with or avoid while taking Capecitabine-DRLA.

How to take Capecitabine-DRLA

How much to take

Take Capecitabine-DRLA exactly as your doctor has prescribed.

Capecitabine-DRLA may be given with or without chemotherapy. Your doctor will tell you how many Capecitabine-DRLA tablets to take each day and how often to take them. Your doctor will calculate the dose based on your height and weight.

Your doctor may want you to take a combination of 150 mg (light peach colour) and 500 mg (peach colour) tablets for each dose.

If a combination of tablets is prescribed, it is very important that you correctly identify the tablets.

Your doctor may vary your dose depending on the nature of your illness and your response to Capecitabine-DRLA. Elderly patients may need to receive less.

Use in elderly

The same dose is recommended for elderly patients given Capecitabine-DRLA alone. A lower dose may be given to elderly patients taking Capecitabine-DRLA in combination with other medicines to treat cancer. Please follow your doctor's instructions carefully.

How to take it

Swallow the tablets whole with a glass of water.

Do not chew the tablets.

When to take it

Take Capecitabine-DRLA tablets twice a day (morning and evening).

Capecitabine-DRLA tablets should be taken with food. You should take Capecitabine-DRLA no later than 30 minutes after food.

Take Capecitabine-DRLA tablets at about the same time each day.

Taking your tablets at the same time each day will have the best effect. It will also help you remember when to take the tablets.

When taken in combination with chemotherapy, your doctor will advise which days of your

treatment cycle Capecitabine-DRLA should be taken.

If you are not sure when to take Capecitabine-DRLA, ask your doctor.

How long to take it

The duration of treatment with Capecitabine-DRLA varies, depending on the nature of your illness and your individual response to the treatment.

Your Capecitabine-DRLA therapy is made up of a series of treatment cycles which usually lasts for 21 days. Your doctor will advise you how many cycles of treatment you will have and whether there are any rest days in the cycle.

In most cases, your treatment cycle will consist of intermittent Capecitabine-DRLA therapy, where you will take Capecitabine-DRLA for 14 days, followed by a rest period of 7 days. During the rest period, you will not take any Capecitabine-DRLA.

Alternatively, your treatment cycle may be continuous, which involves 21 days of Capecitabine-DRLA treatment and no rest period.

Continue taking Capecitabine-DRLA until your doctor tells you to stop.

If you forget to take Capecitabine-DRLA

Do not take an extra dose. Wait until the next dose and take your normal dose then.

Do not try to make up for the dose that you missed by taking more than one dose at a time.

If you are not sure what to do, ask your doctor or pharmacist.

If you take too much (overdose)

Immediately telephone your doctor or the Poisons Information Centre (Australia telephone 13 11 26) for advice or go to Accident and Emergency at your nearest hospital if you think that you or anyone else may have taken too much Capecitabine-DRLA.

Do this even if there are no signs of discomfort or poisoning.

You may need urgent medical attention.

While you are taking Capecitabine-DRLA

Things you must do

Tell all doctors, dentists and pharmacists who are treating you that you are using this medicine.

If you are about to be started on any new medicine, tell your doctor and pharmacist that you are using this medicine.

If you plan to have surgery that needs a general anaesthetic, tell your doctor or dentist that you are using this medicine.

If you become pregnant while taking Capecitabine-DRLA, stop using it and tell your doctor immediately.

Tell your doctor immediately if you develop diarrhoea (more than 4 bowel movements each day).

Capecitabine can sometimes cause diarrhoea in some people. Your doctor may stop your treatment and treat your diarrhoea before starting you on Capecitabine-DRLA tablets again.

Tell your doctor immediately if you develop nausea (feeling like you want to vomit) and it has affected your appetite significantly.

Capecitabine-DRLA can cause nausea in some people. Your doctor may stop your treatment and treat your nausea before starting you on Capecitabine-DRLA tablets again.

Tell your doctor immediately if you develop vomiting, and vomit more than once in a 24 hour period.

Capecitabine-DRLA can cause vomiting in some people. Your doctor may stop your treatment and treat your vomiting before starting you on Capecitabine-DRLA tablets again.

Tell your doctor immediately if you develop redness or swelling of your hands and/or feet that affects your normal activities

Capecitabine-DRLA can cause redness and swelling of hands and/or feet that can affect your normal activities. Your doctor may decide to treat this with other medicines, and/or stop your capecitabine treatment until the side effect settles.

Tell your doctor immediately if you develop pain, redness, swelling or sores in the mouth.

Capecitabine-DRLA can cause pain, redness, swelling or sores in the mouth in some people. Your doctor may treat this with other medicines, and/or may decide to stop your capecitabine treatment until the side effect settles.

Tell your doctor if, for any reason, you have not taken your medicine exactly as prescribed.

Otherwise, your doctor may think that it was not effective and change your treatment unnecessarily.

Tell your doctor if you feel the tablets are not helping your

condition.

Be sure to keep all of your appointments with your doctor so that your progress can be checked.

Things you must not do

Do not stop taking Capecitabine-DRLA or change the dose without first checking with your doctor.

Do not let yourself run out of medicine over the weekend or on holidays.

Do not give Capecitabine-DRLA to anyone else even if their symptoms seem similar to yours.

Do not take any other medicines whether they require a prescription or not without first telling your doctor or consulting with a pharmacist.

Things to be careful of

Be careful driving or operating machinery until you know how Capecitabine-DRLA affects you.

Side effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking Capecitabine-DRLA.

Capecitabine-DRLA helps people with bowel cancer, breast cancer, stomach cancer and cancer of the oesophagus (food pipe), but it may have unwanted side effects.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. Your doctor has weighed the risks of using this medicine against the benefits they expect it will have for you.

Do not be alarmed by this list of possible side effects.

You may not experience any of them.

Tell your doctor if you notice any of the following and they worry you:

- diarrhoea
- vomiting
- nausea (feeling like you want to vomit)
- fatigue (tiredness), weakness or weariness
- skin rashes, dry or itchy skin
- abdominal (gut) pain
- fever, or increased temperature sensitivity
- constipation
- headache
- dizziness
- loss of appetite, weight loss
- hair loss
- increased eye watering or irritation, conjunctivitis (itchy eyes and crusty eyelids)
- taste disturbance
- indigestion, wind
- dry mouth, thirst
- sore mouth, mouth ulcers, cold sores
- nail disorders
- sore throat, cough, nose bleeds
- shortness of breath, difficulty in breathing, or tightening of the chest
- redness or swelling of your hands and/or feet
- tingling or numbness of the hands or feet
- muscle and joint pain
- dark coloured urine
- difficulty sleeping

These are the more common side effects of Capecitabine-DRLA that you are likely to notice. Your doctor will tell you more about them. Your doctor may also recommend that you change the dose of Capecitabine-DRLA that you are taking if you experience any of the above side effects.

Tell your doctor immediately and stop taking Capecitabine-DRLA if you notice any of the following:

- severe diarrhoea with more than 4 bowel movements each day
- nausea that has reduced your appetite significantly
- vomiting more than once in a 24 hour period
- pain, redness and/or swelling of your hands and/or feet that has affected your normal activities (hand-foot- syndrome)
- pain, redness, swelling or ulcers in the mouth (stomatitis)

You need to stop taking Capecitabine-DRLA if you experience the above side effects. Your doctor will treat your side effects before they start you on Capecitabine-DRLA again.

If any of the following happen, stop using this medicine and tell your doctor immediately, or go to Accident and Emergency at your nearest hospital:

- **swelling of the face, lips, mouth or throat, which may cause difficulty in swallowing or breathing**
- **chest pain**
- **irregular heart beat**
- **shortness of breath**
- **confusion**

- **poor balance or lack of co- ordination**
- **numbness or weakness of arms or legs**
- **signs of infection such as swelling, redness and increased temperature**
- **signs of liver disease such as yellowing of the skin and eyes**
- **blood in the faeces**

These are serious side effects. You may need urgent medical attention or hospitalisation.

These side effects are very rare.

This is not a complete list of all possible side effects. Others may occur in some people and there may be some side effects not yet known.

These side effects may differ when taking Capecitabine-DRLA in combination with a chemotherapy medicine.

Please consult your doctor for possible side effects that may be caused by taking Capecitabine-DRLA with a chemotherapy medicine.

Tell your doctor if you notice anything else that is making you feel unwell, even if it is not on this list.

Do not be alarmed by this list of possible side effects.

You may not experience any of them.

After taking this medicine

Storage

Keep your tablets in their container until it is time to take them.

If you take the tablets out of their container they may not keep well.

Keep Capecitabine-DRLA in a cool dry place where the temperature stays below 25°C.

Do not store it, or any other medicine, in a bathroom or near a sink.

Do not leave it in the car or on window sills.

Heat and dampness can destroy some medicines.

Keep this medicine where children cannot reach it.

A locked cupboard at least one-and- a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking Capecitabine-DRLA, or the medication has passed its expiry date, your pharmacist can dispose of the remaining medicine safely.

Product description

Availability

Capecitabine-DRLA tablets are available in two strengths, 150 mg and 500 mg.

Capecitabine-DRLA tablets come in blister packs in the following pack sizes:

- 150 mg - 60 tablets
- 500 mg - 120 tablets

What Capecitabine-DRLA looks like

- 150 mg: Light peach film-coated tablet of biconvex, oblong shape with the marking "150" on one side and "RDY" on other side.

- 500 mg: Peach, film-coated tablet of biconvex, oblong shape with the marking "500" on one side and "RDY" on the other side.

Ingredients

Active ingredient

- capecitabine

Inactive ingredients

- lactose
- croscarmellose sodium
- hypromellose
- microcrystalline cellulose
- magnesium stearate

The tablets have a film-coating which contains:

- hypromellose
- purified talc
- titanium dioxide
- iron oxide yellow (CI77492)
- iron oxide red (CI77491)

Capecitabine-DRLA tablets are gluten free, tartrazine-free and free of other azo dyes.

Sponsor:

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Australian Registration Number

Capecitabine-DRLA 150 mg Tablets: AUST R 200935

Capecitabine-DRLA 500 mg Tablets: AUST R 200933

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