	<u> </u>	187.5 mm										
157.5 mm		18/	.5 mm									
	62756PJP10406A											
IGHLIGHTS OF PRESCRIBING INFORMATION	 Increased Risk of Severe or Fatal Adverse Reactions in Patients with Low or Absent Dihydropyrimidine Dehydrogenase (DPD) Activity: Withhold or permanently discontinue capecitabine in patients with evidence of acute early- 	In 251 patients with metastatic breast cancer who received a combination of capecitabine and docetaxel, grade 3 (1.5 to 3 x ULN) hyperbilirubinemia occurred in 7% (n=17) and grade 4 (>3 x ULN) hyperbilirubinemia occurred in 2% (n=5).	Table 7 Percent Incidence of A Patients Participating in the Ca	pecitabine and				el Monother	apy Study			
nese highlights do not include all the information needed to use CAPECITABINE ABLETS safely and effectively. See full prescribing information for CAPECITABINE ABLETS.	onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No capecitabine dose has been proven safe in patients	If drug-related grade 3 to 4 elevations in bilirubin occur, administration of capecitabine should be immediately interrupted until the hyperbilirubinemia decreases to \leq 3 X ULN [see recommended dose modifications under Dosage and Administration (2.3)].	Adverse Event	1250 mg/m ² /bid With Docetaxel 75 mg/m ² /3 weeks (n=251)				Docetaxel 100 mg/m²/3 weeks (n=255)				
APECITABINE tablets, for oral use	 with absent DPD activity. (5.4) Dehydration and Renal Failure: Interrupt capecitabine treatment until dehydration is corrected. Potential risk of acute renal failure secondary to dehydration. Monitor 	5.9 Hematologic In 875 patients with either metastatic breast or colorectal cancer who received a dose of 1250 mg/m ² administered		Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %			
tial U.S. Approval: 1998 WARNING: CAPECITABINE-WARFABIN INTERACTION	 and correct dehydration. (5.5). Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive 	twice daily as monotherapy for 2 weeks followed by a 1-week rest period, 3.2%, 1.7%, and 2.4% of patients had grade 3 or 4 neutropenia, thrombocytopenia or decreases in hemoglobin, respectively. In 251 patients with metastatic breast cancer who received a dose of capecitable in combination with docetaxel, 68% had grade 3 or 4	Number of Patients With at Least One Adverse Event	99	76.5	29.1	97	57.6	31.8			
See full prescribing information for complete boxed warning.	potential of the potential risk to a fetus and to use effective contraception. (5.6, 8.1, 8.3)	neutropenia, 2.8% had grade 3 or 4 thrombocytopenia, and 9.6% had grade 3 or 4 anemia. Patients with baseline neutrophil counts of <1.5 x 10°/L and/or thrombocyte counts of <100 x 10°/L should not be	Body System/Adverse Event									
atients receiving concomitant capecitabine and oral coumarin-derivative nticoagulants such as warfarin and phenprocoumon should have their	 Mucocutaneous and Dermatologic Toxicity: Severe mucocutaneous reactions, 	treated with capecitabine. If unscheduled laboratory assessments during a treatment cycle show grade 3 or 4	GI									
anticoagulants such as warrarin and phenprocoumon should have their anticoagulant response (INR or prothrombin time) monitored frequently in	Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), have been	hematologic toxicity, treatment with capecitabine should be interrupted.	Diarrhea	67	14	<1	48	5	<1			
order to adjust the anticoagulant dose accordingly. Altered coagulation	reported. Capecitabine should be permanently discontinued in patients who	5.10 Geriatric Patients	Stomatitis	67	17	<1	43	5	-			
parameters and/or bleeding, including death, have been reported during	experience a severe mucocutaneous reaction during treatment. Capecitabine may	Patients ≥80 years old may experience a greater incidence of grade 3 or 4 adverse reactions. In 875 patients with either metastatic breast or colorectal cancer who received capecitabine monotherapy, 62% of the 21 patients ≥80	Nausea	45	7	-	36	2	-			
concomitant use.	induce hand-and-foot syndrome. Persistent or severe hand-and-foot syndrome	years of age treated with capecitabine experienced a treatment-related grade 3 or 4 adverse event: diarrhea in	Vomiting	35	4	1	24	2	-			
	can lead to loss of fingerprints which could impact patient identification. Interrupt capecitabine treatment until the hand-and-foot syndrome event resolves or	6 (28.6%), nausea in 3 (14.3%), hand-and-foot syndrome in 3 (14.3%), and vomiting in 2 (9.5%) patients. Among the 10 patients 70 years of age and greater (no patients were >80 years of age) treated with capecitabine in	Constipation	20	2	-	18	-	-			
 Occurrence: Within several days and up to several months after initiating capecitabine therapy; may also be seen within 1 month after stopping 	decreases in intensity. (5.7)	combination with docetaxel, 30% (3 out of 10) of patients experienced grade 3 or 4 diarrhea and stomatitis, and 40% (4 out of 10) experienced grade 3 hand-and-foot syndrome.	Abdominal Pain Dyspepsia	30 14	<3	<1	24 8	2				
capecitabine	• Hyperbilirubinemia: Interrupt capecitabine treatment immediately until the	Among the 67 patients > 00 years of an resoluting associations is combination with decateval the incidence of	Dry Mouth	6	<1		5	1				
\circ Predisposing factors: age>60 and diagnosis of cancer	hyperbilirubinemia resolves or decreases in intensity. (5.8)	Among the 67 patients ≥60 years of age receiving capecitabine in combination with docetaxel, the incidence of grade 3 or 4 treatment-related adverse reactions, treatment-related serious adverse reactions, withdrawals due to	Skin and Subcutaneous	0	<1	-	5	-				
	• Hematologic: Do not treat patients with neutrophil counts $<1.5 \times 10^{9}/L$ or thrombocyte counts $<100 \times 10^{9}/L$. If grade 3 to 4 neutropenia or	adverse reactions, treatment discontinuations due to adverse reactions and treatment discontinuations within the first two treatment cycles was higher than in the <60 years of age patient group.	Hand-and-Foot Syndrome	63	24	NA	8	1	NA			
INDICATIONS AND USAGE	thrombocytopenia occurs, stop therapy until condition resolves. (5.9)		Alopecia	41	6	-	42	7	-			
pecitabine is a nucleoside metabolic inhibitor with antineoplastic activity indicated		In 995 patients receiving capecitabine as adjuvant therapy for Dukes' C colon cancer after resection of the primary tumor, 41% of the 398 patients ≥65 years of age treated with capecitabine experienced a treatment-related grade 3	Nail Disorder	14	2	_	15	-	_			
······································	ADVERSE REACTIONS	or 4 adverse event: hand-and-foot syndrome in 75 (18.8%), diarrhea in 52 (13.1%), stomatitis in 12 (3%),	Dermatitis	8	_	_	11	1	_			
Adjuvant Colon Cancer (1.1)	Most common adverse reactions (\geq 30%) were diarrhea, hand-and-foot syndrome,	neutropenia/granulocytopenia in 11 (2.8%), vomiting in 6 (1.5%), and nausea in 5 (1.3%) patients. In patients ≥65 years of age (all randomized population; capecitabine 188 patients, 5-FU/LV 208 patients) treated for Dukes' C	Rash Erythematous	9	<1	_	5	-	_			
Patients with Dukes' C colon cancer	nausea, vomiting, abdominal pain, fatigue/weakness, and hyperbilirubinemia. Other adverse reactions, including serious adverse reactions, have been reported. (6)	colon cancer after resection of the primary tumor, the hazard ratios for disease-free survival and overall survival for	Nail Discoloration	6	_	_	4	<1				
Metastatic Colorectal Cancer (1.1)	α a voise reactions, including serious auveise reactions, flave deeff equilibrium (0)	capecitabine compared to 5-FU/LV were 1.01 (95% C.I. 0.8 to 1.27) and 1.04 (95% C.I. 0.79 to 1.37), respectively.	Onycholysis	5	1	_	5	1				
 First-line as monotherapy when treatment with fluoropyrimidine therapy alone is preferred 	To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical	5.11 Hepatic Insufficiency Patients with mild to moderate hepatic dysfunction due to liver metastases should be carefully monitored when	Pruritus	4	-	-	5	-	-			
Metastatic Breast Cancer (1.2)	Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or	capecitabine tablets are administered. The effect of severe hepatic dysfunction on the disposition of capecitabine is	General									
• In combination with docetaxel after failure of prior anthracycline-containing	www.fda.gov/medwatch.	not known [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].	Pyrexia	28	2	-	34	2	-			
therapy	DRUG INTERACTIONS	5.12 Combination With Other Drugs Use of capecitabine in combination with irinotecan has not been adequately studied.	Asthenia	26	4	<1	25	6	-			
• As monotherapy in patients resistant to both paclitaxel and an anthracycline-	Anticoagulants: Monitor anticoagulant response (INR or prothrombin time)	טיט איז אראיזאר איז	Fatigue	22	4	-	27	6	-			
containing regimen	frequently in order to adjust the anticoagulant dose as needed. (5.2, 7.1)	6. ADVERSE REACTIONS	Weakness	16	2	-	11	2	-			
DOSAGE AND ADMINISTRATION	Phenytoin: Monitor phenytoin levels in patients taking capecitabine concomitantly	Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the	Pain in Limb	13	<1	-	13	2	-			
Take capecitabine tablets with water within 30 min after a meal (2.1)	with phenytoin. The phenytoin dose may need to be reduced. (7.1)	clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.	Lethargy	7	-	-	6	2	-			
Monotherapy: 1250 mg/m ² twice daily orally for 2 weeks followed by a one week	 Leucovorin: The concentration of 5-fluorouracil is increased and its toxicity may be appaaed by laucacierin (7.1) 	6.1 Adjuvant Colon Cancer	Pain	7	<1	-	5	1	- 1			
rest period in 3-week cycles (2.2)	enhanced by leucovorin. (7.1) • CYP2C9 substrates: Care should be exercised when capecitabine is	Table 4 shows the adverse reactions occurring in ≥5% of patients from one phase 3 trial in patients with Dukes' C	Chest Pain (non-cardiac)	4	<1	-	6	2	-			
Adjuvant treatment is recommended for a total of 6 months (8 cycles) (2.2)	 create should be exercised when capechabile is coadministered with CYP2C9 substrates. (7.1) 	colon cancer who received at least one dose of study medication and had at least one safety assessment. A total of 995 patients were treated with 1250 mg/m² twice a day of capecitabine tablets administered for 2 weeks followed	Influenza-like Illness	5	-	-	5	-	-			
In combination with docetaxel, the recommended dose of capecitabine is	 Allopurinol: Avoid the use of allopurinol during treatment with capecitabine. 	by a 1-week rest period, and 974 patients were administered 5-FU and leucovorin (20 mg/m² leucovorin IV followed	Neurological									
1250 mg/m ² twice daily for 2 weeks followed by a 7-day rest period, combined with	• Food reduced both the rate and extent of absorption of capecitabine. (2, 7.2, 12.3)	by 425 mg/m ² IV bolus 5-FU on days 1 to 5 every 28 days). The median duration of treatment was 164 days for capecitabine-treated patients and 145 days for 5-FU/LV-treated patients. A total of 112 (11%) and 73	Taste Disturbance	16	<1	-	14	<1	_			
docetaxel at 75 mg/m ² as a 1-hour IV infusion every 3 weeks (2.2) Capecitabine dosage may need to be individualized to optimize patient management		(7%) capecitabine and 5-FU/LV-treated patients, respectively, discontinued treatment because of adverse	Headache	15	3	-	15	2	-			
(2.3)	USE IN SPECIFIC POPULATIONS	reactions. A total of 18 deaths due to all causes occurred either on study or within 28 days of receiving study drug: 8 (0.8%) patients randomized to capecitabine and 10 (1%) randomized to 5-FU/LV.	Paresthesia	12	<1	-	16	1	-			
Reduce the dose of capecitabine by 25% in patients with moderate renal	 Lactation: Advise women not to breastfeed. (8.2) 		Dizziness	12	_	_	8	<1	_			

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Artwork Type: **PACKAGE OUTSERT** Artwork Code: PJPI0406A Void Code: PJPI0406 Dimension: 380x820 mm Void A/W Reason: CHANGE IN TEXT AS PER RA DRAFT (REFER RA ATTACHMENT) Country: ANDA-US Language: ENGLISH Mfg. Location: **HALOL** Specification/Type of Paper: 28 GSM SUPER FINE BIBLE PAPER Folding: Open size : 380x820 mm

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• Reduce the dose of capecitabine by 25% in patients with moderate renal		dvise women not to bre									Dizziness	12	-	-	8	<1	-
impairment (2.4)		Males of Reproducti							Insomnia	8	-	_	10	<1	_		
			tablets. Advise males w	vith female partners of	assessment.			ady modification	und nud ut iou	or one survey	Peripheral Neuropathy	6	-	-	10	1	-
DOSAGE FORMS AND STRENGTHSDOSAGE FORMS AND STRENGTHS		•	ve contraception. (8.3) erse reactions. Monitorine	a required (9.5)	Table 4 Percent Inc	idence of Adverse	e Reactions Rend	rted in ≥5% of	Patients Treat	ed	Hypoaesthesia	4	<1	_	8	<1	_
 Tablets: 150 mg and 500 mg (3) 			recommended in patient	U I ()	With Capecitabine or S						Metabolism						
	 hepatic impai 	0	recommended in patient								Anorexia	13	1	_	11	<1	_
CONTRAINDICATIONS			itabine starting dose in	natients with moderate			Adjuvant Treatme	nt for Colon Ca			Appetite Decreased	10	_	_	5	-	_
• Severe Renal Impairment (4.1)		nent (2.4, 8.7, 12.3)	and starting dood in				Capecitabine (N=995)		5-FU/LV (N=974		Weight Decreased	7	_	_	5	_	
Hypersensitivity (4.2)	i on an impairing				Body System/ Adverse Event	All Grad	es Grad	e 3/4 A		Grade 3/4	Dehydration	10	2	-		<1	<1
WARNINGS AND PRECAUTIONS	See 17 for PA	TIENT COUNSELING	G INFORMATION and F	FDA-approved patient	Gastrointestinal Disorders	47		2	05	14		10	2	-		<1	<1
Coagulopathy: May result in bleeding, death. Monitor anticoagulant response (e.g.,	labeling				Diarrhea Nausea	34		2	65 47	14 2	Eye	10			<u> </u>		
INR) and adjust anticoagulant dose accordingly. (5.1)					Stomatitis	22 15		2	60 21	14 2	Lacrimation Increased	12	-	-	7	<1	-
• Diarrhea : May be severe. Interrupt capecitabine treatment immediately until				Revised: 09/2019	Vomiting	15		3	16	2	Conjunctivitis	5	-	-	4	-	-
diarrhea resolves or decreases to grade 1. Recommend standard antidiarrhea					Abdominal Pain Constipation	9		-	11	<1	Eye Irritation	5	-	-	1	-	-
treatments. (5.2)					Upper Abdominal Pain	6		:1 :1	5	<1	Musculoskeletal						
• Cardiotoxicity: Common in patients with a prior history of coronary artery disease.					Dyspepsia	-					Arthralgia	15	2	-	24	3	-
(5.3)					Skin and Subcutaneous Tissue Disorders	60		7	9	<1	Myalgia	15	2	-	25	2	-
					Hand-and-Foot Syndrome	6		-	22	<1	Back Pain	12	<1	-	11	3	-
					Alopecia Rash	7		- 1	8	-	Bone Pain	8	<1	-	10	2	-
					Erythema						Cardiac	33	<2		34	<3	1
					General Disorders and				10		Edema	33	<2	-	- 34	< 3	
FULL PRESCRIBING INFORMATION: CONTENTS*	7 DRUG INTERA 7.1 Drug-I	ACTIONS Drug Interactions			Administration Site Condition	IS 16 7		:1 :1	16 9	1 <1	Blood Neutropenic Fever	16	3	13	21	5	16
WARNING: CAPECITABINE-WARFARIN INTERACTION	7.2 Drug-F	Food Interaction			Pyrexia	10		1	10	1	Respiratory				<u> </u>		
	8 USE IN SPECI 8.1 Pregna	IFIC POPULATIONS ancy			Asthenia Lethargy	10	<	:1	9	<1		14	2	<1	16	2	
1 INDICATIONS AND USAGE 1.1 Colorectal Cancer	8.2 Lactati	tion			Nervous System Disorders						Dyspnea		1	<1	-		_
1.2 Breast Cancer	8.3 Female 8.4 Pediati	es and Males of Reproductive tric Use	e Potential		Dizziness	5		:1	6	<1	Cough	13		-	22	<1	-
2 DOSAGE AND ADMINISTRATION 2.1 Important Administration Instructions	8.5 Geriatr	ric Use			Headache Dysgeusia	6		-	9	-	Sore Throat	12	2	-	11	<1	-
2.2 Standard Starting Dose		ic Insufficiency Insufficiency			Metabolism and Nutrition						Epistaxis	7	<1	-	6	-	-
 2.3 Dose Management Guidelines 2.4 Adjustment of Starting Dose in Special Populations 	10 OVERDOSAGI	E			Disorders	9	<	:1	11	<1	Rhinorrhea	5	-	-	3	-	-
3 DOSAGE FORMS AND STRENGTHS	11 DESCRIPTION 12 CLINICAL PH/	N Armacology			Anorexia						Pleural Effusion	2	1	-	7	4	-
4 CONTRAINDICATIONS 4.1 Severe Renal Impairment	12.1 Mecha	anism of Action			Eye Disorders Conjunctivitis	5	<	:1	6	<1	Infection				<u> </u>		
4.2 Hypersensitivity	12.3 Pharm 13 NONCLINICAL	nacokinetics L TOXICOLOGY			Blood and Lymphatic	_					Oral Candidiasis	7	<1	-	8	<1	-
5 WARNINGS AND PRECAUTIONS 5.1 Coagulopathy	13.1 Carcin	nogenesis, Mutagenesis, Impa	airment of Fertility		System Disorders	2	<	:1	8	5	Urinary Tract Infection	6	<1	-	4	-	-
5.2 Diarrhea	14 CLINICAL STU 14.1 Adjuva	UDIES ant Colon Cancer			Neutropenia						Upper Respiratory Tract	4	-	-	5	1	-
5.3 Cardiotoxicity 5.4 Dihydropyrimidine Dehydrogenase Deficiency	14.2 Metast	tatic Colorectal Cancer			Respiratory Thoracic and				_		Vascular	5			5		
5.5 Dehydration and Renal Failure	14.3 Breast 15 REFERENCES				Mediastinal Disorders Epistaxis	2		-	5	-	Flushing Lymphoedema	3	<1	-	5	1	-
5.6 Embryo-Fetal Toxicity 5.7 Mucocutaneous and Dermatologic Toxicity	16 HOW SUPPLI	ED/STORAGE AND HANDLIN	IG]	Psychiatric				<u> </u>		
5.8 Hyperbilirubinemia	17 PATIENT COU	INSELING INFORMATION			Table 5 Percent Incident						Depression	5	-	-	5	1	-
5.9 Hematologic 5.10 Geriatric Patients	*Sections or subsecti	ions omitted from the full pres	cribing information are not listed.		Receiving Capecitabine N	lonotherapy for A	djuvant Treatmei	it of Colon Can	cer (Safety Pop	oulation)	 Not observed 						
5.11 Hepatic Insufficiency							Capecitabine		IV 5-FU/LV	I	NA = Not Applicable						
5.12 Combination With Other Drugs 6 ADVERSE REACTIONS					Adverse Event		(n=995) Grade 3/4 %		(n=974) Grade 3/4 S								
6.1 Adjuvant Colon Cancer 6.2 Metastatic Colorectal Cancer							1.6			/0	Table 8 Percent of	f Patients With L	Laboratory Abn	ormalities	Participati	na in the	
					Increased ALAT (SGPT)				0.6								
6.3 Breast Cancer					Increased ALAT (SGPT) Increased calcium		1.1		0.6 0.7		Capecitabine an		mbination vs D	ocetaxel M			
 6.3 Breast Cancer 6.4 Clinically Relevant Adverse Events in <5% of Patients 					Increased calcium Decreased calcium				0.7			nd Docetaxel Cor	Capecitabine			y Study]
6.3 Breast Cancer					Increased calcium Decreased calcium Decreased hemoglobin Decreased lymphocytes		1.1 2.3 1 13		0.7 2.2 1.2 13			nd Docetaxel Cor C 1250 mg/r		cetaxel	lonotherap	y Study Docetaxel 0 mg/m²/3 w	eeks
 6.3 Breast Cancer 6.4 Clinically Relevant Adverse Events in <5% of Patients 					Increased calcium Decreased calcium Decreased hemoglobin Decreased lymphocytes Decreased neutrophils*	cytes	1.1 2.3 1		0.7 2.2 1.2		Capecitabine an	nd Docetaxel Cor C 1250 mg/r	Capecitabine m²/bid With Doo	cetaxel	lonotherap	y Study Docetaxel 0 mg/m²/3 w (n=255)	
 6.3 Breast Cancer 6.4 Clinically Relevant Adverse Events in <5% of Patients 	Table 3 Do	ocetaxel Dose Reduction Sc	chedule in Combination with Ca	apecitabine Tablets	Increased calcium Decreased calcium Decreased hemoglobin Decreased hemoglobin Decreased neutrophils* Decreased neutrophils/granulo Decreased platelets	cytes	1.1 2.3 1 13 2.2 2.4 1		0.7 2.2 1.2 13 26.2 26.4 0.7		Capecitabine an	nd Docetaxel Cor C 1250 mg/r 75 r Total	Capecitabine m²/bid With Doo mg/m²/3 weeks (n=251) Grade 3	cetaxel Grade 4	lonotherap 10 Total	y Study Docetaxel 0 mg/m²/3 w (n=255) Grade 3	Grade 4
6.3 Breast Cancer 6.4 Clinically Relevant Adverse Events in <5% of Patients 6.5 Postmarketing Experience FULL PRESCRIBING INFORMATION	[Increased calcium Decreased calcium Decreased hemoglobin Decreased lymphocytes Decreased neutrophils* Decreased neutrophils/granulo	cytes	1.1 2.3 1 13 2.2		0.7 2.2 1.2 13 26.2 26.4		Capecitabine an Adverse Event Body System/Adverse Event	nd Docetaxel Cor C 1250 mg/r 75 r Total %	Capecitabine m²/bid With Doo mg/m²/3 weeks (n=251) Grade 3 %	cetaxel Grade 4 %	lonotherapy 10 Total %	y Study Docetaxel 0 mg/m²/3 w (n=255) Grade 3 %	Grade 4 %
 6.3 Breast Cancer 6.4 Clinically Relevant Adverse Events in <5% of Patients 6.5 Postmarketing Experience 	Table 3 Do Toxicity NCIC Grades*	ocetaxel Dose Reduction So Grade 2	chedule in Combination with Ca Grade 3	apecitabine Tablets Grade 4	Increased calcium Decreased calcium Decreased hemoglobin Decreased hemoglobin Decreased neutrophils* Decreased neutrophils/granulo Decreased platelets		1.1 2.3 1 13 2.2 2.4 1 20	3% in the capec	0.7 2.2 1.2 13 26.2 26.4 0.7 6.3	4.9% in the IV	Capecitabine an Adverse Event Body System/Adverse Event Hematologic Leukopenia	nd Docetaxel Cor C 1250 mg/r 75 r Total	Capecitabine m²/bid With Doo mg/m²/3 weeks (n=251) Grade 3 % 37	cetaxel Grade 4	lonotherap 10 Total	y Study Docetaxel 0 mg/m²/3 w (n=255) Grade 3	Grade 4
6.3 Breast Cancer 6.4 Clinically Relevant Adverse Events in <5% of Patients 6.5 Postmarketing Experience FULL PRESCRIBING INFORMATION WARNING: CAPECITABINE-WARFARIN INTERACTION Capecitabine Warfarin Interaction: Patients receiving concomitant capecitabine and oral coumarin-	Toxicity	Grade 2 Delay treatment until		Grade 4	Increased calcium Decreased hemoglobin Decreased hemoglobin Decreased hemoglobin Decreased neutrophils* Decreased neutrophils/granulo Decreased plateiets Increased plateiets Increased bilirubin**	hite blood cell abr	1.1 2.3 1 13 2.2 2.4 1 20		0.7 2.2 1.2 13 26.2 26.4 0.7 6.3		Capecitabine an Adverse Event Body System/Adverse Event Hematologic Leukopenia Neutropenia/Granulocytopenia	nd Docetaxel Cor 1250 mg/r 75 r Total % 91 86 41	Capecitabine m²/bid With Doo mg/m²/3 weeks (n=251) Grade 3 %	Grade 4 % 24 49 1	Ionotherapy 10 Total % 88 87 23	Bocetaxel 0 mg/m²/3 w (n=255) Grade 3 % 42 10 1	Grade 4 % 33 66 2
6.3 Breast Cancer 6.4 Clinically Relevant Adverse Events in <5% of Patients 6.5 Postmarketing Experience FULL PRESCRIBING INFORMATION WARNING: CAPECITABINE-WARFARIN INTERACTION Capecitabine Warfarin Interaction: Patients receiving concomitant capecitabine and oral coumarin- derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time)	Toxicity	Grade 2 Delay treatment until resolved to grade 0 to 1; Resume treatment with	Grade 3 Delay treatment until resolved to grade 0 to 1; Resume treatment at 55 me/02 of	Grade 4	Increased calcium Decreased calcium Decreased hemoglobin Decreased hemoglobin Decreased neutrophils* Decreased neutrophils/granulo Decreased platelets Increased platelets Increased bilirubin** * The incidence of grade 3/4 w 5-FU/LV arm. ** It should be noted that gradin hyperbilirubinemia grade 3 in	rhite blood cell abr ng was according t idicates a bilirubin	1.1 2.3 1 3 2.2 2.4 1 20 vormalities was 1.	on 1 (May, 1994 upper limit of n	0.7 2.2 1.2 13 26.2 26.4 0.7 6.3 : itabine arm and - 4). In the NCIC-C ormal (ULN) ran	CTC Version 1, ige, and grade	Capecitabine an Adverse Event Body System/Adverse Event Hematologic Leukopenia Neutropenia/Granulocytopenia Thrombocytopenia Anemia	nd Docetaxel Cor C 1250 mg/r 75 r Total % 91 86	Capecitabine m²/bid With Doo mg/m²/3 weeks (n=251) Grade 3 % 37 20	Grade 4 %	Ionotherapy 10 Total % 88 87	Docetaxel 0 mg/m²/3 w (n=255) Grade 3 % 42	Grade 4 % 33 66
6.3 Breast Cancer 6.4 Clinically Relevant Adverse Events in <5% of Patients 6.5 Postmarketing Experience FULL PRESCRIBING INFORMATION Capecitabine Warfarin Interaction: Patients receiving concomitant capecitabine and oral coumarin- derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important Capecitabine-Warfarin drug interaction was demonstrated in a clinical phramacology trial <i>[see Warnings</i>	Toxicity NCIC Grades*	Grade 2 Delay treatment until resolved to grade 0 to 1; Resume treatment with original dose of 75 mg/m	Grade 3 Delay treatment until resolved to grade 0 to 1; Resume treatment at 55 me/02 of	Grade 4	Increased calcium Decreased calcium Decreased acalcium Decreased hemoglobin Decreased neutrophils* Decreased neutrophils/granulo Decreased platelets Increased bilirubin** * The incidence of grade 3/4 w 5-FU/LV arm. ** It should be noted that gradir hyperbilirubinemia grade 3 in 4 a value of > 3 × ULN. The I	hite blood cell abr g was according t dicates a bilirubin NCI CTC Version 2	1.1 2.3 1 3 2.2 2.4 1 20 vormalities was 1.	on 1 (May, 1994 upper limit of n	0.7 2.2 1.2 13 26.2 26.4 0.7 6.3 : itabine arm and - 4). In the NCIC-C ormal (ULN) ran	CTC Version 1, ige, and grade	Capecitabine an Adverse Event Body System/Adverse Event Hematologic Leukopenia Neutropenia/Granulocytopenia Thrombocytopenia Anemia Lymphocytopenia	nd Docetaxel Cor 1250 mg/r 75 r Total % 91 86 41 80	Gapecitabine m²/bid With Doim mg/m²/3 weeks (n=251) Grade 3 % 37 20 2 7	Grade 4 % 24 49 1 3	10000000000000000000000000000000000000	Study Docetaxel 0 mg/m²/3 w (n=255) Grade 3 % 42 10 1 5	Grade 4 % 33 66 2 <1
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Aftered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine tablets concomitantly with coumarinderivative anticoagulants such as warfarin and phenprocoumon. Postmarketing reports have shown clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants at the time capecitabine therapy and, in a few cases, within 1 month after stopping capecitabine. These events occurred in patients with and without liver metastases. Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy. 1 INCLETIONS AND USAGE 2 Osticabine tablets are indicated as a single agent for adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary turnor when treatment with fluoropyrimidine therapy alone is preferred. Capecitabine tablets were non-interior to 5-fluorouraci and leucovorin (5-FU/LV) for disease-free survival (DFS). Physicians should consider results of combination chemotherapy trials, which have shown improvement in DFS and OS, when 	Toxicity NCIC Grades* 1st appearance 2nd appearance 3rd appearance * National Cancer In [see Warnings and Renal Impairment No adjustment to the : (creatinine clearance impairment (baseline starting dose when us daily) is recommended dose adjustment is in develops a grade 2 to recommendations for	Grade 2 Delay treatment until resolved to grade 0 to 1; Resume treatment with original dose of 75 mg/m docetaxel Delay treatment until resolved to grade 0 to 1; Resume treatment at 55 mg/m² of docetaxel. 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Pullov Jonn cancer. 1 INDICATIONS AND USAGE 2 Capecitabine tablets are indicated as first-line treatment of patients with metastatic colorectal carcinom	Toxicity NCIC Grades* 1st appearance 2nd appearance 3rd appearance 3rd appearance * National Cancer In <i>[see Warnings and</i>] 2.4 Adjustment of Renal Impairment No adjustment to the : (creatinine clearance impairment (baseline starting dose when us at grade 2 th recommendations for capecitabine tablets in Cockroft and Gault Eq Creatinin Creatinine clearance for	Grade 2 Delay treatment until resolved to grade 0 to 1; Resume treatment with original dose of 75 mg/mi docetaxel Delay treatment until resolved to grade 0 to 1; Resume treatment at 55 mg/m² of docetaxel. 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Postmarketing reports have shown clinically significant increases in prothrombin time (P1) and INR in patients who were stabilized on anticoagulants at the time capacitabine was introduced. These events occurred within several days and up to several months after initiating capacitabine therapy and, in a few cases, whitin 1 month after initiating capacitabine therapy and, in a few cases, whitin 1 month after stopping capacitabine. These events occurred in patients with and without liver metastases. Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy. C. Colonication Cancer O specificabine tablets are indicated as a single agent for adjuvant treatment with Blueropytrimidine treatment with Blueropytrimidine therapy adone is preferred. Compacitabine tablets are instead of S-FU/LV for disease-free survival (D5). 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A total of nt because of tudy or within andomized to f Patients Grade 4 % 9 2 <1 <1 1 - - - -</th> <th>Capecitabine an Adverse Event Body System/Adverse Event Hematologic Leukopenia Neutropenia/Granulocytopenia Thrombocytopenia Anemia Lymphocytopenia Hepatobiliary Hyperbilirubinemia Monotherapy The following data are shown for the administered twice daily for 2 we we at 114 days. A total of 13 out of 162 piliness. 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<section-header><section-header> 9.3 Breat Gancer 9.5 Postmarketing Experience 9.5 Postmarketing Experience 9.5 Postmarketing Experience 9.5 Postmarketing Experience 9.5 CLI PEESCHEING INFORMATION 9.5 CLI PEESCHEING Variant Interaction: Patients receiving concomitant capacitabine and oral cournaring deviative autocaguinat therapy should have their anticoaguiant response (NR o prothomitining monitored frequently in order to adjust the anticoaguiant dosone accordingly. A clinically important capacitabine Variant drug interactions we demonstrated in a clinical pharmacology trial <i>fees Warnings and Precautions (S.2) and Drug Interactions (G.1)</i>. Altered coaguiation parameters and/or bleeding, including death, have been reported in patients taking capacitabine tablets concomitantly with cournarinderviative autocaguiants at the linit capacitabine tablets or events occurred within several tablets of coaguiopation. 9.5 CLI DECIDENENEE 9.5 CLI DECIDENE CL</section-header></section-header>	Toxicity NCIC Grades* 1st appearance 2nd appearance 3rd appearance * National Cancer In <i>[see Warnings and</i>] * National Cancer In <i>[see Warnings and</i>] 2.4 Adjustment of Renal Impairment No adjustment to the = (creatinine clearance impairment (baseline starting dose when us daily) is recommended dose adjustment is rn develops a grade 2 t recommendations for capecitabine tablets in Cockroft and Gault Equination Creation Cockroft and Gault Equination Creation Creatinics Physicians should exa are available to provid 3. DOSAGE FOR Capecitabine tablets, peach colored tablets and each peach colo capecitabine USP. 4. 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A total of 8 y: 50 (8.4%) patie orectal Trials: Per Ca S55 43 27 25 35 10 14	1.1 2.3 1 1 3 2.2 2.4 1 20 Promalities was 1. o NCIC CTC Versive value of 1.5 to 3 > and above define ≥5% of patients f ditients with meta daministered for 2 prin in the Mayo r days). In the pool patients and 140 patients and	on 1 (May, 1994) upper limit of n a grade 3 bilirul rom pooling the static colorect static colorect weeks followed egimen (20 mg) gade colorectal da days for 5-FU/ pspectively, discu acapecitabine a f Adverse Read rade 4 % 9 94 - 2 61 - 2 61 - 2 61 - 2 61 - 7 <1	0.7 2.2 1.2 13 26.2 26.4 0.7 6.3 citabine arm and .4 0.7 4). In the NCIC-C normal (ULN) ran 10 1 12 13 26.2 26.4 0.7 6.3 citabine arm and .4 4). 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RONT SIDE 820

Approved by RA:

APPROVAL HISTORY ATTACHED

No. of Colors: 1



The recommended do		is 1250 mg/m ² administered orally twice daily (morning and) for 2 weeks followed by a 1-week rest period given as 3-week 4.2 Hypersensitivity			Capecitabine is contraining and the patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]) [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].	Hand-and-Foot Syndrome Dermatitis	54 27	17	NA _	6 26	1	NA C	Ayalgia C ardiac Edema		9	1		-
	patients with Dukes' C colon cance 50 mg/m ² orally twice daily for 2 week cles (24 weeks)].				Capecitable is contraindicated in patients with known hypersensitivity to capecitable or to any of its components. Capecitable is contraindicated in patients who have a known hypersensitivity to 5-fluorouracil.	Skin Discoloration Alopecia	7	<1	-	5 21	- <1	- N	Blood Jeutropenia Thromb Anemia	locytopenia	26 24 72 94	2 3 3 44		2 1 1 15
Table 1	Capecitabine Tablets Dose Calculati	on According t	to Body Surfac	ce Area	5. WARNINGS AND PRECAUTIONS	General	40			46		Н	ymphopenia Iepatobiliary			44 9		2
Dose	Level 1250 mg/m²	Number of 1	Tablets to be Tablets	faken at Each Dose	5.1 Coagulopathy	Fatigue/Weakness Pyrexia	42	4	-	46 21	2	- -	lyperbilirubinemia		22	9		2
	Twice a Day	(1	(Morning and E	Evening)	Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely with great frequency and the anticoagulant	Edema	15	1	_	9	1		Not observed					
Surface Area (m	, , , ,	150 n		500 mg	dose should be adjusted accordingly [see Boxed Warning and Drug Interactions (7.1)].	Pain	12	1	-	10	1	-	= Not Applicable					
≤ 1.25	3000	0		3	5.2 Diarrhea Capecitabine can induce diarrhea, sometimes severe. Patients with severe diarrhea should be carefully monitored	Chest Pain	6	1	-	6	1			evant Adverse Events in erse events reported in <		with capecitab	ne either as mo	onotherapy or in
1.26 to 1.37 1.38 to 1.51	3300	2		3	and given fluid and electrolyte replacement if they become dehydrated. In 875 patients with either metastatic breast	Neurological								etaxel that were cons rade 3 and 4 adverse ever			treatment are	shown below;
1.52 to 1.65	4000	0		4	or colorectal cancer who received capecitabine monotherapy, the median time to first occurrence of grade 2 to 4 diarrhea was 34 days (range from 1 to 369 days). The median duration of grade 3 to 4 diarrhea was 5 days. National	Peripheral Sensory Neuropathy	10	-	-	4	-	_	-	tic Colorectal Cancer, Ad			Breast Cancer)	
1.66 to 1.77	4300	1		4	Cancer Institute of Canada (NCIC) grade 2 diarrhea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhea as an increase of 7 to 9 stools/day or incontinence and malabsorption, and grade 4 diarrhea as an		10	1	_	7	_		trointestinal:	abdominal distension, o	dysphagia, proctalgia	ascites (0.1%		r (0.1%), ileus:
1.78 to 1.91	4600	2		4	increase of ≥10 stools/day or grossly bloody diarrhea or the need for parenteral support. If grade 2, 3 or 4 diarrhea occurs, administration of capecitabine should be immediately interrupted until the diarrhea resolves or decreases in	Dizziness*	8	<1	_	8	<1	-		(0.3%), toxic dilation of i		. ,		
1.92 to 2.05	5000	0		5	intensity to grade 1 [see Dosage and Administration (2.3)]. Standard antidiarrheal treatments (e.g., loperamide) are	Insomnia	7	_	-	7	_	– Skin		nail disorder (0.1%), s ulceration, pruritus, radi			nsitivity reaction	n (0.1%), skin
2.06 to 2.17	5300	1		5	recommended.	Taste Disturbance	6	1	-	11	<1	1 Gen	neral:	chest pain (0.2%), influ	ienza-like illness, hot	flushes, pain (0.1%), hoarsen	ness, irritability,
≥ 2.18	5600	2		5	Necrotizing enterocolitis (typhlitis) has been reported.	Metabolism								difficulty in walking, thi sedation				
* Total Daily Dose div	ided by 2 to allow equal morning and ev	ening doses			5.3 Cardiotoxicity The cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias,	Appetite Decreased	26	3	<1	31	2	<1 . New		insomnia, ataxia (0.5	5%) tremor dvenh	acia encenh	alonathy (0.1º	%) abnormal
In Combination With Do	cetaxel (Metastatic Breast Cancer)				cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse reactions may be more common in patients with a prior history of coronary artery disease.	Dehydration	7	2	<1	8	3	1 ////		coordination, dysarthria				/oj, abitorittai
	ocetaxel, the recommended dose of ca est period, combined with docetaxel at				5.4 Dihydropyrimidine Dehydrogenase Deficiency	Eye Irritation	13		_	10	<1	_ Meta		increased weight, ca	achexia (0.4%), hy	pertriglyceride	mia (0.1%),	hypokalemia,
3 weeks. Pre-medication	on, according to the docetaxel labeling the capecitabine tablets plus docetaxel (, should be sta	arted prior to do	ocetaxel administration	Based on postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations	Vision Abnormal	5	_	_	2	_	-		hypomagnesemia				
	body surface area and the number of ta				in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by capecitabine	Respiratory						Eye:		conjunctivitis				
2.3 Dose Managen	nent Guidelines				(e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by capecitabine.	Dyspnea	14	1	-	10	<1	1 Resp		cough (0.1%), epistaxis dyspnea	s (0.1%), asthma (0.2	%), hemoptysis	s, respiratory di	istress (0.1%),
General Capecitabine tablets do	osage may need to be individualized to	o optimize pati	ient manageme	ent. Patients should be	Withhold or permanently discontinue capecitabine based on clinical assessment of the onset, duration and severity	Cough	7	<1	1	8	-	-			1			
	or toxicity and doses of capecitable al patient tolerance to treatment [see				of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No capecitabine dose has been proven safe for patients with	Pharyngeal Disorder	5	-	-	5	-	_ Card		tachycardia (0.1%), bra myocarditis (0.1%), peri		uon, ventricula	r extrasystoles,	extrasystoles,
tablets administration	may be managed by symptomatic	treatment, dos	ose interruption	ns and adjustment of	complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial	Epistaxis Sore Throat	3	<1	-	6 6	_	_ Infec	ctions:	laryngitis (1%), bronc	:hitis (0.2%), pneun	nonia (0.2%),	bronchopneun	monia (0.2%),
capecitabine tablets on	se. Once the dose has been reduced, hitted for toxicity are not replaced or res				DPD activity as measured by any specific test.	Musculoskeletal	2	-	-	0	_	_	r	keratoconjunctivitis, sep	osis (0.3%), fungal infe	ctions (includir	ng candidiasis) ((0.2%)
treatment cycles.					5.5 Dehydration and Renal Failure Dehydration has been observed and may cause acute renal failure which can be fatal. Patients with pre-existing	Back Pain	10	2	-	9	<1	_ Mus	sculoskeletal:	myalgia, bone pain (0.19	%), arthritis (0.1%), m	uscle weakness	3	
	and the dose of coumarin-derivative a ncomitantly with capecitabine tablets [s			e reduced when either	compromised renal function or who are receiving concomitant capecitabine with known nephrotoxic agents are at higher risk. Patients with anorexia, asthenia, nausea, vomiting or diarrhea may rapidly become dehydrated. Monitor	Arthralgia	8	1	-	6	1	_ Bloo		leukopenia (0.2%), co				ession (0.1%),
Monotherapy (Metastat	ic Colorectal Cancer, Adjuvant Colorect	tal Cancer. Meta	astatic Breast C	Cancer)	patients when capecitabine is administered to prevent and correct dehydration at the onset. If grade 2 (or higher) dehydration occurs, capecitabine treatment should be immediately interrupted and the dehydration corrected.	Vascular								idiopathic thrombocytop	,		,	
	ose modification scheme as describ				Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications should be applied for the precipitating adverse event as necessary [see Dosage	Venous Thrombosis	8	3	<1	6	2			hypotension (0.2%), hy (0.2%), cerebrovascular		/mpnoedema	(0.1%), puimon	hary embolism
	able 2 Recommended Dose Modifica	tions of Canao	aitahina Tahlata		and Administration (2.3)].	Psychiatric	5			6		Psyc	chiatric:	depression, confusion (0.1%)			
					Patients with moderate renal impairment at baseline require dose reduction [see Dosage and Administration (2.4)].	Mood Alteration Depression	5	_	_	4	<1	– Rena	ial:	renal impairment (0.6%))			
Toxicity NCIC Grades*	During a Course of Therap	py D		nt for Next Treatment starting dose)	Patients with mild and moderate renal impairment at baseline should be carefully monitored for adverse reactions. Prompt interruption of therapy with subsequent dose adjustments is recommended if a patient develops a grade 2	Infections						Ear:		vertigo				
Grade 1	Maintain dose level		Maintai	ain dose level	to 4 adverse event as outlined in Table 2 [see Dosage and Administration (2.3), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)].	Viral	5	<1	-	5	<1	-		-	\rightarrow boostitic (0.19/)	halaatatia han	atitia (0,1%)	abnormal liver
Grade 2					5.6 Embryo-Fetal Toxicity	Blood and Lymphatic						Пере		hepatic fibrosis (0.1%) function tests), nepaulus (0.1 <i>%</i>), t	ποιεδιατιό περ	auus (0.170), a	adhunnar nver
-1st appearance	Interrupt until received to grade	0 to 1		100%	Based on findings from animal reproduction studies and its mechanism of action, capecitabine may cause fetal harm when given to a pregnant woman [see Clinical Pharmacology (12.1)]. Limited available data are not sufficient	Anemia	80	2	<1	79	1		nune System:	drug hypersensitivity (0.	1%)			
-2nd appearance -3rd appearance	Interrupt until resolved to grade	0 10 1		75% 50%	to inform use of capecitabine tablets in pregnant women. In animal reproduction studies, administration of	Neutropenia	13	1	2	46	8	13 <u>Cap</u>	ecitabine In Combi	nation With Docetaxel (M	letastatic Breast Canci	er)		
-4th appearance	Discontinue treatment perman	ently		-	capecitabine to pregnant animals during the period of organogenesis caused embryolethality and teratogenicity in mice and embryolethality in monkeys at 0.2 and 0.6 times the exposure (AUC) in patients receiving the		48	18	5	17	3	3 Gasi	trointestinal:	ileus (0.4%), necrotizir	na enterocolitis (0.49	%), esophagea	l ulcer (0.4%).), hemorrhagic
Grade 3					recommended dose respectively [see Use in Specific Populations (8.1)]. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6		10	10	0		Ŭ	0		diarrhea (0.8%)	3	,,,		,
-1st appearance	Interrupt until resolved to grade	0 to 1		75%	months following the last dose of capecitabine tablets [see Use in Specific Populations (8.3)].	 Not observed * Excluding vertigo 						Neu	irological:	ataxia (0.4%), syncope ((1.2%), taste loss (0.8	%), polyneurop	athy (0.4%), mi	igraine (0.4%)
-2nd appearance				50%	5.7 Mucocutaneous and Dermatologic Toxicity Severe mucocutaneous reactions, some with fatal outcome, such as Stevens-Johnson syndrome and Toxic	NA = Not Applicable						Card	diac:	supraventricular tachyca	ardia (0.4%)			
-3rd appearance	Discontinue treatment perman	ently		-	Epidermal Necrolysis (TEN) can occur in patients treated with capecitabine [see Adverse Reactions (6.4)]. Capecitabine should be permanently discontinued in patients who experience a severe mucocutaneous reaction	6.3 Breast Cancer In Combination with Docetaxel						Infec	ction:	neutropenic sepsis (2.49	%), sepsis (0.4%), bro	nchopneumoni	a (0.4%)	
Grade 4	Discontinue permanently	,			possibly attributable to capecitabine treatment.	The following data are shown for breast cancer in Table 7 and 1							od & Lymphatic: a	agranulocytosis (0.4%),	prothrombin decreas	ed (0.4%)		
-1st appearance	OR If physician deems it to be in the pa			50%	Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) is a	capecitabine administered orally 1 week without treatment) for a	y 1250 mg/m² twic	e daily as inter	nittent thera	py (2 weeks	of treatment fo	lowed by		hypotension (1.2%), ve	-	. ,	(0.4%), postura	ral hypotension
- 13t appearance	interest to continue, interrupt until r			00/0	cutaneous toxicity. Median time to onset was 79 days (range from 11 to 360 days) with a severity range of grades 1 to 3 for patients receiving capecitabine monotherapy in the metastatic setting. Grade 1 is characterized by any of the	dose of 75 mg/m² on the first day	ay of each 3-week c	ycle for at leas	6 weeks. In	the monoth	erapy arm doce	taxel was		(0.8%)			,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	
	grade 0 to 1				following: numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 hand-and-foot syndrome is defined as painful	administered as a 1-hour in 3-week cycle for at least 6 wee	eks. The mean du	ration of treatr	nent was 12	29 days in tl	he combination	arm and Rena	al:	renal failure (0.4%)				
*National Cancer Institution [see Warnings and Pred	ute of Canada Common Toxicity Criteri cautions (5)].	a were used ex	cept for the har	nd-and-foot syndrome	erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 hand-and-foot syndrome is defined as moist desquamation, ulceration, blistering or severe pain of the	98 days in the monotherapy a monotherapy arm withdrew from	m the study because	e of adverse rea	ctions. The	percentage	of patients requi	ring dose Hepa		jaundice (0.4%), abnorn		(0.4%), hepati	c failure (0.4%)), hepatic coma
	cetaxel (Metastatic Breast Cancer)				hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. Persistent or severe hand-and-foot syndrome (grade 2 and above) can eventually lead to loss of fingerprints	reductions due to adverse reac percentage of patients requiring						vas 79%.		(0.4%), hepatotoxicity (0	J.4%)			
Dose modifications of o	capecitabine tablets for toxicity should to a treatment cycle, if a treatment				which could impact patient identification. If grade 2 or 3 hand-and-foot syndrome occurs, administration of	Treatment interruptions were part docetaxel monotherapy-treated		fication schen	ie for the co	mbination th	ierapy arm but r	ot for the Imm	nune System: h	hypersensitivity (1.2%)				
docetaxel, then adminis	stration of both agents should be delaye				capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-and-foot syndrome, subsequent doses of capecitabine should be decreased [see Dosage and Administration								Postmarketing following adverse	JExperience reactions have been ob	oserved in the postma	rketing setting	hepatic failure	e, lacrimal duct
met.					(2.3)].							sten	nosis, acute renal f	failure secondary to deh is erythematosus, corne	nydration including fat	al outcome [s	ee Warnings ar	ind Precautions
The dose reduction sch metastatic breast cance	edule for docetaxel when used in comb er is shown in Table 3 .	bination with ca	apecitabine table	lets for the treatment of	5.8 Hyperbilirubinemia In 875 patients with either metastatic breast or colorectal cancer who received at least one dose of capecitabine							skin	reactions such as	s Stevens-Johnson Syn rsistent or severe hand-	drome and Toxic Epic	lermal Necroly	sis (TEN) [see	Warnings and
					1250 mg/m ² twice daily as monotherapy for 2 weeks followed by a 1-week rest period, grade 3 (1.5 to 3 x ULN) hyperbilirubinemia occurred in 15.2% (n=133) of patients and grade 4 (>3 x ULN) hyperbilirubinemia occurred in								rnings and Precautio		and-tool syndronne ca	an eventually le	au to 1033 01 111	igerprints [see
					3.9% (n=34) of patients. Of 566 patients who had hepatic metastases at baseline and 309 patients without hepatic metastases at baseline, grade 3 or 4 hyperbilirubinemia occurred in 22.8% and 12.3%, respectively. Of the 167									re to crushed capecitabi				
					patients with grade 3 or 4 hyperbilirubinemia, 18.6% (n=31) also had postbaseline elevations (grades 1 to 4,							irrita	ation and swelling, s	skin rash, diarrhea, pares	stnesia, headache, gas	tric irritation, v	omiting, and nau	JSea.
					without elevations at baseline) in alkaline phosphatase and 27.5% (n=46) had postbaseline elevations in transaminases at any time (not necessarily concurrent). The majority of these patients, 64.5% (n=20) and 71.7%							7.	DRUG INTERAC	CTIONS				
					(n=33), had liver metastases at baseline. In addition, 57.5% $(n=96)$ and 35.3% $(n=59)$ of the 167 patients had elevations (grades 1 to 4) at both prebaseline and postbaseline in alkaline phosphatase or transaminases,							7.1	Drug-Drug Inte	eractions				
					respectively. Only 7.8% (n=13) and 3% (n=5) had grade 3 or 4 elevations in alkaline phosphatase or transaminases.							Antio	icoagulants	rameters and/or bleeding	a have been reported	n natiente takir	n canecitabine	concomitantly
					In the 596 patients treated with capecitabine as first-line therapy for metastatic colorectal cancer, the incidence of							with	n coumarin-derivati	ive anticoagulants such n several days and up to	as warfarin and ph	enprocoumon	[see Boxed Wa	/arning]. These
					grade 3 or 4 hyperbilirubinemia was similar to the overall clinical trial safety database of capecitabine monotherapy. The median time to onset for grade 3 or 4 hyperbilirubinemia in the colorectal cancer population was 64 days and							case	es, within 1 month	h after stopping capeci	tabine. These events	occurred in p	atients with an	nd without liver
					median total bilirubin increased from 8 µm/L at baseline to 13 µm/L during treatment with capecitabine. Of the 136 colorectal cancer patients with grade 3 or 4 hyperbilirubinemia, 49 patients had grade 3 or 4 hyperbilirubinemia as							the r	mean AUC of S-wa	nteraction study with sin rfarin <i>[see Clinical Phan</i>	macology (12.3)]. The	e maximum ob:	served INR valu	ue increased by
					their last measured value, of which 46 had liver metastases at baseline.								6. This interaction tabolites.	is probably due to an	ininidition of cytochr	ume P450 2C	э by capecitab	Jirie and/or its

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157.5 mm			33 11111	→			187	187.5 mm					
													
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Phenytoin The level of phenytoin should be carefully monitored in patients taking capecitabine and phenytoin dose may need	13. NONCLINICAL TOXICOLOGY		Table 16 Baseline De										
to be reduced <i>[see Dosage and Administration (2.3)]</i> . Postmarketing reports indicate that some patients receiving capecitable and phenytoin had toxicity associated with elevated phenytoin levels. Formal drug-drug interaction	13.1 Carcinogenesis, Mutagenesis, Impairmen Adequate studies investigating the carcinogenic po		been conducted. Capecitabine	Docetaxel Combination vs Docetaxel in Breast Cancer Trial Capecitabine + Docetaxel Docetaxel					Patient Information				
studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by capecitabine and/or its metabolites.	was not mutagenic <i>in vitro</i> to bacteria (Ames test) o assay). Capecitabine was clastogenic <i>in vitro</i> to hur	or mammalian cells (Chinese ham	ster V79/HPRT gene mutation	Are (medien years)		(n=2	· ·	(n=256) 51	Capecitabine (KAP e SYE ta been) Tablets, USP				
	mouse bone marrow (micronucleus test). Fluorour causes chromosomal abnormalities in the mouse m	racil causes mutations in bacteri	Age (median, years)		90		90	What is the most important information I should know about capecitabine tablets?					
Leucovorin The concentration of 5-fluorouracil is increased and its toxicity may be enhanced by leucovorin. Deaths from severe			Karnofsky PS (median) Site of Disease		90	Capecitabine tablets can cause serious side effects, including:							
enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil.	In studies of fertility and general reproductive 760 mg/kg/day (about 2300 mg/m²/day) disturbed			Ce Lymph nodes 121 (47%) 125 (49%)					 Capecitabine tablets can interact with blood thinner medicines, such as warfarin (COUMADIN[®]). capecitabine tablets with these medicines can cause changes in how fast your blood clots a 				
CYP2C9 substrates	that became pregnant, no fetuses survived this dos caused degenerative changes in the testes, including	e. The disturbance in estrus was	reversible. In males, this dose	Liver		116 (4	,	122 (48%)	cause bleeding that can lead to death. This can happen as soon as a few days after you s capecitabine tablets, or later during treatment, and possibly even within 1 month after you s				
Other than warfarin, no formal drug-drug interaction studies between capecitabine and other CYP2C9 substrates	separate pharmacokinetic studies, this do	ose in mice produced 5'-[DFUR AUC values about	Bone		107 (4	,	119 (46%)	capecitabine tablets. Your risk may be higher because you have cancer, and if you are over 6				
have been conducted. Care should be exercised when capecitabine is coadministered with CYP2C9 substrates.	0.7 times the corresponding values in patients admin	inistered the recommended daily c	dose.	Lung		95 (3	7%)	99 (39%)	age. • Before taking capecitabine tablets, tell your healthcare provider if you are taking				
Allopurinol Concomitant use with allopurinol may decrease concentration of capecitabine's active metabolites [see Clinical	14. CLINICAL STUDIES			Skin		73 (2	9%)	73 (29%)	 (COUMADIN[*]) or another blood thinner medicine. If you take warfarin (COUMADIN[*]) or another blood thinner that is like warfarin (COUMADI 				
Pharmacology (12.3)], which may decrease capecitabine efficacy. Avoid the use of allopurinol during treatment				Prior Chemotherapy					treatment with capecitabine tablets, your healthcare provider should do blood tests often				
with capecitabine.	14.1 Adjuvant Colon Cancer A multicenter randomized, controlled phase 3 clinic	cal trial in patients with Dukes' C c	colon cancer (X-ACT) provided	Anthracycline ¹		255 (1	00%)	256 (100%)	how fast your blood clots during and after you stop treatment with capecitabine tab healthcare provider may change your dose of the blood thinner medicine if needed.				
7.2 Drug-Food Interaction Food was shown to reduce both the rate and extent of absorption of capecitabine [see Clinical Pharmacology	data concerning the use of capecitabine for the a objective of the study was to compare disease-fr		5-FU		196 (7	7%)	189 (74%)	See "What are the possible side effects of capecitabine tablets?" for more information about si effects.					
(12.3)]. In all clinical trials, patients were instructed to administer capecitabine within 30 minutes after a meal. It is	receiving IV 5-FU/LV alone. In this trial, 1987 pat	tients were randomized either to	Paclitaxel		25 (1	0%)	22 (9%)	What are capecitabine tablets?					
recommended that capecitabine be administered with food [see Dosage and Administration (2)].	1250 mg/m ² orally twice daily for 2 weeks followed 8 cycles (24 weeks) or IV bolus 5-FU 425 mg/m ² and			Resistance to an Anthracycline					Capecitabine tablets are prescription medicine used to treat people with:				
8. USE IN SPECIFIC POPULATIONS	for a total of 6 cycles (24 weeks). Patients in the si histologically-confirmed Dukes' stage C colon canc			h No resistance 19 (7%) Progression on anthracycline therapy 65 (26%) Stable disease after 4 cycles of anthracycline therapy 41 (16%)			,	19 (7%)	 cancer of the colon that has spread to lymph nodes in the area close to the colon (Dukes' C st they have surgery. 				
	(within 8 weeks prior to randomization) comple	ete resection of the primary tur	mor without macroscopic or				,	73 (29%)	 cancer of the colon or rectum (colorectal) that has spread to other parts of the body (metastati breast cancer that has spread to other parts of the body (metastatic) together with another 				
8.1 Pregnancy Risk Summary	microscopic evidence of remaining tumor. Patients immunotherapy (except steroids), and have an ECO						6%)	40 (16%)	called docetaxel after treatment with certain other anti-cancer medicines have not worked.				
Based on findings in animal reproduction studies and its mechanism of action, capecitabine can cause fetal harm when administered to a pregnant woman <i>[see Clinical Pharmacology (12.1)]</i> . Limited available human data are not	platelets ≥ 100x10 ⁹ /L, serum creatinine ≤ 1.5 ULN normal limits at time of randomization.	I, total bilirubin \leq 1.5 ULN, AST/A	ALT \leq 2.5 ULN and CEA within	adjuvant therapy	caon or ananacyclin	78 (3	1%)	74 (29%)	 breast cancer that has spread to other parts of the body and has not improved after treat paclitaxel and certain other anti-cancer medicines, or who cannot receive any more treat 				
sufficient to inform the drug-associated risk during pregnancy. In animal reproduction studies, administration of				Experienced a brief response to anthracycline therapy, with subsequent progression while on therapy or within 51 (20%) 50 (20%)				50 (00%)	certain anti-cancer medicines. It is not known if capecitabine tablet is safe and effective in children.				
capecitabine to pregnant animals during the period of organogenesis caused embryo lethality and teratogenicity in mice and embryo lethality in monkeys at 0.2 and 0.6 times the exposure (AUC) in patients receiving the		nd 5-FU/LV patients are shown	n in Table 10 . The baseline	with subsequent progression while on therapy or within 51 (20%) 12 months after last dose			0%)	50 (20%)					
recommended dose respectively [see Data]. Apprise pregnant women of the potential risk to a fetus.	Table 10 Ba	aseline Demographics		No. of Prior Chemotherapy Regi	imens for Treatment				Do not take capecitabine tablet if you: have severe kidney problems. 				
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically		Capecitabine	5-FU/LV	of Metastatic Disease		89 (3	5%)	80 (31%)	 are allergic to capecitabine, 5-fluorouracil, or any of the ingredients in capecitabine tablets. S of this leaflet for a complete list of ingredients in capecitabine tablets. 				
recognized pregnancies is 2 to 4% and 15 to 20%, respectively.		(n=1004)	(n=983)	1		123 (4	,	135 (53%)	Talk to your healthcare provider before taking capecitabine tablets if you are not sure if you have conditions listed above.				
Data Animal Data	Age (median, years)	62	63	2		43 (1	,	39 (15%)					
Animal Data Oral administration of capecitabine to pregnant mice during the period of organogenesis at a dose of	Range	(25 to 80)	(22 to 82)	3		0 (0	,	2 (1%)	Before taking capecitabine tablets, tell your healthcare provider about all your medical c including if you:				
198 mg/kg/day caused malformations and embryo lethality. In separate pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values that were approximately 0.2 times the AUC values in patients administered the				¹ Includes 10 patients in combination a	and 18 patients in mor	otherapy arms treated	l with an anthrace		See "What is the most important information I should know about capecitabine tablets?" have had heart problems. 				
recommended daily dose. Malformations in mice included cleft palate, anophthalmia, microphthalmia, oligodactyly, polydactyly, syndactyly, kinky tail and dilation of cerebral ventricles. Oral administration of	Male (n, %)	542 (54)	532 (54)	Capecitabine in combination with do					 have kidney or liver problems. have been told that you lack the enzyme DPD (dihydropyrimidine dehydrogenase). 				
capecitabine to pregnant monkeys during the period of organogenesis at a dose of 90 mg/kg/day, caused fetal	5000 P2	461 (46)	451 (46)	progression, overall survival and obj					are pregnant or plan to become pregnant. Capecitabine tablets can harm your unborn b				
lethality. This dose produced 5'-DFUR AUC values that were approximately 0.6 times the AUC values in patients administered the recommended daily dose.	0 (n, %)	849 (85)	830 (85)	Table 17, Figure 4, and Figure 5.					healthcare provider should do a pregnancy test before you start treatment with capecitabine to your healthcare provider right away if you become pregnant or think you might be pregna				
8.2 Lactation	1 (n, %)	152 (15)	147 (15)	Table 17 Efficacy of Capecitab	oine and Docetaxel C Param		taxel Monotheraj	py Efficacy	treatment with capecitabine tablets. o Females who are able to become pregnant should use effective birth control during trea				
	Staging – Primary Tumor			[[Combination				for 6 months after the final dose. Talk to your healthcare provider about birth control ch				
Risk Summary There is no information regarding the presence of capecitabine in human milk, or on its effects on milk production or	PT1 (n, %)	12 (1)	6 (0.6)		Therapy	Monotherapy	p-value	Hazard Ratio	may be right for you during treatment with capecitabine tablets. • Males who have female partners who are able to become pregnant should use effer				
the breast-fed infant. Capecitabine metabolites were present in the milk of lactating mice [see Data]. Because of the potential for serious adverse reactions from capecitabine exposure in breast-fed infants, advise women not to		90 (9)	92 (9)	Time to Disease Progression Median Days	186	128	0.0001	0.643	 control during treatment and for 3 months after the final dose. are breastfeeding or plan to breastfeed. It is not known if capecitabine passes into your breast 				
breastfeed during treatment with capecitabine tablets and for 2 weeks after the final dose.	PT3 (n, %)	763 (76)	746 (76)	95% C.I.	(165 to 198)	(105 to 136)	0.0001	0.0.0	not breastfeed during treatment with capecitabine tablets and for 2 weeks after the final dose.				
Data	PT4 (n, %)	138 (14)	139 (14)	Overall Survival	442	352	0.0106	0.775	Tell your healthcare provider about all the medicines you take, including prescription and over-th medicines, vitamins, and herbal supplements. Capecitabine tablets may affect the way other in the supplement of the supplement				
Lactating mice given a single oral dose of capecitabine excreted significant amounts of capecitabine metabolites into the milk.	Other (n, %)	1 (0.1)	0 (0)	Median Days 95% C.I.	(375 to 497)	(298 to 387)	0.0126	0.775	work, and other medicines may affect the way capecitabine tablet works. Know the medicines you take. Keep a list of them to show your healthcare provider and pharma				
	Staging – Lymph Node			Response Rate ¹	32%	22%	0.009	NA ²	you get a new medicine.				
8.3 Females and Males of Reproductive Potential Pregnancy Testing	pN1 (n, %)	695 (69)	694 (71)	-									

Lactating mice given a single oral dose of capecitabine excreted significant amounts of capecitabine metabolites into the milk.	Other (n, %)	1 (0.1)	0 (0)	95% C.I.	(375 to 497)	(298 to 387)	0.0126	0.775	work, and other medicines may affect the way capecitabine tablet works. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when		
8.3 Females and Males of Reproductive Potential	Staging – Lymph Node	COF (CO)	CO4 (71)	Response Rate ¹	32%	22%	0.009	NA ²	you get a new medicine.		
Pregnancy Testing Pregnancy testing is recommended for females of reproductive potential prior to initiating capecitabine tablets.	pN1 (n, %)	695 (69)	694 (71) 288 (29)	¹ The response rate reported represents a	racanciliation	f the investigator and I	C accoccmente r	orformed by the	 How should I take capecitabine tablets? Take capecitabine tablets exactly as your healthcare provider tells you to take it. 		
	pN2 (n, %) Other (n, %)	305 (30)	1 (0.1)	sponsor according to a predefined algorith		n uie investigator and i	10 235535116113 4	Jei Toi Theu by the	 Your healthcare provider will tell you how much capecitabine tablets to take and when to take it. 		
Contraception Females		4 (0.4)	1 (0.1)	2 NA = Not Applicable					 Take capecitabine tablets 2 times a day, 1 time in the morning and 1 time in the evening. Take capecitabine tablets within 30 minutes after finishing a meal. 		
Capecitabine can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment and for 6 months	All patients with normal renal function or mild renal					for Time to Disease I cetaxel vs Docetaxel	Progression		 Swallow capecitabine tablets whole with water. Do not crush or cut capecitabine tablets. If you cannot swallow capecitabine tablets whole, tell your healthcare provider. 		
following the final dose of capecitabine tablets.	1250 mg/m ² orally twice daily. The starting dose w (calculated creatinine clearance 30 to 50 mL/min)			(2.4)].		CEIAXEI VS DUCEIAXEI			Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with		
Males	Subsequently, for all patients, doses were adjusted w capecitabine included dose reductions, cycle delays and			hent for Estimated Probability					 capecitabine tablets if you develop side effects. If you take too much capecitabine tablets, call your healthcare provider or go to the nearest hospital 		
Based on genetic toxicity findings, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months following the last dose of capecitabine tablets /see			, ,		Docetaxe	el 100 (mg/sqm/3 weeks)			emergency room right away.		
Nonclinical Toxicology (13.1)].	Table 11 Summary of Dose	Modifications in X-AC	-	0.8	oup Capecita	bine 1250 (mg/sqm twice da	ily) intermittent		What are the possible side effects of capecitabine tablets?		
Infertility			Capecitabine 5-FU N = 995 N =		W/ UUCELA	axel 75 (mg/sqm/3 weeks)			Capecitabine tablets may cause serious side effects including: See "What is the most important information I should know about capecitabine tablets?".		
Based on animal studies, capecitabine tablets may impair fertility in females and males of reproductive potential [see Nonclinical Toxicology (13.1)].	Median relative dose intensity (%)		93 93	0.5	>				 Diarrhea. Diarrhea is common with capecitabine tablets and can sometimes be severe. Stop taking capecitabine tablets and call your healthcare provider right away if the number of bowel movements you 		
	Patients completing full course of treatment (%)		0.4	VIV -			have in a day increases by 4 or more than is usual for you. Ask your healthcare provider about what				
8.4 Pediatric Use The safety and effectiveness of capecitabine in pediatric patients have not been established. No clinical benefit was	Patients with treatment interruption (%)		15 5	0.2		_			medicines you can take to treat your diarrhea. If you have severe bloody diarrhea with severe abdominal pain and fever, call your healthcare provider or go to the nearest hospital emergency room right away.		
demonstrated in two single arm trials in pediatric patients with newly diagnosed brainstem gliomas and high grade gliomas. In both trials, pediatric patients received an investigational pediatric formulation of capecitabine	Patients with cycle delay (%) Patients with dose reduction (%)		46 29			······			 Heart problems. Capecitabine tablets can cause heart problems including: heart attack and decreased blood flow to the heart, chest pain, irregular heartbeats, changes in the electrical activity of your heart 		
concomitantly with and following completion of radiation therapy (total dose of 5580 cGy in 180 cGy fractions). The	Patients with treatment interruption, cycle delay, or o	dose reduction (%)	57 5	— Ó 🕇	200	400 600	800		seen on an electrocardiogram (ECG), problems with your heart muscle, heart failure, and sudden death. Stop taking capecitabine tablets and call your healthcare provider right away if you get any of the		
relative bioavailability of the investigational formulation to capecitabine was similar.			0. 0.	128	3 T 186		Time (Days)		following symptoms:		
The first trial was conducted in 22 pediatric patients (median age 8 years, range 5 to 17 years) with newly diagnosed non-disseminated intrinsic diffuse brainstem gliomas and high grade gliomas. In the dose-finding	The median follow-up at the time of the analysis was capecitabine compared to 5-FU/LV was 0.88 (95% C.I				nates of Surviva	al Capecitabine and D	ocetaxel vs Doce	etaxel	o chest pain o shortness of breath		
portion of the trial, patients received capecitabine with concomitant radiation therapy at doses ranging from 500 mg/m ² to 850 mg/m ² every 12 hours for up to 9 weeks. After a 2 week break, patients received 1250 mg/m ²	upper 2-sided 95% confidence limit of hazard ratio was I	ess than 1.2, capecitabir	ne was non-inferior to 5-FL	/LV. The					o feeling faint o irregular heartbeats or skipping beats		
capecitabine every 12 hours on Days 1 to 14 of a 21 day cycle for up to 3 cycles. The maximum tolerated dose	choice of the non-inferiority margin of 1.2 corresponds on DFS. The hazard ratio for capecitabine compared to	5-FU/LV with respect to a	overall survival was 0.86 (5% C.I. Probability					o sudden weight gain		
(MTD) of capecitabine administered concomitantly with radiation therapy was 650 mg/m ² every 12 hours. The major dose limiting toxicities were palmar-plantar erythrodysesthesia and alanine aminotransferase (ALT)	0.74 to 1.01). The 5-year overall survival rates were 71.4	4% for capecitabine and 6	ire 2). 1	Group Do	ocetaxel 100 (mg/sqm/3 weeks)		 swollen ankles or legs Loss of too much body fluid (dehydration) and kidney failure. 				
elevation.	Table 12 Efficacy of Capecitabine vs 5-Fl	J/LV in Adjuvant Treatn	nent of Colon Cancer [®]	0.8		apecitabine 1250 (mg/sqm twice /docetaxel 75 (mg/sqm/3 weeks)			Dehydration can happen with capecitabine tablets and may cause sudden kidney failure that can lead to death. You are at higher risk if you have kidney problems before taking capecitabine tablets and also take		
The second trial was conducted in 34 additional pediatric patients with newly diagnosed non-disseminated intrinsic	All Randomized Population	Capecitabine	5-FU/LV	0.7					other medicines that can cause kidney problems.		
diffuse brainstem gliomas (median age 7 years, range 3 to 16 years) and 10 pediatric patients who received the MTD of capecitabine in the dose-finding trial and met the eligibility criteria for this trial. All patients received		(n=1004)	(n=983)	0.5					Nausea, and vomiting are common with capecitabine tablets. If you lose your appetite, feel weak, and have nausea, vomiting, or diarrhea, you can quickly become dehydrated.		
650 mg/m ² capecitabine every 12 hours with concomitant radiation therapy for up to 9 weeks. After a 2 week break, patients received 1250 mg/m ² capecitabine every 12 hours on Days 1 to 14 of a 21-day cycle for up to	Median follow-up (months)	83	83	0.4			~		 Stop taking capecitabine tablets and call your doctor right away if you: vomit 2 or more times in a day. 		
3 cycles.	5-year Disease-free Survival Rates (%) ^b	59.1	54.6	0.2			······		 are only able to eat or drink a little now and then, or not at all due to nausea. have diarrhea. See "diarrhea" above. 		
There was no improvement in one-year progression-free survival rate and one-year overall survival rate in pediatric	Hazard Ratio (capecitabine /5-FU/LV) (95% C.I. for Hazard Ratio)		0.88 7 to 1.01)	0					Serious skin and mouth reactions.		
patients with newly diagnosed intrinsic brainstern gliomas who received capecitabine relative to a similar population of pediatric patients who participated in other clinical trials.	p-value°	p =	= 0.068	0		400 ↑ 600 5 442	800 Time (Deur	\ \	 Capecitabine tablets can cause serious skin reactions that may lead to death. Tell your healthcare provider right away if you develop a skin rash, blisters and peeling of your skin. Your healthcare 		
The adverse reaction profile of capecitabine was consistent with the known adverse reaction profile in adults, with	^a Approximately 93.4% had 5-year DFS information ^b Based on Kaplan-Meier estimates			<u>Monotherapy</u>	001.	J 442	Time (Days)	provider may tell you to stop taking capecitabine tablets if you have a serious skin reaction. Do not take capecitabine tablets again if this happens.		
the exception of laboratory abnormalities which occurred more commonly in pediatric patients. The most	"Test of superiority of capecitabine vs 5-FU/LV (Wald chi-	-square test)		The antitumor activity of capecitabine as					· Capecitabine tablets can also cause "hand and foot syndrome." Hand and foot syndrome is		
frequently reported laboratory abnormalities (per-patient incidence ≥ 40%) were increased ALT (75%), lymphocytopenia (73%), leukopenia (73%), hypokalemia (68%), thrombocytopenia (57%), hypoalbuminemia	Figure 1 Kaplan-Meier Estimates of Diseas	se-Free Survival (All Ra	andomized Population)*	in 24 centers in the U.S. and Canada. A to endpoint was tumor response rate in patie					in your hands and feet, or cause redness, pain, swelling of your hands and feet. Stop taking		
(55%), neutropenia (50%), low hematocrit (50%), hypocalcernia (48%), hypophosphaternia (45%) and hyponatrernia (45%).	Survival		• •	in sum of the products of the perpendicul Capecitabine was administered at a dose					capecitabine tablets and call your healthcare provider right away if you have any of these symptoms and you are not able to do your usual activities. Hand and foot syndrome can lead to loss of		
	1-			and given as 3-week cycles. The baselin	ne demographics	and clinical character	istics for all patier	nts (n=162) and	fingerprints which could impact your identification.		
8.5 Geriatric Use Physicians should pay particular attention to monitoring the adverse effects of capecitabine in the elderly (see	0.9 - 0.8 - 0.8			those with measurable disease (n=135) while on treatment, with or without an init					capecitabine tablets and call your healthcare provider if you get painful redness, swelling, or ulcers		
Warnings and Precautions (5.10)].	0.7			anthracycline-containing adjuvant chemo	otherapy regimer	n.			 in your mouth and tongue, or if you are having problems eating. Increased level of bilirubin in your blood and liver problems. Increased bilirubin in your blood is 		
8.6 Hepatic Insufficiency Exercise caution when patients with mild to moderate hepatic dysfunction due to liver metastases are treated with	0.6 - 0.5 -			Table 18 Baseline Demog	graphics and Cli Cance		Single-Arm Brea	ist	common with capecitabine tablets. Your healthcare provider will check you for these problems during treatment with capecitabine tablets.		
capecitabine. The effect of severe hepatic dysfunction on capecitabine is not known [see Warnings and	0.4 - 0.3 -								 Decreased white blood cells, platelets, and red blood cell counts. Your healthcare provider will do blood tests during treatment with capecitabine tablets to check your blood cell counts. 		
Precautions (5.11) and Clinical Pharmacology (12.3)].		5-FU+LEUCOVORIN —	CAPECITABINE		Patients V	With Measurable Dise (n=135)		Patients 1=162)	If your white blood cell count is very low, you are at increased risk for infection. Call your healthcare		
8.7 Renal Insufficiency Patients with moderate (creatinine clearance = 30 to 50 mL/min) and severe (creatinine clearance <30 mL/min)	0		· · · · · · ·	Age (median, years)		55		56	provider right away if you develop a fever of 100.5°F or greater or have other signs and symptoms of infection.		
renal impairment showed higher exposure for capecitabine, 5'-DFUR, and FBAL than in those with normal renal	0 6 12 18 24 30 36 natrisk		78 84 90 96 Months Since Randomization	Karnofsky PS		90		90	People 80 years of age or older may be more likely to develop severe or serious side effects with capecitabine tablets.		
function [see Contraindications (4.2), Warnings and Precautions (5.5), Dosage and Administration (2.4), and Clinical Pharmacology (12.3)].	5-FU+LEUCOVORIN 983 902 801 720 640 596			No. Disease Sites					The most common side effects of capecitabine tablets include:		
	CAPECITABINE 1004 928 836 748 696 658	609 574 532 497 432	332 228 137 66 8 3	1 to 2		43 (32%)	60	0 (37%)	 diarrhea hand and foot syndrome 		
 OVERDOSAGE The manifestations of acute overdose would include nausea, vomiting, diarrhea, gastrointestinal irritation and 	°Capecitabine has been demonstrated to be non-inferi	ior to 5-FU/LV.		3 to 4		63 (46%)		9 (43%)	 nausea vomiting 		
bleeding, and bone marrow depression. Medical management of overdose should include customary supportive	Figure 2 Kaplan-Meier Estimates of Ove	erall Survival (All Rand	lomized Population)	>5		29 (22%)	34	4 (21%)	 stomach-area (abdominal) pain tiredness 		
medical interventions aimed at correcting the presenting clinical manifestations. Although no clinical experience using dialysis as a treatment for capecitabine overdose has been reported, dialysis may be of benefit in reducing	Survival			Dominant Site of Disease Visceral ¹		101 (75%)		0 (68%)	• weakness		
circulating concentrations of 5'-DFUR, a low-molecular-weight metabolite of the parent compound.	1-			Soft Tissue		101 (75%) 30 (22%)		5 (22%)	 increased amounts of red blood cell breakdown products (bilirubin) in your blood Capecitabine tablets may cause fertility problems in females and males. This may affect the ability to have a 		
Single doses of capecitabine were not lethal to mice, rats, and monkeys at doses up to 2000 mg/kg (2.4, 4.8, and 9.6 times the recommended human daily dose on a mg/m² basis).	0.9 - 0.8 -			Bone		4 (3%)		7 (10%)	child. Talk to your healthcare provider if you have concerns about fertility. These are not all the possible side effects of capecitabine tablets.		
o.o แก่เอ แต่ เออาการการเอน กับเกล่า นสมรู นี่บอธิ ปีกล กญากับ ของเอj.	0.7 - 0.6 -			Prior Chemotherapy					Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.		
11. DESCRIPTION	0.5 - 0.4 -			Paclitaxel		135 (100%)		2 (100%)			
Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil.	0.3 -			Anthracycline ²		122 (90%)		7 (91%)	 How should I store capecitabine tablets? Store capecitabine tablets at room temperature between 68°F to 77°F (20°C to 25°C). 		
	0.2 - TREATMENT GROUP 0.1 -			5-FU		110 (81%)	13	3 (82%)	 Keep capecitabine tablets in a tightly closed container. Ask your healthcare provider or pharmacist how to safely throw away any unused capecitabine tablets. 		
The chemical name for capecitabine is 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine and has a molecular weight of 359.35. Capecitabine has the following structural formula:	0	12 48 54 60 66 72 78	3 84 90 96	Resistance to Paclitaxel		103 (76%)	12	.4 (77%)	Keep capecitabine tablets and all medicines out of the reach of children.		
0. N NH> 0	n at risk	Mo	onths Since Randomization	Resistance to an Anthracycline ²		55 (41%)	6	7 (41%)	General information about the safe and effective use of capecitabine tablets.		
	5-FU+LEUCOVORIN 983 964 934 903 850 795			Resistance to both Paclitaxel and an Anthracycline ²		43 (32%)	5	1 (31%)	Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use capecitabine tablets for a condition for which it was not prescribed. Do not give capecitabine tablets		
	CAPECITABINE 1004 983 964 929 888 849	000 / 09 / 35 / 02 005 :	501 434 200 174 55 50	1	I		I		to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about capecitabine tablets that is written for health		
	14.2 Metastatic Colorectal Cancer General			 ¹ Lung, pleura, liver, peritoneum ² Includes 2 patients treated with an anthr 	racenedione				professionals.		
НО́ОН	The recommended dose of capecitabine was determine efficacy and safety of continuous therapy with capec				disease resistan	it to both paclitaxel ar	d an anthracycli	ne are shown in	What are the ingredients in capecitabine tablets?		
Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20° C.	intermittent therapy with capecitabine (2510 mg/m²/day	r in two divided doses, n =	=34), and intermittent ther	py with Table 19.			a an ananaoyom		Active ingredient: capecitabine Inactive ingredients: microcrystalline cellulose, croscarmellose sodium, hypromellose, anhydrous lactose,		
Capecitabine tablets, USP are supplied as oval, biconvex, film-coated tablets for oral administration. Each light	capecitabine in combination with oral leucovorin (LV) (c leucovorin 60 mg/day) in patients with advanced and/or	metastatic colorectal ca	arcinoma in the first-line m	tastatic Table 19 Response Rates in	Doubly-Resista	ant Patients Single-Ar	m Breast Cancer	Trial	talc and magnesium stearate. The peach or light peach film coating contains hypromellose, titanium		
peach colored tablets debossed with '150' on one side and plain on other side contains 150 mg of capecitabine USP and each peach colored tablet debossed with '500' on one side and plain on other side contains 500 mg of	setting. There was no apparent advantage in response in was increased. Capecitabine, 1250 mg/m ² twice daily					Resistance to B	oth Paclitavel on	d an	dioxide, lactose monohydrate, polyethylene glycol, red iron oxide and yellow iron oxide.		
capecitabine USP. The inactive ingredients in capecitabine tablets include: microcrystalline cellulose, croscarmellose sodium, hypormellose, anhydrous lactose, talc and magnesium stearate. The peach or light peach	further clinical development based on the overall safety a				vcline (n=43)	For more information, call 1-800-818-4555.					
film coating contains hypromellose, titanium dioxide, lactose monohydrate, polyethylene glycol, red iron oxide and	Monotherapy	CR			0		This Patient Information has been approved by the U.S. Food and Drug Administration.				
yellow iron oxide.	Data from two open-label, multicenter, randomized, con of capecitabine in the first-line treatment of patients with						11		*All trademark names are the property of their respective owners.		
12. CLINICAL PHARMACOLOGY	were identical in design and were conducted in 120 ce U.S., Canada, Mexico, and Brazil; Study 2 was conduc	enters in different countri	ies. Study 1 was conduct	d in the CR + PR'			11		Distributed by:		
	Alles alles is half tight 200 salisate	Lisa in Europe, islael, Al	Loadina, ivov Loadinu, dilu	Idiwali. Besponse Bate ¹			25.6%				

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics Absorption

Distribution

12.1 Mechanism of Action Enzymes convert capecitabine to 5-fluorouracil (5-FU) *in vivo*. Both normal and tumor cells metabolize 5-FU to 5-

inhibit ed livision. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uritime triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesis of RNA. This metabolic error can interfere with RNA processing and protein the synthesi synthesis.

Following oral administration of 1255 mg/m² BID to cancer patients, capecitabine reached peak blood levels in about 1.5 hours ($T_{\rm ms}$) with peak 5-FU levels occurring slightly later, at 2 hours. Food reduced both the rate and extent

of absorption of capecitabine with mean $C_{\mbox{\tiny max}}$ and $AUC_{\mbox{\tiny 0},\infty}$ decreased by 60% and 35%, respectively. The $C_{\mbox{\tiny max}}$ and

by 1.5 hours [see Warnings and Precautions (5), Dosage and Administration (2), and Drug-Food Interaction

AUC_n∞ of 5-FU were also reduced by food by 43% and 21%, respectively. Food delaved T____ of both parent and 5-FU

Age (median, years)

Survival (Median, days, 95% C.I.)

Overall Response Rate

Time to Progression

Median, days, 95% C.I.)

95% C.I. for Hazard Ratio

(Median, days, 95% C.I.)

95% C.I. for Hazard Ratio

Hazard Ratio (capecitabine/5-FU/LV)

Hazard Ratio (capecitabine/5-FU/LV)

Estimated

(%, 95% C.I.)

(p-value)

Survival

Hazard Ratio (capecitabine/5-FU/LV) 95% C.I. for Hazard Ratio

The baseline demographics for capecitabine and 5-FU/LV patients are shown in Table 13. Table 13 Baseline

Altogether, in both trials, 603 patients were randomized to treatment with capecitabine at a dose of 1250 mg/m²

13 Baseline Der	mographics of Co	ntrolled Colored	tal Trials		chemothe
	Stud	y 1	Stud	/ 2	
	Capecitabine (n=302)	5-FU/LV (n=303)	Capecitabine (n=301)	5-FU/LV (n=301)	15. RE 1. "OSH/
	64 (23 to 86)	63 (24 to 87)	64 (29 to 84)	64 (36 to 86)	http://v

hand and foot syndrome nausea vomiting stomach-area (abdominal) pain tiredness weakness increased amounts of red blood cell breakdown products (bilirubin) in your blood pecitabine tablets may cause fer tility problems in females and males. This may affect the ability to have a ld. Talk to your healthcare provider if you have concerns about fertility. see are not all the possible side effects of capecitabine tablets. Il your doctor for medical advice about side effects. You may report side effects to FDA at 00-FDA-1088.
w should I store capecitabine tablets? Store capecitabine tablets at room temperature between 68°F to 77°F (20°C to 25°C). Keep capecitabine tablets in a tightly closed container. Ask your healthcare provider or pharmacist how to safely throw away any unused capecitabine tablets. ep capecitabine tablets and all medicines out of the reach of children.
neral information about the safe and effective use of capecitabine tablets. dicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do use capecitabine tablets for a condition for which it was not prescribed. Do not give capecitabine tablets other people, even if they have the same symptoms you have. It may harm them. You can ask you armacist or healthcare provider for information about capecitabine tablets that is written for health fessionals.
at are the ingredients in capecitabine tablets? ive ingredient: capecitabine ctive ingredients: microcrystalline cellulose, croscarmellose sodium, hypromellose, anhydrous lactose c and magnesium stearate. The peach or light peach film coating contains hypromellose, titanium xide, lactose monohydrate, polyethylene glycol, red iron oxide and yellow iron oxide.
r more information, call 1-800-818-4555. s Patient Information has been approved by the U.S. Food and Drug Administration.
s raten mornation has been approved by the c.c. rood and Drug Administration.

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For the subgroup of 43 patients who were doubly resistant, the median time to progression was 102 days and the median survival was 255 days. The objective response rate in this population was supported by a response rate of 18.5% (1 CR, 24 PRs) in the overall population of 135 patients with measurable disease, who were less resistant to chemotherapy (see **Table 18**). The median time to progression was 90 days and the median survival was 306 days.

25.6% (13.5, 41.2)

154

(63 to 233)

REFERENCES

Response Rate¹ (95% C.I.)

Duration of Response,¹ Median in days² (Range)

HA Hazardous Drugs." OSHA. ://www.osha.gov/SLTC/hazardousdrugs/index.html.

(1.2)].	Range
The pharmacokinetics of capecitabine and its metabolites have been evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m²/day. Over this range, the pharmacokinetics of capecitabine and its metabolite, 5-DFCR were dose proportional and did not change over time. The increases in the AUCs of 5-DFUR and 5-FU.	Gender Male (%) Female (%)
however, were greater than proportional to the increase in dose and the AUC of 5-FU was 34% higher on day 14 than on day 1. The interpatient variability in the G_{max} and AUC of 5-FU was greater than 85%.	Karnofsky PS (med Range

Plasma protein binding of capecitabine and its metabolites is less than 60% and is not concentration-dependent.

Capecitabine was primarily bound to human albumin (approximately 35%). Capecitabine has a low potential for

Metabolic Pathway of capecitabine to 5-FU

The enzyme dihydropyrimidine dehydrogenase hydrogenates 5-FU, the product of capecitabine metabolism, to the

The enzyme universe promotion of the enzyme university of the product of the product of the product of the enzyme university of the enzyme universe enzyme university of the enzyme university o

In vitro enzymatic studies with human liver microsomes indicated that capecitabine and its metabolites (5'-DFUR,

2-5-DFCR, 5-FU, and FBAL) did not inhibit the metabolism of test substrates by cytochrome P450 iscenzymes 1A2, 2A6, 3A4, 2C19, 2D6, and 2E1.

Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered capecitabine dose is

recovered in urine. Fecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged

A population analysis of pooled data from the two large controlled studies in patients with metastatic colorectal cancer (n=505) who were administered capecitabine at 1250 mg/m² twice a day indicated that gender (202 females and 303 males) and race (455 white/Caucasian patients, 22 black patients, and 28 patients of other race) have no influence on the pharmacokinetics of 5'-DFUR and 5-FU over the range of 27 to 86 years. A 20% increase in age results in a 15% increase in 400 ef DRM.

Following oral administration of 825 mg/m² capecitabine twice daily for 14 days, Japanese patients (n=18) had about 36% lower C_{max} and 24% lower AUC for capecitabine than the Caucasian patients (n=22). Japanese patients had also about 25% lower C_{max} and 34% lower AUC for FBAL than the Caucasian patients. The clinical significance of

these differences is unknown. No significant differences occurred in the exposure to other metabolites (5-DFCR, 5-DFUR, and 5-FU).

Effect of Hepatic Insufficiency Capecitabine has been evaluated in 13 patients with mild to moderate hepatic dysfunction due to liver metastases

defined by a composite score including bilirubin. AST/ALT and alkaline phosphatase following a single 1255 mg/m² dose of capecitabine. Both AUC₆ \sim and C_{max} of capecitabine increased by 60% in patients with hepatic

dysfunction compared to patients with normal hepatic function (n=14). The AUC_{0, ∞} and C_{max} of 5-FU were not

increase in AUC of FBAL [see Warnings and Precautions (5.11) and Dosage and Administration (2.4)].

5'-DFUF

drug. The elimination half-life of both parent capecitabine and 5-FU was about 0.75 hour.

Effect of Age, Gender, and Race on the Pharmacokinetics of Capecitabine

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Gender Male (%) Female (%)	181 (60) 121 (40)	197 (65) 106 (35)	172 (57) 129 (43)	173 (57) 128 (43)	16. HOW SUPPLIED/STORAGE AND HANDLING Capecitabine tablets, USP are available as follows:
Karnofsky PS (median) Range	90 (70 to 100)	90 (70 to 100)	90 (70 to 100)	90 (70 to 100)	150 mg - Light peach colored, oval, biconvex, film coated tablets debossed with '150' on one side and plain on other side.
Colon (%) Rectum (%)	222 (74) 79 (26)	232 (77) 70 (23)	199 (66) 101 (34)	196 (65) 105 (35)	Bottles of 60's with Child Resistant CapNDC 62756-238-86 Bottles of 100's with Child Resistant CapNDC 62756-238-88
Prior radiation therapy (%)	52 (17)	62 (21)	42 (14)	42 (14)	Bottles of 1000's with Non Child Resistant CapNDC 62756-238-18
Prior adjuvant 5-FU (%)	84 (28)	110 (36)	56 (19)	41 (14)	500 mg - Peach colored, oval, biconvex, film coated tablets debossed with '500' on one side and plain on other side.

Bioactivation and Metabolism

which is cleared in the urine.

harmacokinetic interactions related to plasma protein binding

Capecitabine is extensively metabolized enzymatically to 5-FU. In the liver, a 60 kDa carboxylesterase hydrolyzes much of the compound to 5-deoxy-5-fluorocytidine (5-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5-DFCR to 5'-DFUR. The enzyme, thymidine phosphorylase (dThdPase), then hydrolyzes 5'-DFUR to the active drug 5-FU. Many tissues throughout the body express thymidine phosphorylase. Some human carcinomas express this enzyme in higher concentrations than surrounding normal tissues. Following oral administration of capecitabine 7 days before surgery in patients with colorectal cancer, the median ratio of 5-FU concentration in colorectal tumors to adjacent tissues was 2.9 (range from 0.9 to 8). These ratios have not been evaluated in breast cancer patients or compared to 5-FU infusion.

he efficacy endpoints for the two phase 3 t Table 14 Efficacy of Cap	rials are shown in Table 14 and Tal ecitabine vs 5-FU/LV in Colorect		Bottles of 30's with Child Resistant Cap
	Capecitabine (n=302)	5-FU/LV (n=303)	Storage and Handling
Overall Response Rate (%, 95% C.l.)	21 (16 to 26)	11 (8 to 15)	 Store capecitabine tablets at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° a 86°F) [see USP Controlled Room Temperature]. KEEP TIGHTLY CLOSED.
(p-value)	0.	.0014	
Time to Progression (Median, days, 95% C.I.)	128 (120 to 136)	131 (105 to 153)	Capecitabine is a cytotoxic drug. Follow applicable special handling and disposal procedures. ¹ Any unused produst should be disposed of in accordance with local requirements, or drug take back programs.
Hazard Ratio (capecitabine/5-FU/LV) 95% C.I. for Hazard Ratio		0.99 9 to 1.17)	17. PATIENT COUNSELING INFORMATION

0.99 (0.84 to 1.17) 17. PATIENT COUNSELING INFORMATION Advise the patient to read the FDA-approved patient labeling (Patient Information). 407 (366 to 446)

Diarrhea Inform patients experiencing grade 2 diarrhea (an increase of 4 to 6 stools/day or nocturnal stools) or greater or experiencing severe bloody diarrhea with severe abdominal pain and fever to stop taking capecitabine tablets. Advise patients on the use of antidiarrheal treatments (e.g., loperamide) to manage diarrhea [see Warnings and Precautions (5.2)].

Table 15 Efficacy of Capecitabine vs 5-FU/LV in Colorectal Cancer (Study 2) <u>Cardiotoxicity</u> Advise patients of the risk of cardiotoxicity and to immediately contact their healthcare provider or to go to an emergency room for new onset of chest pain, shortness of breath, dizziness, or lightheadedness [see Warnings Capecitabine (n=301) 5-FU/LV (n=301) and Precautions (5.3)]. 14 (10 to 18)

Hand-and-Foot Syndrome

Embryo-Fetal Toxicity

. (8.1 and 8.3)].

identification [see Adverse Reactions (6.1)].

Dihydropyrimidine Dehydrogenase Deficiency Advise patients to notify their healthcare provider if they have a known DPD deficiency. Advise patients if they have complete or near complete absence of DPD activity they are at an increased risk of acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by capecitabine tablets (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity) [see Warnings and Precautions (5.4)].

<u>Dehydration and Renal Failure</u> Instruct patients experiencing grade 2 or higher dehydration (IV fluids indicated < 24 hours) to stop taking capecitabine tablets immediately and to call their healthcare provider to correct the dehydration. Advise patients to on restart capecitable tablets until rehydrated and any precipitating causes have been corrected or controlled [see Warnings and Precautions (5.5)].

<u>Nausea</u> Instruct patients experiencing grade 2 nausea (food intake significantly decreased but able to eat intermittently) or greater to stop taking capecitabine tablets immediately and to contact their healthcare provider for management of nausea [see Adverse Reactions (6.1)].

<u>Vomiting</u> Instruct patients experiencing grade 2 vomiting (2 to 5 episodes in a 24-hour period) or greater to stop taking

capecitabine tablets immediately and to contact their healthcare provider for management of vomiting *[see Adverse Reactions (6.1)]*.

Instruct patients experiencing grade 2 hand-and-foot syndrome (painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patients' activities of daily living) or greater to stop taking capecitabine tablets immediately and to contact their healthcare provider. Inform patients that initiation of symptomatic treatment is

recommended and hand-and-foot syndrome can lead to loss of fingerprints which could impact personal

<u>Fever and Neutropenia</u> Inform patients who develop a fever of 100.5°F or greater or other evidence of potential infection to contact their

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with capecitabine tablets and for 6 months after the last dose. Advise females to inform their healthcare

provider of a known or suspected pregnancy [see Warnings and Precautions (5.6), Use in Specific Populations

Important Administration Instructions Advise patients to swallow capecitabine tablets whole with water within 30 minutes of a meal. Advise patients and caregivers not to crush or cut capecitabine tablets. Advise patients if they cannot swallow capecitabine tablets whole, to inform their healthcare provider [see Dosage and Administration (2.1)].



380 (321 to 434)

21 (16 to 26)

137 (128 to 165)

404 (367 to 452)

Figure 3 Kaplan-Meier Curve for Overall Survival of Pooled Data (Studies 1 and 2)

. (0.84 to 1.18)

0.027

0.97

(0.82 to 1.14)

0.92

(0.78 to 1.09)

131 (102 to 156)

369 (338 to 430)

Capecitabine was superior to 5-FU/LV for objective response rate in Study 1 and Study 2. The similarity of

literature comparing 5-FU to regimens of 5-FU/LV that were similar to the control arms used in these Studies 1 and 2. The method for comparing the treatments was to examine the worst case (95% confidence upper bound) for the difference between 5-FU/LV and capecitabine, and to show that loss of more than 50% of the 5-FU/LV survival effect was ruled out. It was demonstrated that the percent of the survival effect of 5-FU/LV maintained was at least 61% for Study 2 and 10% for Study 1. The pooled result is consistent with a retention of at least 50% of the effect of 5-FU/LV. It should be noted that these values for preserved effect are based on the upper bound of the 5-FU/LV vs capecitabine difference. These results do not exclude the possibility of true equivalence of capecitabine to 5-FU/LV (see Table 14, Table 15, and Figure 3).

by 16% and 35%, respectively, for capecitable and by 18% and 22%, respectively, for 5'-DFCR. No effect was observed on the other three major metabolites (5'-DFUR, 5-FU, FBAL) of capecitable.

Effect of Allopurinol on Capecitabine

Published literature reported that concomitant use with allopurinol may decrease conversion of capecitabine to the active metabolites, FdUMP and FUTP; however, the clinical significance was not fully characterized.

capecitabine was superior to 3-FU/LV for objective response rate in Study 7 and Study 2. The similarly of capecitabine and 5-FU/LV for objective response rate in Study 7 and Study 2. The similarly of sectors and 5-FU/LV in these studies was assessed by examining the potential difference between the two treatments. In order to assure that capecitabine has a clinically meaningful survival effect, statistical analyses were performed to determine the percent of the survival effect of 5-FU/LV that was retained by capecitabine. The estimate of the survival effect of 5-FU/LV was derived from a meta-analysis of ten randomized studies from the published Adverse Reactions (6.1)].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with capecitabine tablets and for 3 months after the last dose [see Use in Specific Populations (8.3)]. The dose of capecitabine used in the phase 3 clinical trial in combination with docetaxel was based on the results of

a phase 1 study, where a range of doses of docetaxel administered in 3-week cycles in combination with 00cetaxel was based on the results of a phase 1 study, where a range of doses of docetaxel administered in 3-week cycles in combination with a intermittent regimen of capecitabine (14 days of tratement, followed by a 7-day rest period) were evaluated. The combination with 1250 mg/m² twice daily for 14 days of capecitabine (14 days of tratement, followed by a 7-day rest period) were evaluated. The combination with 1250 mg/m² twice daily for 14 days of capecitabine (14 days of tratement, followed by a 7-day rest period) were evaluated. The combination with 1250 mg/m² twice daily for 14 days of capecitabine administered in 3-week cycles of docetaxel in combination with 1250 mg/m² twice daily for 14 days of capecitabine administered in 3-week

Capecitabine in combination with docetaxel was assessed in an open-label, multicenter, randomized trial in 75 centers in Europe, North America, South America, Asia, and Australia. A total of 511 patients with metastatic breast cancer resistant to, or recurring during or after an anthracycline-containing therapy, or relapsing during or recurring within 2 years of completing an anthracycline-containing adjuvant therapy were enrolled. Two hundred

cycles. The approved dose of 100 mg/m² of docetaxel administered in 3-week cycles was the control arm of the

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affected. In patients with mild to moderate hepatic dysfunction due to liver metastases, caution should be exercised when capecitabine tablets are administered. The effect of severe hepatic dysfunction on capecitabine is not known [see Warnings and Precautions (5.11) and Use in Special Populations (8.6)].

Effect of Renal Insufficiency Following oral administration of 1250 mg/m² capecitabine twice a day to cancer patients with varying degrees of renal impairment, patients with moderate (creatinine clearance = 30 to 50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment showed 85% and 258% higher systemic exposure to FBAL on day 1 compared to normal renal function patients (creatinine clearance >80 mL/min). Systemic exposure to 5'-DFUR was 42% and 71% greater in moderately and severely renal impaired patients, respectively, than in normal patients. Systemic exposure to capecitabine was about 25% greater in both moderately and severely renal impaired patients. *Several Provulations (8, 7)*.

Special Populations (8.7)]. Effect of Capecitabine on the Pharmacokinetics of Warfarin In four patients with cancer, chronic administration of capecitabine (1250 mg/m² bid) with a single 20 mg dose of warfarin increased the mean AUC of S-warfarin by 57% and decreased its clearance by 37%. Baseline corrected AUC of INR in these 4 patients increased by 2.8-fold, and the maximum observed mean INR value was increased by 14.3 Breast Cancer Capecitabine has been evaluated in clinical trials in combination with docetaxel (Taxotere $^{\circ}$ *) and as monotherapy.

In Combination With Docetaxel

phase 3 study.

Effect of Capecitabine on the Pharmacokinetics of Docetaxel and Vice Versa A Phase 1 study evaluated the effect of capecitabine on the pharmacokinetics of docetaxel (Taxotere*+) and the effect of docetaxel on the pharmacokinetics of capecitabine was conducted in 26 patients with solid turns. Capecitabine was found to have no effect on the pharmacokinetics of docetaxel (C_{mun} and AUC) and docetaxel has no effect on the pharmacokinetics of capecitabine and the 5-FU precursor 5'-DFUR.

91% [see Boxed Warning and Drug Interactions (7.1)]. *Effect of Antacids on the Pharmacokinetics of Capecitabine* When Maalox^{**} (20 mL), an aluminum hydroxide- and magnesium hydroxide-containing antacid, was administered immediately after capecitabine tablets (1250 mg/m², n=12 cancer patients), AUC and C_{max} increased



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