For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Rx

Capecitabine Tablets IP

XORTIB™ 150/500 éÉÉUËOoÉ 150/500

COMPOSITION

XORTIB™ 150

Each film coated tablet contains:

Capecitabine IP	150 mg
Excipients	q.s.

XORTIB™ 500

Each film coated tablet contains:

Capecitabine IP	500 mg
Excipients	q.s.

PHARMACEUTICAL FORM

Film-coated tablet.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Antineoplastic (antimetabolites)

ATC code: L01BC06

Mechanism of Action

Certain enzymes convert capecitabine to 5-fluorouracil (5-FU) *in vivo*. Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by 2 different mechanisms. First, FdUMP and the folate cofactor, N5-10 methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

Pharmacokinetic Properties

Capecitabine is readily absorbed from the gastrointestinal tract, with peak plasma concentrations occurring at about 1.5 hours. Food reduces the rate and extent of absorption. The plasma protein binding of capecitabine is less than 60%. Capecitabine is hydrolyzed in the liver to 5'-deoxy-5-fluorocytidine (5'-DFCR), then converted to 5'-deoxy-5-fluorocytidine (5'-DFUR; doxifluridine), and subsequently to 5-fluorouracil in body tissues, which is further metabolised. About 3% of a dose of capecitabine is excreted in the urine unchanged.

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

Patients with Hepatic Impairment Due to Liver Metastases: According to a pharmacokinetic study in cancer patients with mild to moderate liver impairment due to liver metastases, the bioavailability of capecitabine and exposure to 5-FU may increase compared to patients with no liver impairment. There are no pharmacokinetic data on patients with severe hepatic impairment.

Patients with Renal Impairment: Based on a pharmacokinetic study in cancer patients with mild to severe renal impairment, there is no evidence for an effect of creatinine clearance on the pharmacokinetics of intact drug and 5-FU. Creatinine clearance was found to influence the systemic exposure to 5'-DFUR (35% increase in area under the concentration-time curve [AUC] when creatinine clearance decreases by 50%) and to FBAL (114% increase in AUC when creatinine clearance decreases by 50%). FBAL is a metabolite without anti-proliferative activity.

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

Ethnic Factors: Following oral administration of 825 mg/m^2 capecitabine twice daily for 14 days in Japanese patients (n=18), there was a 36% lower C_{max} and 24% lower AUC than in Caucasian patients (n=22). There was about 25% lower C_{max} and 34% lower AUC of FBAL in the Japanese patients than the Caucasian patients. The clinical relevance of these differences is unknown. No significant differences occurred in the exposure to other metabolites (5'-DFCR, 5'-DFUR, and 5-FU).

Preclinical Safety Data

In repeat-dose toxicity studies, daily oral administration of capecitabine to cynomolgus monkeys and mice produced toxic effects on the gastrointestinal, lymphoid, and haemopoietic systems, typical for fluoropyrimidines. These toxicities were reversible. Skin toxicity, characterised by degenerative/regressive changes, was observed with capecitabine. Capecitabine was devoid of hepatic and central nervous system (CNS) toxicities. Cardiovascular toxicity (eg, PR- and QT-interval prolongation) was detectable in cynomolgus monkeys after intravenous administration (100 mg/kg) but not after repeated oral dosing (1379 mg/m^2/day).

A 2-year mouse carcinogenicity study produced no evidence of carcinogenicity by capecitabine.

During standard fertility studies, impairment of fertility was observed in female mice receiving capecitabine; however, this effect was reversible after a drug-free period. In addition, during a 13-week study, atrophic and degenerative changes occurred in the reproductive organs of male mice; however these effects were reversible after a drug-free period.

In embryotoxicity and teratogenicity studies in mice, dose-related increases in foetal resorption and teratogenicity were observed. In monkeys, abortion and embryolethality were observed at high doses, but there was no evidence of teratogenicity.

Capecitabine was not mutagenic *in vitro* to bacteria (Ames test) or mammalian cells (Chinese hamster V79/HPRT gene mutation assay). However, similar to other nucleoside analogues (ie, 5-FU), capecitabine was clastogenic in human lymphocytes (*in vitro*) and a positive trend occurred in mouse bone marrow micronucleus tests (*in vivo*).

CLINICAL PARTICULARS

Therapeutic Indications

- Capecitabine is indicated as a single agent for adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor.
- It is indicated for the treatment of metastatic colorectal cancer.
- It is indicated for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen.
- Capecitabine in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy.

Posology and Method of Administration

Capecitabine should only be prescribed by a qualified physician experienced in the utilisation of anti-neoplastic agents. Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Treatment should be discontinued if progressive disease or intolerable toxicity is observed. Standard and reduced dose calculations according to body surface area for starting doses of capecitabine of 1250 mg/m^2 and 1000 mg/m^2 are provided in Table 1 and Table 2, respectively.

Recommended Posology

Monotherapy

Colon, Colorectal, and Breast Cancer

Given as single agent, the recommended starting dose for capecitabine in the adjuvant treatment of colon cancer, in the treatment of metastatic colorectal cancer or of locally advanced or metastatic breast cancer is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 14 days followed by a 7-day rest period. Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

Combination Therapy

Colon, Colorectal, and Gastric Cancer

In combination treatment, the recommended starting dose of capecitabine should be reduced to 800 to 1000 mg/m^2 when administered twice daily for 14 days followed by a 7-day rest period or to 625 mg/m^2 twice daily when administered continuously. The inclusion of biological agents in a combination regimen has no effect on the starting dose of capecitabine. Premedication to maintain adequate hydration and anti-emesis according to the cisplatin summary of product characteristics should be started prior to cisplatin administration for patients receiving the capecitabine plus cisplatin combination. Premedication with anti-emetics according to the oxaliplatin summary of product characteristics is recommended for patients receiving the capecitabine plus oxaliplatin combination. Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

Breast Cancer

In combination with docetaxel, the recommended starting dose of capecitabine in the treatment of metastatic breast cancer is 1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period, combined with docetaxel at 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks. Pre-medication with an oral corticosteroid such as dexamethasone according to the docetaxel summary of product characteristics should be started prior to docetaxel administration for patients receiving the capecitabine plus docetaxel combination.

Capecitabine Dose Calculations

Table 1: Standard and Reduced Dose Calculations According to Body Surface Area for a Starting Dose of Capecitabine of 1250 mg/m^2

Dose Level: 1250 mg/m^2 (twice daily)					
	Full Dose 1250 mg/m^2	Number of 150 mg Tablets and/or 500 mg Tablets per Administration (each administration to be given morning and evening)		Reduced Dose (75%) 950 mg/m^2	Reduced Dose (50%) 625 mg/m^2
Body Surface Area (m^2)	Dose per Administration (mg)	150 mg	500 mg	Dose per Administration (mg)	Dose per Administration (mg)
≤1.26	1500	-	3	1150	800
1.27-1.38	1650	1	3	1300	800
1.39-1.52	1800	2	3	1450	950
1.53-1.66	2000	-	4	1500	1000
1.67-1.78	2150	1	4	1650	1000
1.79-1.92	2300	2	4	1800	1150
1.93-2.06	2500	-	5	1950	1300
2.07-2.18	2650	1	5	2000	1300
≥2.19	2800	2	5	2150	1450

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

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

Dose Adjustments During Treatment

General

Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction). Once the dose has been reduced, it should not be increased at a later time. For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening (eg, alopecia, altered taste, nail changes) treatment can be continued at the same dose without reduction or interruption. Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of capecitabine omitted for toxicity are not replaced. The recommended dose modifications for toxicity are provided in Table 3.

Table 3: Capecitabine Dose Reduction Schedule (3-weekly Cycle or Continuous Treatment)

Toxicity Grades*	Dose Changes Within a Treatment Cycle	Dose Adjustment for Next Cycle/Dose (% of starting dose)
• **Grade 1**	Maintain dose level	Maintain dose level
• **Grade 2**		
-1st Appearance	Interrupt until resolved to grade 0-1	100%
-2nd Appearance		75%
-3rd Appearance		50%
-4th Appearance	Discontinue treatment permanently	Not applicable
• **Grade 3**		
-1st Appearance	Interrupt until resolved to grade 0-1	75%
-2nd Appearance		50%
-3rd Appearance	Discontinue treatment permanently	Not applicable
• **Grade 4**		
-1st Appearance	Discontinue permanently or If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
-2nd Appearance	Discontinue permanently	Not applicable

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

Hematology

Patients with baseline neutrophil counts of <1.5 × 10^9/L and/or thrombocyte counts of <100 × 10^9/L should not be treated with capecitabine. If unscheduled laboratory assessments during a treatment cycle show that the neutrophil count drops below 1.0 × 10^9/L or that the platelet count drops below 75 × 10^9/L, treatment with capecitabine should be interrupted.

Dose Modifications for Toxicity When Capecitabine is Used as a 3-weekly Cycle in Combination With Other Agents.

Dose modifications for toxicity when capecitabine is used as a 3-weekly cycle in combination with other agents should be made according to Table 3 for capecitabine and according to the appropriate summary of product characteristics for the other agent(s). At the beginning of a treatment cycle, if a treatment delay is indicated for either capecitabine or the other agent(s) then administration of all agents should be delayed until the requirements for restarting all drugs are met. During a treatment cycle for those toxicities considered by the treating physician not to be related to capecitabine, capecitabine should be continued and the dose of the other agent should be adjusted accordingly. If the other agent(s) have to be discontinued permanently, capecitabine treatment can be resumed when the requirements for restarting capecitabine are met.

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

Dose Modifications for Toxicity When Capecitabine is Used Continuously in Combination With Other Agents

Dose modifications for toxicity when capecitabine is used continuously in combination with other agents should be made according to Table 3 for capecitabine and according to the appropriate summary of product characteristics for the other agent(s).

Posology Adjustments for Special Populations

Hepatic Impairment

Insufficient safety and efficacy data are available in patients with hepatic impairment to provide a dose adjustment recommendation. No information is available on hepatic impairment due to cirrhosis or hepatitis.

Renal Impairment

Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockcroft and Gault] at baseline). The incidence of grade 3 or 4 adverse reactions in patients with moderate renal impairment (creatinine clearance 30-50 mL/min at baseline) is increased compared to the overall population. In patients with moderate renal impairment at baseline, a dose reduction to 75% for a starting dose of 1250 mg/m^2 is recommended. In patients with moderate renal impairment at baseline, no dose reduction is required for a starting dose of 1000 mg/m^2. In patients with mild renal impairment (creatinine clearance 51-80 mL/min at baseline) no adjustment of the starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3, or 4 adverse event during treatment and subsequent dose adjustment as outlined in Table 3. If the calculated creatinine clearance decreases during treatment to a value below 30 mL/min, capecitabine should be discontinued. These dose adjustment recommendations for renal impairment apply both to monotherapy and combination use (see also section Elderly).

There is no experience in children (under 18 years).

Elderly

During capecitabine monotherapy, no adjustment of the starting dose is needed. However, grade 3 or 4 treatment-related adverse reactions were more frequent in patients ≥60 years of age compared to younger patients. When capecitabine was used in combination with other agents, elderly patients (≥65 years) experienced more grade 3 and grade 4 adverse drug reactions (ADRs), including those leading to discontinuation, compared to younger patients. Careful monitoring of patients ≥60 years of age is advisable.

In Combination With Docetaxel: An increased incidence of grade 3 or 4 treatment-related adverse reactions and treatment-related serious adverse reactions were observed in patients 60 years of age or more. For patients 60 years of age or more, a starting dose reduction of capecitabine to 75% (950 mg/m^2 twice daily) is recommended. If no toxicity is observed in patients ≥60 years of age treated with a reduced capecitabine starting dose in combination with docetaxel, the dose of capecitabine may be cautiously escalated to 1250 mg/m^2 twice daily.

In Combination With Irinotecan: For patients 65 years of age or more, a starting dose reduction of capecitabine to 800 mg/m^2 twice daily is recommended.

Contraindications

- History of severe and unexpected reactions to fluoropyrimidine therapy.
- Hypersensitivity to capecitabine or to any of the excipients or fluorouracil.
- In patients with known dihydropyrimidine dehydrogenase (DPD) deficiency.
- During pregnancy and lactation.
- In patients with severe leucopenia, neutropenia, or thrombocytopenia.
- In patients with severe hepatic impairment.
- In patients with severe renal impairment (creatinine clearance below 30 mL/min).
- Treatment with sorivudine or its chemically related analogues, such as brivudine.
- If contraindications exist to any of the agents in the combination regimen, that agent should not be used.

Special Warnings and Precautions for Use

Warning: Capecitabine – Warfarin interaction

Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (International Normalised Ratio, INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly.

Occurrence: Within several days and up to several months after initiating capecitabine therapy and, in a few cases, within 1 month after stopping capecitabine.

Predisposing factor: age >60 and diagnosis of cancer.

Dose limiting toxicities include diarrhoea, abdominal pain, nausea, stomatitis and hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia). Most adverse reactions are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced.

Diarrhoea: Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Standard anti-diarrhoeal treatments (eg, loperamide) may be used. NCIC CTC grade 2 diarrhoea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhoea as an increase of 7 to 9 stools/day or incontinence and malabsorption. Grade 4 diarrhoea is an increase of ≥10 stools/day or grossly bloody diarrhoea or the need for parenteral support. Dose reduction should be applied as necessary.

Dehydration: Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting, or diarrhoea may rapidly become dehydrated. If grade 2 (or higher) dehydration occurs, capecitabine treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications applied should be applied for the precipitating adverse event as necessary.

Hand-foot Syndrome (also known as hand-foot skin reaction or palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema).

Grade 1 hand-foot syndrome is defined as numbness, dysesthesia/paraesthesia, tingling, painless swelling, or erythema of the hands and/or feet and/or discomfort which does not disrupt the patient's normal activities.

Grade 2 hand-foot syndrome is painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living.

Grade 3 hand-foot syndrome is moist desquamation, ulceration, blistering, and severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. If grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-foot syndrome, subsequent doses of capecitabine should be decreased. When capecitabine and cisplatin are used in combination, the use of vitamin B6 (pyridoxine) is not advised for symptomatic or secondary prophylactic treatment of hand–foot syndrome, because of published reports that it may decrease the efficacy of cisplatin.

Cardiotoxicity: Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death, and electrocardiographic changes (including very rare cases of QT prolongation). These adverse reactions may be more common in patients with a prior history of coronary artery disease. Cardiac arrhythmias (including ventricular fibrillation, torsade de pointes, and bradycardia), angina pectoris, myocardial infarction, heart failure, and cardiomyopathy have been reported in patients receiving capecitabine. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias, and angina pectoris.

Hypo- or Hypercalcaemia: Hypo- or hypercalcaemia has been reported during capecitabine treatment. Caution must be exercised in patients with pre-existing hypo- or hypercalcaemia.

Central or Peripheral Nervous System disease: Caution must be exercised in patients with central or peripheral nervous system disease, eg, brain metastasis or neuropathy.

Diabetes Mellitus or Electrolyte Disturbances: Caution must be exercised in patients with diabetes mellitus or electrolyte disturbances, as these may be aggravated during capecitabine treatment.

Coumarin-derivative Anticoagulation: In a drug interaction study with single-dose warfarin administration, there was a significant increase in the mean AUC (+57%) of S-warfarin. These results suggest an interaction, probably due to an inhibition of the cytochrome P450 2C9 isoenzyme system by capecitabine. Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (International Normalized Ratio, INR or prothrombin time) monitored closely and the anticoagulant dose adjusted accordingly.

Hepatic Impairment: In the absence of safety and efficacy data in patients with hepatic impairment, capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis. Administration of capecitabine should be interrupted if treatment-related elevations in bilirubin of >3.0 × ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of >2.5 × ULN occur. Treatment with capecitabine monotherapy may be resumed when bilirubin decreases to ≤3.0 × ULN or hepatic aminotransferases decrease to ≤2.5 × ULN.

Renal Impairment: The incidence of grade 3 or 4 adverse reactions in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) is increased compared to the overall population.

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

Drug Interactions

Interaction With Other Medicinal Products:

Coumarin-derivative Anticoagulants: Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These reactions occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within 1 month after stopping capecitabine. In a clinical pharmacokinetic interaction study, after a single 20 mg dose of warfarin, capecitabine treatment increased the AUC of S-warfarin by 57% with a 91% increase in INR value. Since metabolism of R-warfarin was not affected, these results indicate that capecitabine down-regulates isozyme 2C9, but has no effect on isozymes 1A2 and 3A4. Patients taking coumarin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (prothrombin time or INR) and the anti-coagulant dose adjusted accordingly.

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Phenytoin: Increased phenytoin plasma concentrations resulting in symptoms of phenytoin intoxication in single cases have been reported during concomitant use of capecitabine with phenytoin. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.

Folinic Acid: A combination study with capecitabine and folinic acid indicated that folinic acid has no major effect on the pharmacokinetics of capecitabine and its metabolites. However, folinic acid has an effect on the pharmacodynamics of capecitabine and its toxicity may be enhanced by folinic acid: the maximum tolerated dose (MTD) of capecitabine alone using the intermittent regimen is 3000 mg/m^2 per day whereas it is only 2000 mg/m^2 per day when capecitabine was combined with folinic acid (30 mg orally bid).

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

Antacid: The effect of an aluminum hydroxide and magnesium hydroxide-containing antacid on the pharmacokinetics of capecitabine was investigated. There was a small increase in plasma concentrations of capecitabine and 1 metabolite (5'-DFCR); there was no effect on the 3 major metabolites (5'-DFUR, 5-FU, and FBAL).

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

Interaction With Cytochrome P-450: For potential interactions with isozymes 1A2, 2C9, and 3A4, see interactions with Coumarin-derivative Anticoagulants.

Interferon Alpha: The MTD of capecitabine is 2000 mg/m^2 per day when combined with interferon alpha-2a (3 MIU/m^2 per day) compared to 3000 mg/m^2 per day when capecitabine is used alone.

Radiotherapy: The MTD of capecitabine alone using the intermittent regimen is 3000 mg/m^2 per day, whereas, when combined with radiotherapy for rectal cancer, the MTD of capecitabine is 2000 mg/m^2 per day using either a continuous schedule or given daily Monday through Friday during a 6-week course of radiotherapy.

Oxaliplatin: No clinically significant differences in exposure to capecitabine or its metabolites, free platinum, or total platinum occurred when capecitabine was administered in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab.

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

Food Interaction: Administration with food decreases the rate of capecitabine absorption.

Pregnancy and Lactation

Women of Childbearing Potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with capecitabine and if the patient becomes pregnant while receiving capecitabine, the potential hazard to the foetus must be explained.

Pregnancy: Category D

There are no studies in pregnant women using capecitabine; however, it should be assumed that capecitabine may cause foetal harm if administered to pregnant women. In reproductive toxicity studies in animals, capecitabine administration caused embryolethality and teratogenicity. These findings are expected effects of fluoropyrimidine derivatives. Capecitabine is contraindicated during pregnancy.

Breast-feeding

It is not known whether capecitabine is excreted in human breast milk. In lactating mice, considerable amounts of capecitabine and its metabolites were found in milk. Breast-feeding should be discontinued while receiving treatment with capecitabine.

Effects on Ability to Drive and Use Machines

Capecitabine has minor or moderate influence on the ability to drive and use machines. Capecitabine may cause dizziness, fatigue, and nausea.

Undesirable Effects

Summary of the Safety Profile

The overall safety profile of capecitabine is based on data from over 3000 patients treated with capecitabine as monotherapy or capecitabine in combination with different chemotherapy regimens in multiple indications. The safety profiles of capecitabine monotherapy for the metastatic breast cancer, metastatic colorectal cancer, and adjuvant colon cancer populations are comparable.

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

Tabulated Summary of Adverse Reactions

The ADRs considered by the investigator to be possibly, probably, or remotely related to the administration of capecitabine as a single agent are listed in Table 4 and those with capecitabine given in combination with different chemotherapy regimens in multiple indications are listed in Table 5. The following headings are used to rank the ADRs by frequency: very common (≥1/10), common (≥1/100,<1/10) and uncommon (≥1/1,000,<1/100). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Capecitabine Monotherapy

Table 4 lists ADRs associated with the use of capecitabine monotherapy based on a pooled analysis of safety data from 3 major studies which included over 1900 patients (studies M66001, SO14695, and SO14796). The ADRs are added to the appropriate frequency grouping according to the overall incidence from the pooled analysis.

Table 4: Summary of Related ADRs Reported in Patients Treated With Capecitabine Monotherapy

Body System	**Very Common** *All Grades*	**Common** *All Grades*	**Uncommon** ***Severe and/or Life-threatening (grade 3-4) or Considered Medically Relevant***
Infections and infestations	-	Herpes viral infection, nasopharyngitis, lower respiratory tract infection	Sepsis, urinary tract infection, cellulitis, tonsillitis, pharyngitis, oral candidiasis, influenza, gastroenteritis, fungal infection, infection, tooth abscess
Neoplasm benign, malignant and unspecified	-	-	Lipoma
Blood and lymphatic system disorders	-	Neutropenia, anaemia	Febrile neutropenia, pancytopenia, granulocytopenia, thrombocytopenia, leucopenia, haemolytic anaemia, International Normalised Ratio (INR) increased/prothrombin time prolonged.
Immune system disorders	-	-	hypersensitivity
Metabolism and nutrition disorders	Anorexia	Dehydration, decreased appetite, weight decreased	Diabetes, hypokalemia, appetite disorder, malnutrition, hypertriglyceridemia
Psychiatric disorders	-	Insomnia, depression	Confusional state, panic attack, depressed mood, libido decreased
Nervous system disorders	-	Headache, lethargy dizziness, paraesthesia dysgeusia	Aphasia, memory impairment, ataxia, syncope, balance disorder, sensory disorder, neuropathy peripheral
Eye disorders	-	Lacrimation increased, conjunctivitis, eye irritation	Visual acuity reduced, diplopia
Ear and labyrinth disorders	-	-	Vertigo, ear pain
Cardiac disorders	-	-	Angina unstable, angina pectoris, myocardial ischaemia, atrial fibrillation, arrhythmia, tachycardia, sinus tachycardia, palpitations.
Vascular disorders	-	Thrombophlebitis	Deep vein thrombosis, hypertension, petechiae, hypotension, hot flush, peripheral coldness
Respiratory, thoracic, and mediastinal disorders	-	Dyspnoea, epistaxis, cough, rhinorrhea	Pulmonary embolism, pneumothorax, haemoptysis, asthma, dyspnoea exertional
Gastrointestinal disorders	Diarrhea, Vomiting, Nausea, Stomatitis, Abdominal pain	Gastrointestinal haemorrhage, constipation, upper abdominal pain, dyspepsia, flatulence, dry mouth	Intestinal obstruction, ascites, enteritis, gastritis, dysphagia, abdominal pain lower, oesophagitis, abdominal discomfort, gastrooesophageal reflux disease, colitis, blood in stool.
Hepatobiliary disorders	-	Hyperbilirubinemia, liver function test abnormalities	Jaundice
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome	Rash, alopecia, erythema, dry skin, pruritus, skin hyper-pigmentation, rash macular, skin desquamation, dermatitis, pigmentation disorder, nail disorder	Skin ulcer, rash, urticaria, photosensitivity reaction, palmar erythema, swelling face, purpura
Musculoskeletal and connective tissue disorders	-	Pain in extremity, back pain, arthralgia	Joint swelling, bone pain, facial pain, musculoskeletal stiffness, muscular weakness
Renal and urinary disorders	-	-	Hydronephrosis, urinary incontinence, haematuria, nocturia, blood creatinine increased
Reproductive system and breast disorders	-	-	Vaginal haemorrhage
General disorders and administration site conditions	Fatigue, Asthenia	Pyrexia, lethargy, oedema peripheral, malaise, chest pain	Oedema, chills, influenza-like illness, rigors, body temperature increased
Injury, poisoning, and procedural complications	-	-	Blister, overdose

Capecitabine in Combination Therapy

Table 5 lists ADRs associated with the use of capecitabine in combination with different chemotherapy regimens in multiple indications based on safety data from over 3000 patients. The ADRs are added to the appropriate frequency grouping *(very common or common)* according to the highest incidence seen in any of the major clinical trials and are only added when they were seen in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy (see Table 4). Uncommon ADRs reported for capecitabine in combination therapy are consistent with the ADRs reported for capecitabine monotherapy or reported for monotherapy with the combination agent.

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

Table 5: Summary of Related ADRs Reported in Patients Treated With Capecitabine in Combination Treatment in Addition to Those Seen With Capecitabine Monotherapy or Seen at a Higher Frequency Grouping Compared to Capecitabine Monotherapy

Body System	**Very Common** *All Grades*	**Common** *All Grades*
Infections and infestations	-	Herpes zoster, urinary tract infection, oral candidiasis, upper respiratory tract infection, rhinitis, influenza, +infection, oral herpes
Blood and lymphatic system disorders	+Neutropenia, +leucopenia, +anemia, +neutropenic fever, thrombocytopenia	Bone marrow depression, +febrile neutropenia
Immune system disorders	-	Hypersensitivity
Metabolism and nutrition disorders	Appetite decreased	Hypokalemia, hyponatremia, hypomagnesemia, hypocalcemia, hyperglycemia
Psychiatric disorders	-	Sleep disorder, anxiety
Nervous system disorders	Taste disturbance, paraesthesia and dysaesthesia, peripheral neuropathy, peripheral sensory neuropathy, dysgeusia, headache	Neurotoxicity, tremor, neuralgia, hypersensitivity reaction, hypoaesthesia
Eye disorders	Lacrimation increased	Visual disorders, dry eye, eye pain, visual impairment, vision blurred
Ear and labyrinth disorders	-	Tinnitus, hypoacusis
Cardiac disorders	-	Atrial fibrillation, Cardiac ischemia/infarction
Vascular disorders	Lower limb oedema, hypertension, +embolism and thrombosis	Flushing, hypotension, hypertensive crisis, hot flush, phlebitis
Respiratory, thoracic and mediastinal system disorders	Sore throat, dysaesthesia pharynx	Hiccups, pharyngolaryngeal pain, dysphonia
Gastrointestinal disorders	Constipation, dyspepsia	Upper gastrointestinal haemorrhage, mouth ulceration, gastritis, abdominal distension, gastroesophageal reflux disease, oral pain, dysphagia, rectal haemorrhage, abdominal pain lower, oral dysaesthesia, paraesthesia oral, hypoaesthesia oral, abdominal discomfort
Hepatobiliary disorders	-	Hepatic function abnormal
Skin and subcutaneous tissue disorders	Alopecia, nail disorder	Hyperhidrosis, rash erythematous, urticaria, night sweats
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia, pain in extremity	Pain in jaw , muscle spasms, trismus, muscular weakness
Renal and urinary disorder	-	Haematuria, proteinuria, creatinine renal clearance decreased, dysuria
General disorders and administration site conditions	Pyrexia, weakness, +lethargy, temperature intolerance	Mucosal inflammation, pain in limb, pain, chills, chest pain, influenza-like illness, +fever, infusion related reaction, injection site reaction, infusion site pain, injection site pain
Injury, poisoning and procedural complications	-	Contusion

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

Post-Marketing Experience

The following additional serious adverse reactions have been identified during post-marketing exposure: Very rare: lacrimal duct stenosis; hepatic failure, and cholestatic hepatitis have been reported during post-marketing exposure similar to those in clinical trials; ventricular fibrillation, QT prolongation, torsade de pointes, and bradycardia.

Overdose

The manifestations of acute overdose include nausea, vomiting, diarrhoea, mucositis, gastrointestinal irritation, bleeding, and bone marrow depression. Medical management of overdose should include customary therapeutic and supportive medical interventions aimed at correcting the presenting clinical manifestations and preventing their possible complications.

PHARMACEUTICAL PARTICULARS

Incompatibilities

Not applicable.

Shelf Life

24 months.

Storage and Precautions

Store at a temperature not exceeding 30°C. Keep out of reach of children.

Special Precautions for Disposal and Other Handling

No special requirements.

Nature and Contents of Container

Blister of 10 film-coated tablets.

For further details, please contact:
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