Capeda®

Capecitabine

FORMS AND PRESENTATION

Capeda®: Film coated tablets: Box of 60.

Capeda®: Film coated tablets: Box of 120.

COMPOSITION

Capeda®: Each film coated tablet contains Capecitabine 500mg.

Excipients: lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate, yellow iron oxide, talc, titanium dioxide, red iron oxide.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Antineoplastic agents.

ATC code: L01BC06.

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Capecitabine is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found in tumor tissues, but also in normal tissues, albeit usually at lower levels. In human cancer xenograft models Capecitabine demonstrated a synergistic effect in combination with docetaxel, which may be related to the up-regulation of thymidine phosphorylase by docetaxel.

There is evidence that the metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid, thereby interfering with the synthesis of deoxyribonucleic acid (DNA). The incorporation of 5-FU also leads to inhibition of RNA and protein synthesis. Since DNA and RNA are essential for cell division and growth, the effect of 5-FU may be to create a thymidine deficiency that provokes unbalanced growth and death of a cell. The effects of DNA and RNA deprivation are most marked on those cells which proliferate more rapidly and which metabolize 5-FU at a more rapid rate.

Pharmacokinetic properties

Absorption

After oral administration, Capecitabine is rapidly and extensively absorbed, followed by extensive conversion to the metabolites, 5'-DFCR and 5'-DFUR. Administration with food decreases the rate of Capecitabine absorption, but only results in a minor effect on the AUC of 5'-DFUR, and on the AUC of the subsequent metabolite 5-FU. At the dose of 1250 mg/m^2 on day 14 with administration after food intake, the peak plasma concentrations (C_{max} in µg/ml) for Capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 4.67, 3.05, 12.1, 0.95 and 5.46 respectively. The time to peak plasma concentrations (T_{max} in hours) were 1.50, 2.00, 2.00, 2.00 and 3.34. The $AUC_{0-\infty}$ values in µg•h/ml were 7.75, 7.24, 24.6, 2.03 and 36.3.

Protein binding

In vitro human plasma studies have determined that Capecitabine, 5'-DFCR, 5'-DFUR and 5-FU are 54%, 10%, 62% and 10% protein bound, mainly to albumin.

Metabolism

Capecitabine is first metabolized by hepatic carboxylesterase to 5'-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumor tissues. Further catalytic activation of 5'-DFUR then occurs by thymidine phosphorylase (ThyPase). The enzymes involved in the catalytic activation are found in tumor tissues but also in normal tissues, albeit usually at lower levels. The sequential enzymatic biotransformation of Capecitabine to 5-FU leads to higher concentrations within tumor tissues. In the case of colorectal tumors, 5-FU generation appears to be in large part localized in tumor stromal cells. Following oral administration of Capecitabine to patients with colorectal cancer, the ratio of 5-FU concentration in colorectal tumors to adjacent tissues was 3.2 (ranged from 0.9 to 8.0). The ratio of 5-FU concentration in tumor to plasma was 21.4 (ranged from 3.9 to 59.9, n=8) whereas the ratio in healthy tissues to plasma was 8.9 (ranged from 3.0 to 25.8, n=8). Thymidine phosphorylase activity was measured and found to be 4 times greater in primary colorectal tumor than in adjacent normal tissue. According to immunohistochemical studies, thymidine phosphorylase appears to be in large part localized in tumor stromal cells.

5-FU is further catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD) to the much less toxic dihydro-5-fluorouracil (FUH_2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureidopropionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β-alanine (FBAL) which is cleared in the urine. Dihydropyrimidine dehydrogenase (DPD) activity is the rate limiting step. Deficiency of DPD may lead to increased toxicity of Capecitabine.

Elimination

The elimination half-life ($t_{1/2}$ in hours) of Capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 0.85, 1.11, 0.66, 0.76 and 3.23 respectively. Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered Capecitabine dose is recovered in urine. 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 drug.

INDICATIONS

Capeda® is indicated:

- For the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer.
- For the treatment of metastatic colorectal cancer.
- For first-line treatment of advanced gastric cancer in combination with a platinum-based regimen.
- In combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Capeda® is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

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.

PRECAUTIONS

- Dose limiting toxicities include diarrhea, 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.

- Diarrhea: Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Standard antidiarrheal treatments (e.g. loperamide) may be used. NCIC CTC 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. Grade 4 diarrhea is an increase of ≥10 stools/day or grossly bloody diarrhea 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 diarrhea 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/paresthesia, 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 hypercalcemia: Hypo- or hypercalcemia has been reported during Capecitabine treatment. Caution must be exercised in patients with pre-existing hypo- or hypercalcemia.

- Central or peripheral nervous system disease: Caution must be exercised in patients with central or peripheral nervous system disease, e.g. 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 (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 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of >2.5 x ULN occur. Treatment with Capecitabine monotherapy may be resumed when bilirubin decreases to ≤3.0 x ULN or hepatic aminotransferases decrease to ≤ 2.5 x 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.

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.

PREGNANCY AND LACTATION

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Capecitabine. If the patient becomes pregnant while receiving Capecitabine, the potential hazard to the fetus must be explained.

There are no studies in pregnant women using Capecitabine; however, it should be assumed that Capecitabine may cause fetal 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.

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.

DRUG INTERACTIONS

Interaction studies have only been performed in adults.

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 one 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 (PT or INR) and the anti-coagulant dose adjusted accordingly.

- 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 one 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 for 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 anticoagulation.

- Interferon alpha: The MTD of Capecitabine was 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 was 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:

In all clinical trials, patients were instructed to administer Capecitabine within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that Capecitabine be administered with food. Administration with food decreases the rate of Capecitabine absorption.

ADVERSE EFFECTS

The most commonly reported and/or clinically relevant treatment-related adverse drug reactions (ADRs) were gastrointestinal disorders (especially diarrhea, 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.

Adverse effects are listed by frequency: Very common (≥ 1/10; all grades), common (≥ 1/100, < 1/10; all grades) and uncommon (≥ 1/1,000, < 1/100; severe and/or life-threatening (grade 3-4) or considered medically relevant). Within each frequency grouping, adverse effects are presented in order of decreasing seriousness.

Capecitabine monotherapy:

- Infections and infestations: Herpes viral infection, nasopharyngitis, lower respiratory tract infection (common); sepsis, urinary tract infection, cellulitis, tonsillitis, pharyngitis, oral candidiasis, influenza, gastroenteritis, fungal infection, infection, tooth abscess (uncommon).
- Neoplasm benign, malignant and unspecified: Lipoma (uncommon).
- Blood and lymphatic system disorders: Neutropenia, anemia (common); febrile neutropenia, pancytopenia, granulocytopenia, thrombocytopenia, leucopenia, hemolytic anemia, increased International Normalized Ratio (INR) / prolonged prothrombin time (uncommon).
- Immune system disorders: Hypersensitivity (uncommon).
- Metabolism and nutrition disorders: Anorexia (very common); dehydration, decreased appetite, decreased weight (common); diabetes, hypokalemia, appetite disorder, malnutrition, hypertriglyceridemia (uncommon).
- Psychiatric disorders: Insomnia, depression (common); confusional state, panic attack, depressed mood, decreased libido (uncommon).
- Nervous system disorders: Headache, lethargy dizziness, parasthesia, dysgeusia (common); aphasia, memory impairment, ataxia, syncope, balance disorder, sensory disorder, peripheral neuropathy (uncommon).
- Eye disorders: Increased lacrimation, conjunctivitis, eye irritation (common); reduced visual acuity, diplopia (uncommon).
- Ear and labyrinth disorders: Vertigo, ear pain (uncommon).
- Cardiac disorders: Unstable angina, angina pectoris, myocardial ischemia, atrial fibrillation, arrhythmia, tachycardia, sinus tachycardia, palpitations (uncommon).
- Vascular disorders: Thrombophlebitis (common); deep vein thrombosis, hypertension, petechiae, hypotension, hot flush, peripheral coldness (uncommon).
- Respiratory, thoracic and mediastinal disorders: Dyspnea, epistaxis, cough, rhinorrhea (common); pulmonary embolism, pneumothorax, hemoptysis, asthma, exertional dyspnea (uncommon).
- Gastrointestinal disorders: Diarrhea, vomiting, nausea, stomatitis, abdominal pain (very common); gastrointestinal hemorrhage, constipation, upper abdominal pain, dyspepsia, flatulence, dry mouth (common); intestinal obstruction, ascites, enteritis, gastritis, dysphagia, lower abdominal pain, esophagitis, abdominal discomfort, gastro-esophageal reflux disease, colitis, blood in stool (uncommon).
- Hepatobiliary Disorders: Hyperbilirubinemia, liver function test abnormalities (common); jaundice (uncommon).
- Skin and subcutaneous tissue disorders: Palmar-plantar erythrodysesthesia syndrome (very common); rash, alopecia, erythema, dry skin, pruritus, skin hyper-pigmentation, macular rash, skin desquamation, dermatitis, pigmentation disorder, nail disorder (common); skin ulcer, rash, urticaria, photosensitivity reaction, palmar erythema, face swelling, purpura (uncommon).
- Muskuloskeletal and connective tissue disorders: Pain in extremity, back pain, arthralgia (common); joint swelling, bone pain, facial pain, musculoskeletal stiffness, muscular weakness (uncommon).
- Renal and urinary disorders: Hydronephrosis, urinary incontinence, hematuria, nocturia, increased blood creatinine (uncommon).
- Reproductive system and breast disorders: Vaginal hemorrhage (uncommon).
- General disorders and administration site conditions: Fatigue, asthenia (very common); pyrexia, lethargy, peripheral edema, malaise, chest pain (common); edema, chills, influenza like illness, rigors, increased body temperature (uncommon).
- Injury, poisoning and procedural complications: Blister, overdose (uncommon).

Capecitabine in combination therapy:

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

- Infections and infestations: Herpes zoster, urinary tract infection, oral candidiasis, upper respiratory tract infection, rhinitis, influenza, ˚infection, oral herpes (common).
- Blood and lymphatic system disorders: ˚Neutropenia, ˚leucopenia, ˚anemia, ˚neutropenic fever, thrombocytopenia (very common); bone marrow depression, ˚febrile neutropenia (common).
- Immune system disorders: Hypersensitivity (common).
- Metabolism and nutrition disorders: Decreased appetite (very common); hypokalemia, hyponatremia, hypomagnesemia, hypocalcemia, hyperglycemia (common).
- Psychiatric disorders: Sleep disorder, anxiety (common).
- Nervous system disorders: Taste disturbance, paraesthesia and dysesthesia, peripheral neuropathy, peripheral sensory neuropathy, dysgeusia, headache (very common); neurotoxicity, tremor, neuralgia, hypersensitivity reaction, hypoesthesia (common).
- Eye disorders: Increased lacrimation (very common); visual disorders, dry eye, eye pain, visual impairment, blurred vision (common).
- Ear and labyrinth disorders: Tinnitus, hypoacusis (common).
- Cardiac disorders: Atrial fibrillation, cardiac ischemia/infarction (common).
- Vascular disorders: Lower limb edema, hypertension, ˚embolism and thrombosis (very common); flushing, hypotension, hypertensive crisis, hot flush, phlebitis (common).
- Respiratory, thoracic and mediastinal system disorders: Sore throat, pharyngeal dysesthesia (very common); hiccups, pharyngolaryngeal pain, dysphonia (common).
- Gastrointestinal disorders: Constipation, dyspepsia (very common); upper gastrointestinal hemorrhage, mouth ulceration, gastritis, abdominal distension, gastro-esophageal reflux disease, oral pain, dysphagia, rectal hemorrhage, lower abdominal pain, oral dysesthesia, oral paraesthesia, oral hypoesthesia, abdominal discomfort (common).
- Hepatobiliary disorders: Abnormal hepatic function (common).
- Skin and subcutaneous tissue disorders: Alopecia, nail disorder (very common); hyperhidrosis, erythematous rash, urticaria, night sweats (common).
- Musculoskeletal and connective tissue disorders: Myalgia, arthralgia, pain in extremity (very common); pain in jaw, muscle spasms, trismus, muscular weakness (common).
- Renal and urinary disorder: Hematuria, proteinuria, decreased creatinine renal clearance, dysuria (common).
- General disorders and administration site conditions: Pyrexia, weakness, ˚lethargy, temperature intolerance (very common); 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 (common).
- Injury, poisoning and procedural complications: Confusion (common).

For terms marked with a "˚", the frequency count was based on grade 3-4 adverse reactions.

Post-Marketing Experience:

The following additional serious adverse reactions have been identified during post-marketing exposure:

- Very rare: Lacrimal duct stenosis.
- Very rare: Hepatic failure and cholestatic hepatitis have been reported during clinical trials and post-marketing exposure.
- Very rare: ventricular fibrillation, QT prolongation, torsade de pointes and bradycardia.

DOSAGE AND ADMINISTRATION

Capeda® should only be prescribed by a qualified physician experienced in the utilization of anti-neoplastic agents. Capeda® 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 Capeda® of 1250 mg/m^2 and 1000 mg/m^2 are provided in tables 1 and 2, respectively.

Recommended Posology

Monotherapy

- Colon, colorectal and breast cancer: Given as single agent, the recommended starting dose for Capeda® 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 Capeda® should be reduced to 800 – 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 Capeda®. Premedication to maintain adequate hydration and anti-emesis should be started prior to cisplatin administration for patients receiving the Capeda® plus cisplatin combination. Premedication with antiemetics is recommended for patients receiving the Capeda® plus oxaliplatin combination. Adjuvant treatment in patients with stage III colon cancer is recommended for a duration of 6 months.
- Breast cancer: In combination with docetaxel, the recommended starting dose of Capeda® 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 should be started prior to docetaxel administration for patients receiving the Capeda® plus docetaxel combination.

Capeda® Dose Calculations

Table 1 Standard and reduced dose calculations according to body surface area for a starting dose of Capeda® 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 Capeda® 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

Posology Adjustments during Treatment:

General

Toxicity due to Capeda® 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, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption. Patients taking Capeda® should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of Capeda® omitted for toxicity are not replaced. The following are the recommended dose modifications for toxicity:

Table 3 Capeda® 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 treatment permanently	Not applicable

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

Dose modifications for toxicity when Capeda® is used as a 3 weekly cycle in combination with other agents

Dose modifications for toxicity when Capeda® is used as a 3 weekly cycle in combination with other agents should be made according to Table 3 above for Capeda® 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 Capeda® 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 Capeda®, Capeda® should be continued and the dose of the other agent should be adjusted according to the appropriate Prescribing Information.

If the other agent(s) have to be discontinued permanently, Capeda® treatment can be resumed when the requirements for restarting Capeda® are met.

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

Dose modifications for toxicity when Capeda® is used continuously in combination with other agents

Dose modifications for toxicity when Capeda® is used continuously in combination with other agents should be made according to Table 3 above for Capeda® 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: Capeda® 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 above. If the calculated creatinine clearance decreases during treatment to a value below 30 ml/min, Capeda® should be discontinued. These dose adjustment recommendations for renal impairment apply both to monotherapy and combination use.

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

- Elderly: During Capeda® 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 Capeda® was used in combination with other agents, elderly patients (≥65 years) experienced more grade 3 and grade 4 adverse drug reactions, 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 Capeda® 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 Capeda® starting dose in combination with docetaxel, the dose of Capeda® 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 Capeda® to 800 mg/m^2 twice daily is recommended.

OVERDOSAGE

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

STORAGE CONDITIONS

Store below 25°C.

Keep in original pack in intact conditions.

Date of revision: October 2019.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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