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pharmalegal®

XULOX

Film Coated Tablet 500mg

Capecitabine 500mg

NAME OF THE MEDICINE
XULOX Film Coated Tablet 500mg

COMPOSITION
Active ingredient:
Each film-coated tablet contains 500 mg capecitabine.

Excipients:
Lactose Anhydrous (Super tab 21 AN), Microcrystalline Cellulose (Avicel PH 101), Croscarmellose Sodium (Ac di sol), Hydroxy propyl methyl cellulose (Hypromellose 606), Microcrystalline Cellulose (Avicel PH 102), Magnesium Stearate, Opadry Pink 03A84598 (Hypromellose/HPMC 2910, Titanium dioxide, Talc, Iron oxide red and Iron oxide yellow), Purified Water.

PRODUCT DESCRIPTION
Dark pink colored, capsule shaped biconvex film coated tablet debossed with CAP on one side and 500 on other side

PHARMACODYNAMICS
Pharmacotherapeutic group: cytostatic (antimetabolite), ATC code: L01BC06

Capecitabine is a fluoropyrimidine carbamate derivative, which was designed as an orally administered, tumour-activated and tumour-selective cytotoxic agent. Capecitabine is non-cytotoxic *in vitro*. However, *in vivo*, it is sequentially converted to the cytotoxic moiety, 5-fluorouracil (5-FU), which is further metabolised.

Formation of 5-FU is catalysed preferentially at the tumour site by the tumour-associated angiogenic factor thymidine phosphorylase (dThdPase), thereby minimising the exposure of healthy tissues to systemic 5-FU.

The sequential enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations of 5-FU within tumour tissues. Following oral administration of capecitabine to patients with colorectal cancer (N=8), the ratio of 5-FU concentration in colorectal tumours vs adjacent tissues was 3.2 (ranged from 0.9 to 8.0). The ratio of 5-FU concentration in tumour vs plasma was 21.4 (ranged from 3.9 to 59.9) whereas the ratio in healthy tissues to plasma was 8.9 (ranged from 3.0 to 23.8). Thymidine phosphorylase activity was 4 times greater in primary colorectal tumour than in adjacent normal tissue.

Several human tumours, such as breast, gastric, colorectal, cervical and ovarian cancers, have a higher level of thymidine phosphorylase (capable of converting 5'-DFUR (5'-deoxy-5-fluorouridine) to 5-FU) than corresponding normal tissues.

Normal cells and tumour cells metabolise 5-FU to 5-fluoro-2-deoxyuridine monophosphate (F-dUMP) and 5-fluorouridine Triphosphate (FUTP). The metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor $N^{5,10}$-methylenetetrahydrofolate bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from uracil. 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.

PHARMACOKINETICS

Absorption
After oral administration, capecitabine is rapidly and extensively absorbed, followed by extensive conversion to the metabolites, 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-DFUR. Administration with food decreases the rate of capecitabine absorption, but has only a minor effect on the areas under the curve (AUC) of 5'-DFUR, 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 4.47, 3.05, 12.1, 0.95 and 5.46 respectively. The times 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.

Distribution
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 metabolised by hepatic carboxylesterase to 5'-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumour tissues. Formation of 5-FU occurs preferentially at the tumour site by the tumour-associated angiogenic factor dThdPase, thereby minimising the exposure of healthy body tissues to systemic 5-FU. The plasma AUC of 5-FU is 6 to 22 times lower than that following an i.v. bolus of 5-FU (dose of 600 mg/m^2). The metabolites of capecitabine become cytotoxic only after conversion to 5-FU and anabolites of 5-FU. 5-FU is further catabolized to the inactive metabolites dihydro-5-fluorouracil (FUH$_2$), 5-fluoro-ureidopropionic acid (FUPA) and α-fluoro-β-alanine (FBAL) via dihydropyrimidine dehydrogenase (DPD), which is rate limiting.

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. The pharmacokinetics of capecitabine have been evaluated over a dose range of 502 – 3514 mg/m^2/day. The parameters of capecitabine, 5'-DFCR and 5'-DFUR measured on days 1 and 14 were similar. The AUC of 5-FU was 30-35% higher on day 14, but did not increase subsequently (day 22). At therapeutic doses, the pharmacokinetics of capecitabine and its metabolites were dose proportional, except for 5-FU. After oral administration capecitabine metabolites are primarily recovered in the urine. Most (95.5%) of administered capecitabine dose is recovered in urine. Faecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL, which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug.

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

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, ASAT and ALAT had no statistically significant effect on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL.

Patients with hepatic impairment due to liver metastases
No clinically significant effect on the bioactivation and pharmacokinetics of capecitabine was observed in cancer patients with mildly to moderately impaired liver function due to liver metastases. No formal pharmacokinetic study has been conducted and no population pharmacokinetic data was collected in 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 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 antiproliferative activity; 5'-DFUR is the direct precursor of 5-FU.

Geriatric Population
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.

INDICATION
Breast Cancer:
XULOX in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. XULOX is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of a taxane and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

XULOX is indicated in combination with lapatinib ditosylate for the treatment of patients with advanced or metastatic breast cancer whose tumors over express HER2 and who have received prior therapy including an anthracycline, a taxane and trastuzumab.

Colon, Colorectal cancer:
XULOX is indicated for the treatment of patients with metastatic colorectal carcinoma.
Capecitabine is indicated as adjuvant treatment of patients following surgery of Stage III (Duke's Stage C) colon cancer.

Oesophagogastric Cancer:
XULOX is indicated as first-line treatment of patients with advanced oesophagogastric cancer in combination with a platinum-based regimen.

RECOMMENDED DOSAGE

Standard dosage
XULOX tablets should be swallowed whole with water within 30 minutes after a meal. XULOX tablets should not be crushed or cut. If patients cannot swallow XULOX tablets whole and tablets must be crushed or cut, this should be done by a professional trained in the safe handling of cytotoxic drugs.

Monotherapy
Colon, Colorectal and breast cancer
The recommended monotherapy starting dose of XULOX is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 7-day rest period.

Combination therapy
Breast Cancer
In combination with docetaxel
In combination with docetaxel, the recommended dose of XULOX is 1250 mg/m^2 twice daily for 2 weeks 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 according to the docetaxel labelling, should be started prior to docetaxel administration for patients receiving the Capecitabine plus docetaxel combination.

In combination with lapatinib ditosylate
In combination with *lapatinib ditosylate*, the recommended dose of XULOX is 2000 mg/m^2/day administered orally in 2 doses 12 hours apart for 14 days (Day 1-14) in a repeating 21 day cycle combined with lapatinib ditosylate 1250 mg (5 tablets) given orally once daily from Day 1-21. (See manufacturer's prescribing information for lapatinib ditosylate for further information).

Colon, colorectal cancer
In combination with oxaliplatin and/or bevacizumab
In combination with *oxaliplatin and/or bevacizumab* the recommended dose of XULOX is 1000 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period. The first dose of XULOX is given on the evening of day 1 and the last dose is given on the morning of day 15. Given as a 3-weekly schedule, on day 1 every 3 weeks bevacizumab is administered as a 7.5 mg/kg intravenous infusion over 30-90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours.

Premedication to maintain adequate hydration and anti-emesis according to the oxaliplatin product information should be started prior to oxaliplatin administration for patients receiving the XULOX plus oxaliplatin combination. Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

Gastric Cancer
In combination with platinum-based regimen
In combination with a platinum-based compound the recommended dose of XULOX for the treatment of advanced gastric cancer is 1000 mg/m^2 administered twice daily for 14 days followed by a 7 day rest period. The first dose of XULOX should be given on the evening of day 1 and the last dose should be given on the morning of day 15. If epirubicin is added to this regimen the recommended dose of XULOX is 625 mg/m^2 twice daily continuously. Epirubicin at a dose of 50 mg/m^2 should be given as a bolus on day 1 every 3 weeks. The platinum based compound (cisplatin at a dose of 60 mg/m^2 (triple regimen) - 80 mg/m^2 (double regimen) or oxaliplatin at a dose of 130 mg/m^2) should be given on day 1 as a 2 hour intravenous infusion every 3 weeks.

Premedication to maintain adequate hydration and anti-emesis according to the cisplatin/oxaliplatin summary of product characteristics should be started prior to cisplatin/oxaliplatin administration for patients receiving the XULOX plus cisplatin/oxaliplatin combination.

XULOX dose calculations
XULOX dose is calculated according to body surface area. The following tables show the standard and reduced dose calculations (see section *"Dosage adjustments during treatment"*) for a starting dose of capecitabine of either 1250 mg/m^2 or 1000 mg/m^2.

Table 1 Standard and reduced dose calculations according to body surface area for a starting dose of XULOX of 1250 mg/m^2.

	Dose level 1250 mg/m^2 (twice daily)				
	Full dose	Number of tablets per administration (each administration to be given morning and evening)		Reduced dose (75%)	Reduced dose (50%)
	1250 mg/m^2			950 mg/m^2	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

In combination with *irinotecan*: for patients 65 years of age or more, a starting dose reduction of XULOX to 800 mg/m^2 twice daily is recommended.

Renal impairment
In patients with moderate renal impairment (creatinine clearance 30 - 50 mL/min) (Cockroft and Gault)† at baseline, a dose reduction to 75% for a starting dose of 1250 mg/m^2 is recommended. In patients with mild renal impairment (creatinine clearance 51 - 80 mL/min), no adjustment in starting dose is recommended.

Careful monitoring and prompt treatment interruption is recommended if the patient develops a Grade 2, 3, or 4 ADRs with subsequent dose adjustment as outlined in Table 3 above (see also section Pharmacokinetics in Special Populations). If the calculated creatinine clearance decreases during treatment to a value below 30 mL/min, XULOX should be discontinued. The dose adjustment recommendations for patients with moderate renal impairment apply both to monotherapy and combination use. For dosage calculations, see Table 1 and Table 2.

Hepatic Impairment
In patients with mild to moderate hepatic impairment due to liver metastases, no starting dose adjustment is necessary. However, such patients should be carefully monitored (see section Pharmacokinetics in Special Populations and section Warnings and Precautions). Patients with severe hepatic impairment have not been studied.

ROUTE OF ADMINISTRATION

Oral

CONTRAINDICATION
- XULOX is contraindicated in patients with a known hypersensitivity to capecitabine or to any of its excipients.
- XULOX is contraindicated in patients who have a history of severe and unexpected reactions to fluoropyrimidine therapy or with known hypersensitivity to fluorouracil.
- XULOX is contraindicated in patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity (see section Warnings and Precautions).
- XULOX should not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine (see section Interaction with other Medicaments).
- XULOX is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min).
- If contraindications exist to any of the agents in a combination regimen, that agent should not be used.

Table 2 Standard and reduced dose calculations according to body surface area for a starting dose of XULOX of 1000 mg/m^2

	Dose level 1000 mg/m^2 (twice daily)				
	Full dose	Number of tablets per administration (each administration to be given morning and evening)		Reduced dose (75%)	Reduced dose (50%)
	1000 mg/m^2			750 mg/m^2	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	3	3	1500	1000
2.07 – 2.18	2150	1	4	1600	1050
≥2.19	2300	2	4	175	1100

Dosage adjustments during treatment
General
Toxicity due to XULOX administration may be managed by symptomatic treatment and/or modification of the XULOX 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, treatment can be continued at the same dose without reduction or interruption. Dosage modifications are not recommended for Grade 1 events. Therapy with XULOX should be interrupted if a Grade 2 or 3 adverse drug reaction (ADR) occurs. Once the ADR has resolved or decreased in intensity to Grade 1, XULOX therapy may be restarted at full dose or as adjusted according to Table 3. If a Grade 4 ADR occurs, therapy should be discontinued or interrupted until the ADR has resolved or decreased to Grade 1, and therapy should be restarted at 50% of the original dose. Patients taking XULOX should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of XULOX omitted for toxicity are not replaced.

Haematology:
Patients with baseline neutrophil counts of <1.5 X 10^9/L and/or thrombocyte counts of <100 X 10^9/L should not be treated with XULOX. If unscheduled laboratory assessments, during a treatment cycle show grade 3 or 4 haematologic toxicity, treatment with XULOX should be interrupted.

The following table shows the recommended dose modifications following toxicity related to XULOX:

Table 3 XULOX dose reduction schedule

Toxicity NCIC grades*	Dose changes within a treatment cycle	Dose adjustment for next cycle (% of starting dose)
• **Grade 1**	Maintain dose level	Maintain dose level
• **Grade 2**		
1st appearance	Interrupt until resolve to grade 0-1	100%
2nd appearance		75%
3rd appearance		50%
4th appearance	Discontinue treatment permanently	Not applicable
• **Grade 3**		
1st appearance	Interrupt until resolve 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, 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 4.0. For hand-foot syndrome and hyperbilirubinemia, see section Warnings and Precautions.

The following are the recommended dose modification for toxicity when capecitabine and docetaxel are used in combination:

Table 4: XULOX (X) in combination with docetaxel (T) dose reduction schedule

	Recommended Dose Modifications	
	Capecitabine dose changes within a treatment cycle	
Toxicity grade^1	Grade 1	
1st appearance	100% of starting dose (no interruption)	X: 100% of starting dose T: 100% (75 mg/m^2)
Toxicity grade^2	Grade 2	
1st appearance	Interrupt until resolved (grade 0 - 1)	X: 100% of starting dose T: 100% (75 mg/m^2)
2nd appearance of the same toxicity	Interrupt until resolved (grade 0 – 1)	X: 75% of starting dose T: Reduce to 55 mg/m^2
3rd appearance of the same toxicity	Interrupt until resolved (grade 0 – 1)	X: 50% of starting dose **T : Discontinue permanently**
4th appearance of the same toxicity	**Discontinue permanently**	
Toxicity grade^3	Grade 3	
	If grade 3 haematological see section on haematological toxicity, otherwise:	
1st appearance	Interrupt until resolved (grade 0 – 1)	X: 75% of starting dose T: Reduce to 55 mg/m^2
2nd appearance	Interrupt until resolved (grade 0 – 1)	X: 50% of starting dose **T : Discontinue permanently**
3rd appearance	**Discontinue permanently**	
Toxicity grade^4	Grade 4	
	If G4 haematological see section on haematological toxicity, otherwise:	
1st appearance	Discontinue permanently or (if physician deems it to be in the best of the patient) interrupt until resolved (grade 0 – 1)	X: 50% of starting dose **T : Discontinue permanently**
2nd appearance	**Discontinue permanently**	

*National Cancer Institute of Canada Common Toxicity Criteria were used except for hand-foot syndrome (see Warnings and Precautions)

Specific dose adjustment in combination with docetaxel
XULOX and/or docetaxel dose modifications should be made according to the general dose modification scheme above, if nothing else is stated regarding specific dose adjustments. For those toxicities considered 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. At the beginning of a treatment cycle, if either a docetaxel or a XULOX treatment delay is indicated, both docetaxel and XULOX administration should be delayed until the requirements for restarting both drugs are met. If docetaxel has to be discontinued, XULOX treatment can be resumed when the requirements for restarting capecitabine are met.

Hematology: Treatment should only be re-administered when the neutrophil count is ≥1.5 x 10^9/l (Grade 0 - 1). Patients with neutropenia <0.5 x 10^9/l (Grade 4) for more than 1 week, or febrile (>38°C) neutropenia, should have the docetaxel dosage reduced from 75 mg/m^2 to 55 mg/m^2. If Grade 4 neutropenia or febrile neutropenia occurs at 55 mg/m^2 docetaxel, docetaxel should be discontinued. Patients with baseline neutrophil counts of <1.5 x 10^9/l and/or thrombocyte counts of <1.0 x 10^9/l should not be treated with the XULOX/docetaxel combination.

Hypersensitivity: Patients who develop severe hypersensitivity reactions (hypotension with a decrease of ≥20 mm Hg, or bronchospasm, or generalised rash/erythema) should stop treatment immediately and be given appropriate therapy. These patients should not be re-challenged with the drug suspected to have caused hypersensitivity.

Peripheral neuropathy: For 1st appearance of Grade 2 toxicity, reduce the docetaxel dose to 55 mg/m^2. If Grade 3 toxicity appears, discontinue docetaxel treatment. In both instances follow the above dose modification scheme for XULOX.

Fluid retention: Severe (Grade 3 or 4) toxicity such as pleural effusion, pericardial effusion or ascites which is possibly related to docetaxel should be closely monitored. In case of appearance of such toxicity docetaxel treatment should be discontinued, capecitabine treatment may be continued without dose modification.

Hepatic impairment: Docetaxel should generally not be given to patients with serum bilirubin above the upper limit of normal. The following modifications should be applied to the docetaxel dose in the event of abnormal values for ASAT, ALAT, and/or alkaline phosphatase levels:

Table 5: Modifications to the docetaxel dose

ASAT and /or ALAT values		Alkaline phosphatase values	Docetaxel dose modification
≤1.5 x UNL	and	≤5 x UNL	No dose modification
>1.5 x UNL - ≤2.5 x UNL	and	≤2.5 x UNL	No dose modification
>2.5 x UNL - ≤5 x UNL	and	≤2.5 x UNL	Reduce by 25% (not below 55 mg/m^2)
>1.5 x UNL - ≤5 x UNL	and	>2.5 x UNL - ≤5 x UNL	Reduce by 25% (not below 55 mg/m^2)
>5 x UNL	or (unless bone metastases are present in the absence of any liver disorder)	>5 x UNL	Delay dose by a maximum of 2 weeks. If no recovery, discontinue docetaxel.

Once the docetaxel dose is reduced for a given cycle, no further dose reduction is recommended for subsequent cycles unless worsening of the parameters is observed. In case of recovery of liver function tests after previous reduction of the docetaxel dose, the docetaxel dose can be re-escalated to the previous dose level.

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 occur, XULOX 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 those for the precipitating adverse event in accordance with the above guidelines.

Reductions to 75% and 50% of XULOX dose
For patients receiving XULOX monotherapy or XULOX in combination with docetaxel, the following tables show the dosage at 75% and 50%, calculated according to the body surface area:

Table 6: Calculated XULOX dose, reduced to 75% of the standard starting dose

Dose level 950 mg/m^2 (twice daily)		Number of tablets administered in the morning		Number of tablets administered in the evening	
Body surface area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.26	1150	1	2	1	2
1.27 –1.38	1300	2	2	2	2
1.39 –1.52	1450	3	2	3	2
1.53 –1.66	1500	-	3	-	3
1.67 –1.78	1650	1	3	1	3
1.79 –1.93	1800	2	3	2	3
1.93 –2.06	1950	3	3	3	3
2.07 –2.18	2000	-	4	-	4
≥2.19	2150	1	4	1	4

Calculated XULOX dose, reduced to 50% of the standard starting dose

Dose level 625 mg/m^2 (twice daily)		Number of tablets administered in the morning		Number of tablets administered in the evening	
Body surface area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.38	800	2	1	2	1
1.39 – 1.52	950	3	1	3	1
1.53 – 1.66	1000	-	2	-	2
1.67 – 1.78	1000	-	2	-	2
1.79 – 1.92	1150	1	2	1	2
1.93 – 2.06	1300	2	2	2	2
2.07 – 2.18	1300	2	2	2	2
≥2.19	1450	3	2	3	2

Pediatric use
The safety and efficacy of XULOX in children and adolescents (<18 years) have not been established.

Geriatric use
For XULOX monotherapy, no adjustment of the starting dose is needed. However, severe Grade 3 or 4 treatment-related ADRs were more frequent in patients over 80 years of age compared to younger patients.

When capecitabine was used in combination with other antineoplastic agents, geriatric patients (≥65 years) experience more Grade 3 and Grade 4 ADRs and ADRs that led to discontinuation, than younger patients. Careful monitoring of elderly patients is advisable.

In combination with docetaxel: an increased incidence of Grade 3 or 4 treatment-related ADRs and treatment-related serious ADRs was observed in patients 60 years of age or more. For patients 60 years of age or more treated with the combination of XULOX plus docetaxel, a starting dose reduction of XULOX to 75% (950 mg/m^2 twice daily) is recommended. For dosage calculations, see Table 1.

In combination with *irinotecan*: for patients 65 years of age or more, a starting dose reduction of XULOX to 800 mg/m^2 twice daily is recommended.

Renal impairment
In patients with moderate renal impairment (creatinine clearance 30 - 50 mL/min) (Cockroft and Gault)† at baseline, a dose reduction to 75% for a starting dose of 1250 mg/m^2 is recommended. In patients with mild renal impairment (creatinine clearance 51 - 80 mL/min), no adjustment in starting dose is recommended.

Careful monitoring and prompt treatment interruption is recommended if the patient develops a Grade 2, 3, or 4 ADRs with subsequent dose adjustment as outlined in Table 3 above (see also section Pharmacokinetics in Special Populations). If the calculated creatinine clearance decreases during treatment to a value below 30 mL/min, XULOX should be discontinued. The dose adjustment recommendations for patients with moderate renal impairment apply both to monotherapy and combination use. For dosage calculations, see Table 1 and Table 2.

Hepatic Impairment
In patients with mild to moderate hepatic impairment due to liver metastases, no starting dose adjustment is necessary. However, such patients should be carefully monitored (see section Pharmacokinetics in Special Populations and section Warnings and Precautions). Patients with severe hepatic impairment have not been studied.

ROUTE OF ADMINISTRATION

Oral

CONTRAINDICATION
- XULOX is contraindicated in patients with a known hypersensitivity to capecitabine or to any of its excipients.
- XULOX is contraindicated in patients who have a history of severe and unexpected reactions to fluoropyrimidine therapy or with known hypersensitivity to fluorouracil.
- XULOX is contraindicated in patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity (see section Warnings and Precautions).
- XULOX should not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine (see section Interaction with other Medicaments).
- XULOX is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min).
- If contraindications exist to any of the agents in a combination regimen, that agent should not be used.

Capecitabine Tablets 500 mg - KLD Leaflet
Size : 150 x 820 mm Folding size: 150x40 mm

35 mm

WARNINGS AND PRECAUTIONS

Warning

Diarrhoea

Capecitabine can induce diarrhea, which can sometimes be severe. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Standard antidiarrhoeal treatments (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. Dose reduction should be applied as necessary.

Dehydration

Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhoea may rapidly become dehydrated. Dehydration may cause acute renal failure, especially in patients with pre-existing compromised renal function or when capecitabine is given concomitantly with known nephrotoxic agents. Fatal outcome of renal failure has been reported in these situations. 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 should be applied for the precipitating adverse event as necessary (see section Recommended Dosage).

Dihydropyrimidine dehydrogenase (DPD) deficiency

Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of DPD activity, an enzyme involved in fluorouracil degradation.

Patients with certain homozygous or certain compound heterozygous mutations in the DPYD gene locus that cause complete or near complete absence of DPD enzymatic activity are at the highest risk for severe, life-threatening or fatal adverse reactions caused by fluorouracil. These patients should not be treated with capecitabine. No dose has been proven safe for patients with complete absence of DPD activity (see section Contraindications).

Patients with certain heterozygous DPYD variants (e.g. DPYD*2A variants) that may cause partial DPD deficiency have been shown to have increased risk of severe toxicity when treated with capecitabine.

For patients with partial DPD deficiency the benefits of capecitabine are considered to outweigh the risks taking into account the suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen), these patients must be treated with extreme caution, initially with a substantial dose reduction and frequent monitoring and dose adjustment according to toxicity. Testing for DPD deficiency should be considered based on the local availability and current guidelines.

In patients with unrecognized DPD deficiency treated with capecitabine as well as patients who test negative for specific DPYD variations, life-threatening toxicities manifesting as acute overdose may occur. In the event of grade 2-4 acute toxicity, treatment must be discontinued immediately. Permanent discontinuation should be considered based on clinical assessment of the onset, duration and severity of the observed toxicities (see section Symptoms and Treatment of Overdose).

Precautions

The spectrum of cardiotoxicity observed with capecitabine is similar to that of other fluorinated pyrimidines. This includes myocardial infarction, angina, dysrhythmias, cardiac arrest, cardiac failure and electrocardiographic changes. These ADRs may be more common in patients with a prior history of coronary artery disease.

Capecitabine can induce severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN). Capecitabine should be permanently discontinued in patients who experience a severe skin reaction possibly attributed to capecitabine treatment.

Capecitabine can induce hand-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema) which is a cutaneous toxicity. Persistent or severe hand-foot syndrome (grade 2 and above) can eventually lead to loss of fingerprints, which could impact patient identification. For patients receiving capecitabine monotherapy in the metastatic setting, the median time to onset of 79 days, range from 11 to 360 days), with a severity range of Grades 1 to 3.

Grade 1 hand-foot syndrome is defined by numbness, dysesthesia/paresthesia, tingling, or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 is defined as moist desquamation, ulceration, blistering or 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 (see section Recommended Dosage). When capecitabine and cisplatin are used in combination, use of Vitamin B6 (pyridoxine) is not advised for the symptomatic or secondary prophylactic treatment of hand-foot syndrome, because of published reports that it may decrease the efficacy of cisplatin. There is some evidence that dexpanthenol is effective for hand-foot syndrome prophylaxis in patients treated with capecitabine.

Capecitabine can induce hyperbilirubinemia. 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 may be resumed when bilirubin decreases to ≤3.0 x ULN or hepatic aminotransferases decrease to ≤2.5 x ULN.

Care should be exercised when capecitabine is co-administered with drugs, which are metabolized by cytochrome P450 2C9 such as for example warfarin or phenytoin. 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. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations (see section Interactions with other Medicaments).

Lactose

Capecitabine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicine contains less than 1mmol sodium (23mg) per, that is to say essentially 'sodium-free'.

INTERACTION WITH OTHER MEDICAMENTS

Cytochrome P-450 2C9 substrates

No formal drug-drug interaction studies with capecitabine and other drugs known to be metabolized by the cytochrome P450 2C9 isoenzyme have been conducted. Care should be exercised when capecitabine is co-administered with these drugs.

Coumarin anticoagulants

Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. In a clinical interaction study, after a single 20 mg dose of warfarin, capecitabine treatment increased the AUC of S-warfarin by 57% with a 91% increase in INR value. These results suggest an interaction, probably due to an inhibition of the cytochrome P450 2C9 isoenzyme system by capecitabine. Patients taking coumarin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR) and the anticoagulant dose adjusted accordingly (see Warning and Precautions).

Phenytoin

Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme system by capecitabine (see Coumarin anticoagulants). Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.

Antacid

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

Leucovorin (folinic acid)

The effect of leucovorin on the pharmacokinetics of capecitabine was investigated in cancer patients. Leucovorin has no effect on the pharmacokinetics of capecitabine and its metabolites. However, leucovorin has an effect on the pharmacodynamics of capecitabine and its toxicity may be enhanced by leucovorin.

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 in the literature. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, capecitabine should not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine (see section Contraindications). There must be at least a 4-week waiting period between the end of treatment with sorivudine or its chemically related analogues such as brivudine and start of capecitabine therapy.

Oxaliplatin

No clinically significant differences in exposure to capecitabine or its metabolites, free platinum or total platinum occurred when capecitabine and oxaliplatin were administered in combination, with or without bevacizumab.

Bevacizumab

There was no clinically significant effect of bevacizumab on the pharmacokinetic parameters of capecitabine or its metabolites.

Drug-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.

FERTILITY, PREGNANCY AND LACTATION

Use In Special Populations

Female and Males of Reproductive Potential

Fertility

Based on evidence from animal studies, capecitabine may impair fertility in females and males of reproductive potential.

Contraception

Females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with capecitabine. An effective method of contraception should be used during treatment and for 6 months after the last dose of capecitabine. If the patient becomes pregnant while receiving capecitabine, the potential hazard to the fetus must be explained.

Males

Based on genetic toxicity findings, male patients with female partners of reproductive potential should use effective contraception during treatment and for 3 months following the last dose of capecitabine.

Pregnancy

There are no studies in pregnant women using capecitabine; however, based on the pharmacological and toxicological properties of capecitabine, it can 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 should be considered a potential human teratogen. Capecitabine should not be used during pregnancy. If capecitabine is used during pregnancy or if the patient becomes pregnant while receiving this drug, the patient must be apprised of the potential hazard to the fetus.

Lactation

It is not known whether capecitabine is excreted in human breast milk. No studies have been conducted to assess the impact of capecitabine on milk production or its presence in human breast milk. In a study of single oral administration of capecitabine in lactating mice, a significant amount of capecitabine and its metabolites were found in the milk. As the potential for harm to the nursing infant is unknown, breastfeeding should be discontinued during treatment with capecitabine and for 2 weeks after the final dose.

ADVERSE EFFECTS

Clinical Trials

Adverse drug reactions (ADRs) considered by the investigator to be possibly, probably, or remotely related to the administration of capecitabine have been obtained from clinical studies conducted with capecitabine monotherapy (in adjuvant therapy of colon cancer, in metastatic colorectal cancer and metastatic breast cancer), and clinical studies conducted with capecitabine in combination with different chemotherapy regimens for multiple indications. ADRs are added to the appropriate category in the tables below according to the highest incidence from the pooled analysis of seven clinical trials. Within each frequency grouping ADRs are listed in descending order of seriousness. Frequencies are defined as very common ≥ 1/10, common ≥ 1/100 to < 1/10 and uncommon ≥ 1/1000 to < 1/100.

Capecitabine monotherapy

Safety data of capecitabine monotherapy were reported for patients who received adjuvant treatment for colon cancer and for patients who received treatment for metastatic breast cancer or metastatic colorectal cancer. The safety information includes data from a phase III trial in adjuvant colon cancer (995 patients treated with capecitabine and 974 treated with i.v. 5-FU/LV) and from 4 phase II trials in female patients with breast cancer (N=319) and 3 trials (1 phase II and 2 phase III trials) in male and female patients with colorectal cancer (N=630).The safety profile of capecitabine monotherapy is comparable in patients who received adjuvant treatment for colon cancer and in those who received treatment for metastatic breast cancer or metastatic colorectal cancer. The intensity of ADRs was graded according to the toxicity categories of the NCIC CTC Grading System.

Table 7: Summary of ADRs reported in ≥5% of patients treated with capecitabine monotherapy

Body System ADR	Very Common (10%)	Common (5% to <10%)
Metabolism and nutrition disorders	Anorexia (G3/4:1%)	Dehydration (G3/4: 3%) Appetite decreased (G3/4:<1%)
Nervous system disorders		Paraesthesia, Dysgeusia (G3/4:<1%), Headache (G3/4:<1%), Dizziness (incl. vertigo) (G3/4:<1%)
Eye disorders		Lacrimation increased Conjunctivitis (G3/4:<1%)
Gastrointestinal disorders	Diarrhea (G3/4: 13%) Vomiting (G3/4: 4%) Nausea (G3/4: 4%) Stomatitis (all)* (G3/4: 4%) Abdominal pain (G3/4: 3%)	Constipation (G3/4:<1%), Abdominal pain upper (G3/4:<1%), Dyspepsia (G3/4:<1%)
Hepatobiliary disorders		Hyperbilirubinemia (G3/4:1%)
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome **(G3/4: 17%), Dermatitis (G3/4:<1%)	
General disorders and administration site conditions	Fatigue (G3/4: 3%), Lethargy (G3/4:<1%)	Pyrexia (G3/4:<1%), Weakness (G3/4:<1%), Asthenia (G3/4:<1%)

* Stomatitis, mucosal inflammation, mucosal ulceration, mouth ulceration

**Based on the post-marketing experience, persistent or severe palmar-plantar erythrodysaesthesia syndrome can eventually lead to loss of fingerprints (see section Warnings and Precautions).

Skin fissures were reported to be at least remotely related to capecitabine in less than 2% of the patients in seven completed clinical trials (N= 949).

The following ADRs represent known toxicities with fluoropyrimidine therapy and were reported to be at least remotely related to capecitabine in less than 5% of patients in seven completed clinical trials (N = 949):

- Gastrointestinal disorder: dry mouth, flatulence, ADRs related to inflammation/ulceration of mucous membranes such as esophagitis, gastritis, duodenitis, colitis, gastrointestinal hemorrhage.
- Cardiac disorders: edema lower limb, cardiac chest pain including angina, cardiomyopathy, myocardial ischemia/infarction, cardiac failure, sudden death, tachycardia, atrial arrhythmias including atrial fibrillation, and ventricular extrasystoles.
- Nervous system disorders: taste disturbance, insomnia, confusion, encephalopathy, and cerebellar signs such as ataxia, dysarthria, impaired balance, abnormal coordination.
- Infections and infestations: ADRs related to bone marrow depression, immune system compromise, and/or disruption of mucous membranes such as local and fatal systemic infections (including bacterial, viral, fungal etiologies) and sepsis.
- Blood and lymphatic system disorders: anemia, bone marrow depression/ pancytopenia.
- Skin and subcutaneous tissue disorders: pruritus, localized exfoliation skin hyperpigmentation, nail disorders, photosensitivity reactions, radiation recall syndrome.
- General disorders and administration site conditions: pain in limb, chest pain (non-cardiac).
- Eye: eye irritation.
- Respiratory: dyspnoea, cough.
- Musculoskeletal: back pain, myalgia, arthralgia.
- Psychiatric disorders: depression.
- Hepatic failure and cholestatic hepatitis have been reported during clinical trials and post-marketing exposure. A causal relationship with capecitabine treatment has not been established.

Capecitabine in combination therapy

Table 8 lists ADRs associated with the use of capecitabine in combination therapy with different chemotherapy regimens in multiple indications and occurred in addition to those seen with monotherapy and/or at a higher frequency grouping. The safety profile was similar across all indications and combination regimens. These reactions occurred in ≥5% of patients treated with capecitabine in combination with other chemotherapies. Adverse drug reactions are added to the appropriate category in the table below according to the highest incidence seen in any of the major clinical trials. Some of the adverse reactions are reactions commonly seen with chemotherapy (e.g. peripheral sensory neuropathy with docetaxel or oxaliplatin), or with bevacizumab (e.g. hypertension); however, an exacerbation by capecitabine therapy cannot be excluded.

Table 8: Very common and common ADRs for capecitabine in combination with different chemotherapies in addition to those seen for capecitabine monotherapy.

Body System Adverse Event	Very Common ≥10%	Common ≥5% to <10%
Infections and Infestations		Infection + Oral candidiasis
Blood and lymphatic system disorders	Neutropenia +, Leukopenia +, Febrile neutropenia +, Thrombocytopenia +, Anemia +	
Metabolism and nutrition disorders	Appetite decreased	Hypokalemia, Weight Decreased
Psychiatric disorders		Insomnia
Nervous system disorders	Neuropathy peripheral, Peripheral sensory neuropathy, Dysgeusia, Paresthesia, Dysgeusia, Dysaesthesia, Headache	Hypoaesthesia
Eye disorders	Lacrimation increased	
Vascular Disorders	Thromboisis/embolism, Hypertension, Lower limb oedema	
Respiratory, thoracic and mediastinal disorders	Dysaesthesia pharynx, Sore throat	Epistaxis, Dysphonia, Rhinorrhoea, Dyspnoea
Gastrointestinal disorders	Constipation, Dyspepsia	Dry mouth
Skin and subcutaneous tissue disorders	Alopecia, Nail disorder	
Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia, Pain in extremity	Pain in jaw, Back Pain
General disorders and administration site conditions	Pyrexia, Asthenia, Weakness, Temperature intolerance	Fever + Pain

Frequencies based on all grades except those denoted with +, which are based on G3/4 ADRs only.

Hypersensitivity reactions (2%) and cardiac ischaemia/infarction (3%) have been reported commonly for capecitabine in combination with other chemotherapy but in less than 5% of patients.

Rare or uncommon ADRs reported for capecitabine in combination with other chemotherapy are consistent with the ADRs reported for capecitabine monotherapy or the combination product monotherapy (see prescribing information for the combination product).

Laboratory Abnormalities

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

Table 9: Laboratory abnormalitiesa: Capecitabine monotherapy in adjuvant colon cancer and in metastatic breast and colorectal cancer

Parameter*	Capecitabine 1250 mg/m² twice daily intermittent
	Patients with Grade 3 / 4 abnormality (%)
Increased ALAT (SGPT)	1.6
Increased ASAT (SGOT)	1.5
Increased alkaline phosphatase	3.5
Increased calcium	1.5
Decreased calcium	2.3
Decreased granulocytes	0.3
Decreased hemoglobin	3.1
Decreased lymphocytes	44.4
Decreased neutrophils	3.6
Decreased neutrophils/granulocytes	2.4
Decreased platelets	2.0
Increased bilirubin	6.3
Increased serum creatinine	0.5
Decreased sodium	0.4
Increased bilirubin	20.0
Hyperglycemia	4.4

* Laboratory abnormalities were graded according to the categories of the NCIC CTC Grading System

Table 10: Adverse Drug Reactions from Postmarketing Experience

System Organ Class (SOC)	ADR(s)	Frequency
Renal and urinary disorders	Acute renal failure secondary to dehydration including fatal outcome	Rare
Nervous system disorders	Toxic leukoencephalopathy	Unknown
Hepatobiliary disorders	Hepatic failure, Cholestatic hepatitis	Very rare
Metabolism and nutrition disorders	Hypertriglyceridemia	Unknown
Skin and subcutaneous tissue disorders	Cutaneous lupus erythematosus, Severe skin reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (TEN)	Very rare
Eye disorders	Lacrimal duct stenosis NOS, Corneal disorders including keratitis	Very rare

* This subtype of hypersensitivity reaction was reported in the postmarketing setting.

Exposure to crushed or cut capecitabine tablets:

In the instance of exposure to crushed or cut capecitabine tablets, the following ADRs have been reported: eye irritation, eye swelling, skin rash, headache, paresthesia, diarrhea, nausea, gastric irritation, and vomiting.

Special populations

Paediatric patients

The safety and efficacy of capecitabine in paediatric patients below the age of 18 have not been established.

Geriatric patients

Among patients with colorectal cancer aged 60-79 years receiving capecitabine monotherapy in the metastatic setting, the incidence of gastrointestinal toxicity was similar to that in the overall population. In patients aged 80 years or older, a larger percentage experienced reversible Grade 3 or 4 gastrointestinal ADRs, such as diarrhea, nausea and vomiting (see section Recommended Dosage). When capecitabine was used in combination with other agents geriatric patients (≥ 65 years) experienced more Grade 3 and Grade 4 ADRs and ADRs that led to discontinuation than younger patients. An analysis of safety data in patients equal to or greater than 60 years of age treated with capecitabine plus docetaxel combination therapy showed an increase in the incidence of treatment-related Grade 3 and 4 ADRs, treatment-related serious ADRs and early withdrawals from treatment due to ADRs compared to patients less than 60 years of age.

Renal impairment

Physicians should exercise caution when capecitabine is administered to patients with impaired renal function. As seen with 5-FU the incidence of treatment-related Grade 3 or 4 ADRs was higher in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) (see section Recommended Dosage).

Hepatic Impairment

Patients with hepatic impairment should be carefully monitored when Capecitabine is administered. The effect of hepatic impairment not due to liver metastases or severe hepatic impairment on the disposition of capecitabine is not known (see section Pharmacokinetics Recommended Dosage).

SYMPTOMS AND TREATMENT OF OVERDOSE

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.

EFFECT ON ABILITY TO DRIVE AND USE MACHINE

Capecitabine has moderate influence on the ability to drive and use machines. Patients should be advised to use caution when driving or using machines if they experience ADRs such as dizziness, fatigue, and or nausea during treatment with capecitabine (see section Adverse Effects).

STORAGE CONDITIONS

Store below 30°C.

SHELF LIFE

24 months

DOSAGE FORMS AND PACKAGING AVAILABLE

Pack of 120 tablets (12 blisters x 10 tablets)

MANUFACTURER

Shilpa Medicare Limited
Unit 4, Pharmaceutical Formulations SEZ, Plot No. S-20
to S-26, Pharma SEZ, TSIIC,Green Industrial Park,
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