WARNING

Xeloda-Warfarin Interaction: Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important Xeloda -Warfarin interaction was demonstrated in a clinical pharmacology trial. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking Xeloda concomitantly with warfarin. Post-marketing reports have shown clinically significant increases in prothrombin time (PT) and INR in patients who were stabilised on anticoagulants at the time Xeloda was introduced. These events occurred within several days and up to several months after initiating Xeloda therapy and, in a few cases, within one month after stopping Xeloda. These events occurred in patients with and without liver metastases. Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy.

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

Xeloda 150 Film-coated tablet

Xeloda 500 Film-coated tablet

COMPOSITION

Each 150 mg film-coated tablet contains 150 mg of capecitabine.

Each 500 mg film-coated tablet contains 500 mg of capecitabine.

Excipients: anhydrous lactose, croscarmellose sodium, hypromellose, microcrystalline cellulose, magnesium stearate, titanium dioxide, yellow and red iron oxide, talc.

PHARMACOLOGICAL CLASSIFICATION

A26 - Cytostatic agents

PHARMACOLOGICAL ACTION

Pharmacodynamics

Capecitabine is a fluoropyrimidine carbamate and is an orally administered, tumour-activated and tumour-selective prodrug 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 tumor site by the tumour associated angiogenic factor thymidine phosphorylase (dThdPase). Both normal and tumour cells metabolise 5-FU to 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine-triphosphate (FUTP).

The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found in tumour 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 upregulation of thymidine phosphorylase by docetaxel.

These 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.

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 metabolise 5-FU at a more rapid rate.

Pharmacokinetics

The pharmacokinetics of capecitabine have been evaluated over a dose range of 502 – 3 514 mg/ m^2/ day. The

parameters of capecitabine, 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-deoxy-5-fluorouridine (5'-DFUR) measured on days 1 and 14 were similar. The AUC of 5-FU was 30 % – 35 % higher on day 14. Capecitabine dose reduction decreases systemic exposure to 5-FU more than dose-proportionally, due to non-linear pharmacokinetics for the active metabolite.

Absorption: After oral administration, capecitabine is extensively converted to the metabolites 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-deoxy-5-fluorouridine (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 1 250 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 respectively 54 %, 10 %, 62 % and 10 % protein bound, mainly to albumin.

Metabolism: Capecitabine is first metabolised by hepatic carboxylesterase to 5'-deoxy-5-fluorocytidine (5'-DFCR), which is then converted to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase, principally located in the liver and tumour tissues. Further catalytic activation of 5'-DFUR then occurs by thymidine phosphorylase (dThdPase) to form 5-FU. Formation of 5-FU occurs preferentially at the tumor site by the tumour associated angiogenic factor dThdPase.

The metabolites of capecitabine become cytotoxic after conversion to 5-FU and anabolites of 5-FU. 5-FU is further catabolised to the inactive metabolites dihydro-5-fluoruracil (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 – 3 514 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. 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 active ingredient, capecitabine. The interpatient variability in C_{max} and AUC of 5-FU was greater than 85 %.

***Combination therapy*:** Phase I studies evaluating the effect of Xeloda on the pharmacokinetics of either docetaxel or paclitaxel and vice versa showed no effect by Xeloda 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: 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 in patients with colorectal cancer.

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. There are no pharmacokinetic data in patients with severe hepatic impairment. See *Dosing in special populations.*

Patients with renal impairment: Based on a pharmacokinetic study in cancer patients with mild to severe renal impairment, there is no evidence of an effect of creatinine clearance on the pharmacokinetics of intact active ingredient, capecitabine, 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. See *Dosing in special populations,* SPECIAL PRECAUTIONS and CONTRA-INDICATIONS.

INDICATIONS

Breast Cancer

Metastatic breast cancer (Combination therapy): Xeloda in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy which should have included an anthracycline.

Metastatic breast cancer (Monotherapy): Xeloda is 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.

Colorectal cancer

Colon cancer: Xeloda is indicated as adjuvant treatment after surgery, of patients with Dukes C colon cancer.

Metastatic colorectal cancer: Xeloda is indicated as treatment of patients with metastatic colorectal adenocarcinoma. The benefit relates to time to progression, while overall survival was not influenced.

Gastric Cancer: Xeloda is indicated as first line treatment of patients with advanced gastric adenocarcinoma in combination with other anti-chemotherapeutic regimen. The benefit relates to time to progression, while overall survival was not influenced.

CONTRAINDICATIONS

Xeloda is contraindicated in:

- patients with known hypersensitivity to capecitabine or to any of its components.
- patients who have a history of severe and unexpected reactions to fluoropyrimidine therapy, or with known hypersensitivity to fluorouracil (capecitabine metabolite)
- patients with known dihydropyrimidine dehydrogenase (DPD) deficiency
- patients with severe leukopenia, neutropenia, or thrombocytopenia
- patients with severe hepatic impairment
- in patients with severe renal impairment (creatinine clearance below 30 mℓ/min)

Xeloda should not be administered with sorivudine or its chemically related analogues, such as brivudine. See INTERACTIONS. If contra-indications exist for any of the agents in the combination regimen, that agent should not be used.

WARNINGS AND SPECIAL PRECAUTIONS

Xeloda /Warfarin interaction – see boxed warning.

Diarrhoea: Xeloda can induce diarrhoea, which can sometimes be severe. In patients receiving Xeloda monotherapy the median time to first occurrence of Grade 2 - 4 diarrhoea was 31 days, and median duration of Grade 3 or 4 diarrhoea was 4½ days. Patients with severe diarrhoea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. National Cancer Institute of Canada (NCIC) Grade 2 diarrhoea is defined as an increase of 4 to 6 stools/day or nocturnal stools, Grade 3 diarrhoea as an increase of 7 to 9 stools/day or incontinence and malabsorption, and Grade 4 diarrhoea as an increase of ≥ 10 stools/day or grossly bloody diarrhoea or the need for parenteral support. If Grade 2, 3 or 4 diarrhoea occurs, administration of Xeloda should be immediately interrupted until the diarrhoea resolves or decreases in intensity to Grade 1. Following Grade 3 or 4 diarrhoea, subsequent doses of Xeloda should be decreased. See DOSAGE AND DIRECTIONS FOR USE. Standard anti-diarrhoeal treatments (e.g. loperamide) need to be instituted immediately. See SIDE EFFECTS.

Special Precautions

Patients treated with Xeloda should be carefully monitored for toxicity. Most adverse events are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced.

Diarrhoea: Xeloda can induce diarrhoea, sometimes severe. See WARNINGS and DOSAGE AND DIRECTIONS FOR USE.

Geriatric patients: Careful monitoring of elderly patients is advisable. See DOSAGE AND DIRECTIONS FOR USE, subsection - Dosing in special populations, Elderly.

Cutaneous: Xeloda can induce hand-foot syndrome (palmar-plantar erythrodysaesthesia or chemotherapy induced acral erythema) which is a cutaneous toxicity (for patients receiving Xeloda monotherapy, 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 is defined by numbness, dysaesthesia, paraesthesia, tingling erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 hand-and-foot syndrome is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 hand-and-foot syndrome is defined as moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that cause the patient to be unable to work or perform activities of daily living. If Grade 2 or 3 hand-and-foot syndrome occurs, administration of Xeloda should be interrupted until

the event resolves or decreases in intensity to grade 1. Following Grade 3 hand-and-foot syndrome, subsequent doses of Xeloda should be decreased. See DOSAGE AND DIRECTIONS FOR USE.

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

Renal Insufficiency: Xeloda is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mℓ/min). Medical practitioners should exercise caution when Xeloda is administered to patients with impaired renal function. As seen with 5-FU, the incidence of treatment related grade 3 or 4 adverse events was higher in patients with moderate renal impairment (creatinine clearance 30 – 50 mℓ/min). In patients with moderate renal impairment (creatinine clearance 30 - 50 mℓ/min) at baseline or during treatment, a dose reduction to 75 % of starting dose is recommended. The starting dose adjustment recommendation for patients with moderate renal impairment applies both to Xeloda monotherapy and Xeloda in combination use. Careful monitoring and prompt treatment interruption is recommended if the patient develops a Grade 2, 3 or 4 adverse event, with subsequent dose adjustment as outlined in the table under DOSAGE AND DIRECTIONS FOR USE. See *Dosing in special populations*, *Pharmacokinetics in special populations* and CONTRAINDICATIONS.

Hyperbilirubinemia: Xeloda can induce hyperbilirubinemia. Administration of Xeloda 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 decreases to ≤ 2,5 x ULN.

Hepatic insufficiency: Patients with hepatic impairment should be carefully monitored when Xeloda is administered. However, the effect of hepatic impairment not due to liver metastases or severe hepatic impairment on the disposition of Xeloda is not known. See *Dosing in special populations.*

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

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

- lacrimal duct stenosis NOS

- hepatic failure and cholestatic hepatitis

Lactose intolerance: Xeloda contains lactose and should not be administered to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

INTERACTIONS

Phenytoin**:** Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin. Formal interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme system by capecitabine (also refer to blocked WARNING at the beginning of this package insert). Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.

Food interaction*:* In all clinical trials, patients were instructed to take Xeloda within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that Xeloda be administered with food. See *Absorption*.

Antacid: The effect of an aluminium hydroxide and magnesium hydroxide-containing antacid (Maalox) 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: The effect of leucovorin (folinic acid) on the pharmacokinetics of capecitabine was investigated in cancer patients. Leucovorin has no effect on the pharmacokinetics of capecitabine and its metabolites.

Sorivudine and analogues*:* A clinically significant 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, Xeloda should not be administered with sorivudine or its chemically related analogues, such as brivudine. See CONTRAINDICATIONS.

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

Interaction with cytochrome P-450: For potential interactions with isozymes 1A2, 2C9 and 3A4, see interactions with coumarin-derivative anticoagulation in the boxed warning.

Interferon alpha: the Maximum Tolerated Dose (MTD) of Xeloda was 2 000 mg/m^2 per day when combined with interferon alpha-2a (3 MIU/m^2 per day) compared to 3 000 mg/m^2 per day when Xeloda was used alone.

Radiotherapy: the MTD of Xeloda alone using the intermittent regimen is 3 000 mg/m^2 per day, whereas, when combined with radiotherapy for rectal cancer, the MTD of Xeloda is 2 000 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 Xeloda within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that Xeloda be administered with food. Administration with food decreases the rate of capecitabine absorption.

PREGNANCY AND LACTATION

As teratogenicity has been demonstrated, women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Xeloda. It is not known whether Xeloda is excreted in human milk. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving Xeloda.

DOSAGE AND DIRECTIONS FOR USE

Xeloda should only be prescribed by a qualified physician experienced in the utilisation of antineoplastic agents. Xeloda tablets should be swallowed with water within 30 minutes after a meal. Treatment should be discontinued if progressive disease or intolerable toxicity is observed.

Adults

Monotherapy - Colon, colorectal and breast cancer

The recommended monotherapy dose of Xeloda is 1 250 mg/m^2 administered twice daily (morning and evening; equivalent to 2 500 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 maximum of six months.

Combination therapy

Colorectal and Gastric cancer: In combination treatment, the starting dose of Xeloda should be reduced to 1 000 mg/m^2 when administered twice daily for 14 days followed by a 7-day rest period. For the Xeloda Dose Reduction Schedule, please refer to Table 1.

The inclusion of biological agents in a combination regimen has no effect on the starting dose of Xeloda.

Premedication to maintain adequate hydration and anti-emesis according to the cisplatin prescribing information should be started prior to cisplatin administration for patients receiving the Xeloda plus cisplatin combination.

Breast Cancer: In combination with docetaxel for locally advanced or metastatic breast cancer, the recommended dose of Xeloda is 1 250 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 prescribing information should be started prior to docetaxel administration for patients receiving the Xeloda plus docetaxel combination.

Xeloda dose is calculated according to body surface area.

Table 1: Standard and reduced dose calculations according to body surface area for a starting dose of Xeloda of 1 250 mg/m^2

Table 1: Dose level 1 250 mg/m^2 (twice daily)				
Body Surface Area (m^2)	**Full dose** **1 250 mg/m^2**	**Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be**	**Reduced dose (75 %)** **950 mg/m^2**	**Reduced dose (50 %)** **625 mg/m^2**

		given morning and evening)			
	Dose per administration (mg)	**150 mg**	**500 mg**	**Dose per administration (mg)**	**Dose per administration (mg)**
≤ 1,26	1 500	-	3	1 150	800
1,27 – 1,38	1 650	1	3	1 300	800
1,39 – 1,52	1 800	2	3	1 450	950
1,53 – 1,66	2 000	-	4	1 500	1 000
1,67 – 1,78	2 150	1	4	1 650	1 000
1,79 – 1,92	2 300	2	4	1 800	1 150
1,93 – 2,06	2 500	-	5	1 950	1 300
2,07 – 2,18	2 650	1	5	2 000	1 300
≥ 2,19	2 800	2	5	2 150	1 450

Table 2: Standard and reduced dose calculations according to body surface area for a starting dose of Xeloda of 1 000 mg/m^2

Table 2: Dose level 1 000 mg/m^2 (twice daily)					
Body Surface Area (m^2)	**Full dose 1 000 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**
	Dose per			**Dose per**	**Dose per**

	administration (mg)	**150 mg**	**500 mg**	**administration (mg)**	**administration (mg)**
≤ 1,26	1 150	1	2	800	600
1,27 – 1,38	1 300	2	2	1 000	600
1,39 – 1,52	1 450	3	2	1 100	750
1,53 – 1,66	1 600	4	2	1 200	800
1,67 – 1,78	1 750	5	2	1 300	800
1,79 – 1,92	1 800	2	3	1 400	900
1,93 – 2,06	2 000	-	4	1 500	1 000
2,07 – 2,18	2 150	1	4	1 600	1 050
≥ 2,19	2 300	2	4	1 750	1 100

Dose adjustments during treatment

Patients should be carefully monitored for toxicity. Toxicity due to Xeloda administration may be managed by symptomatic treatment and/or modification of the Xeloda dose (treatment interruption or dose reduction).

Dosage modifications are not recommended for Grade 1 events. Therapy with Xeloda should be interrupted upon the occurrence of a Grade 2 or 3 adverse experiences. Once the adverse event has resolved or decreased in intensity to Grade 1, then Xeloda therapy may be restarted at full dose or adjusted according to the table below. If a Grade 4 experience occurs, therapy should be discontinued or interrupted until resolved or decreased to Grade 1, and therapy can then be restarted at 50 % of the original dose.

Patients taking Xeloda should be informed of the need to interrupt treatment immediately if moderate or worse toxicity occurs.

Doses of Xeloda omitted for toxicity are not replaced or restored; instead the patient should resume the planned treatment cycles. Once the dose has been reduced it should not be increased at a later time. See SIDE EFFECTS.

The following table shows the recommended dose modifications following toxicity with Xeloda.

Table 3: Xeloda Dose Reduction Schedule following toxicity (3-weekly cycle or continuous treatment).

Toxicity **NCIC 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	Interrupt until resolved to grade 0 - 1	75 %
3rd appearance	Interrupt until resolved to grade 0 - 1	50 %
4th appearance	Discontinue treatment permanently	
• ***Grade 3***		
1st appearance	Interrupt until resolved to grade 0 - 1	75 %
2nd appearance	Interrupt until resolved to grade 0 - 1	50 %
3rd appearance	Discontinue treatment permanently	
• ***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	

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

For hand-foot syndrome and hyperbilirubinaemia, see SIDE EFFECTS.

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 the Xeloda. If unscheduled laboratory assessments during a treatment cycle show grade 3 or 4 haematologic toxicity, treatment with Xeloda should be interrupted.

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

Dose modifications for toxicity when Xeloda is used as a 3 weekly cycle in combination with other agents should be made according to Table 3 above for Xeloda and according to the appropriate prescribing information for the other agent (s) used.

At the beginning of a treatment cycle, if a treatment delay is indicated for either Xeloda or the other agent(s), then administration of all agents should be delayed until the requirements for restarting all medicines are met.

During a treatment cycle for those toxicities considered by the treating physician not to be related to Xeloda, Xeloda should be continued and the dose of the other agent should be adjusted according to the appropriate prescribing information.

If the other agent(s) has(ve) to be discontinued permanently, Xeloda treatment can be resumed when the requirements for restarting Xeloda are met.

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

Dose modifications for toxicity when Xeloda is used continuously in combination with other agents: Dose modifications for toxicity when Xeloda is used continuously in combination with other agents should be made according to Table 3 above for Xeloda and according to the appropriate prescribing information for the other agent(s).

Dosing in special populations

Patients with hepatic-impairment due to liver metastases: 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. Patients with severe hepatic impairment have not been studied. See SIDE EFFECTS.

Patients with renal impairment: Xeloda is contra-indicated in patients with severe renal impairment (creatinine clearance below 30 mℓ/min). See CONTRAINDICATIONS.

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 (creatinine clearance 30 - 50 mℓ/min) at baseline, a dose reduction to 75 % for starting dose of 1 250 mg/m^2 is recommended. In patients with moderate renal impairment at baseline, no dose reduction is required for a starting dose of 1 000 mg/m^2. 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 adverse event, with subsequent dose adjustment as outlined in the table above. The dose adjustment recommendations for patients with moderate renal impairment apply both to monotherapy and combination use. See *Pharmacokinetics in special populations*, SIDE EFFECTS and CONTRAINDICATIONS.

Children: Safety and efficacy in children have not been established.

Elderly: No adjustment of the starting dose is needed for Xeloda monotherapy. However, severe Grade 3 or 4 treatment-related adverse events were more frequent in patients over 60 years of age compared to younger patients. Careful monitoring of elderly patients is advisable. For treatment with Xeloda

- In combination with docetaxel, an increased incidence of grade 3 or 4 treatment-related adverse reactions and treatment-related serious adverse reactions were observed in patients 60 years of age or more. For patients 60 years of age or more treated with the combination of Xeloda plus docetaxel, a starting dose reduction of Xeloda 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 Xeloda starting dose in combination with docetaxel, the dose of Xeloda may be cautiously escalated to 1 250 mg/m^2 twice daily.
- In combination with irinotecan: for patients 65 years of age or more treated with the combination of Xeloda with irinotecan, a starting dose reduction of Xeloda to 800 mg/m^2 twice daily is recommended.

SIDE EFFECTS

The side effects considered to be related to the administration of Xeloda have been obtained from clinical studies in > 3 000 patients conducted with Xeloda monotherapy (in adjuvant therapy of colon cancer, in metastatic colorectal cancer and metastatic breast cancer), Xeloda in combination with docetaxel in metastatic breast cancer after failure of cytotoxic chemotherapy, Xeloda in combination with oxaliplatin with or without bevacizumab in metastatic colorectal cancer and Xeloda in combination with various agents in advanced gastric cancer. The safety data from the clinical trial population for monotherapy and combination therapy are presented in this section. For post marketing experience, see below.

The most commonly reported treatment-related side effects were gastrointestinal disorders (especially diarrhoea, nausea, vomiting, abdominal pain, stomatitis), fatigue and hand-foot syndrome (palmar-plantar

erythrodysaesthesia).

The following headings are used to rank the side effects by frequency: Very common (≥ 1/10), common (≥ 1/100, < 1/10) and uncommon (≥ 1/1 000, < 1/100). Within each frequency grouping, side-effects are presented in order of decreasing seriousness.

Xeloda Monotherapy:

Safety data for Xeloda monotherapy has been obtained from > 1 900 patients. Table 4 lists side-effects associated with the use of Xeloda monotherapy in three major clinical trials in adjuvant treatment for colon cancer and for metastatic colorectal cancer. Each side effect has been added to the appropriate frequency grouping according to the overall incidence from a pooled analysis of the safety data from these three major clinical studies in colorectal cancer.

The most frequently reported treatment-related side-effects were gastrointestinal disorders, especially diarrhoea, nausea, vomiting, stomatitis, and hand-foot syndrome (palmar-plantar erythrodysaesthesia). The safety profiles of Xeloda monotherapy for the metastatic breast cancer, metastatic colorectal cancer and adjuvant colon cancer populations are comparable.

Table 4: Summary of side effects reported in patients treated with Xeloda monotherapy in adjuvant treatment for colon cancer and metastatic colorectal cancer.

Body System	**Very Common** **(≥ 1/10)** **All Grades**	**Common** **(≥ 1/100 - < 1/10)** **All Grades**	**Uncommon** **(≥ 1/1 000 - < 1/100)** **Severe and/or Life-threatening (Grade 3 - 4) or Considered Medically Relevant**
Infections and infestations	-	Herpes simplex Nasopharyngitis Lower respiratory tract infection	Sepsis Urinary tract infection Cellulitis Tonsillitis Pharyngitis Oral candidiasis Influenza Gastroenteritis Fungal infection Herpes 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

Immune system disorders	-	-	Hypersensitivity
Metabolism and nutrition disorders	Anorexia	Dehydration Decreased appetite	Diabetes Hypokalaemia Appetite disorder Malnutrition Hypertriglyceridaemia
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 Dysrhythmia 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 Rhinorrhoea	Pulmonary embolism Pneumothorax Haemoptysis Asthma Exertional dyspnoea

Gastrointestinal disorders	Diarrhoea Vomiting Nausea Stomatitis Abdominal pain	Gastrointestinal haemorrhage Constipation Upper abdominal pain Dyspepsia Flatulence Dry mouth Loose stools	Intestinal obstruction Ascites Enteritis Gastritis Dysphagia Abdominal pain lower Oesophagitis Abdominal discomfort Gastro-oesophageal reflux disease Colitis
Hepatobiliary Disorders		Hyperbilirubinaemia	Jaundice
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia 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
Reproductive system and breast disorders	-	-	Vaginal haemorrhage
General disorders and administration site conditions	Fatigue Asthenia	Pyrexia Lethargy Oedema peripheral Malaise Non-cardiac chest pain	Oedema Chills Influenza-like illness Rigors
Investigations	-	Weight decreased Liver function test abnormalities	Blood in stool International normalised ratio increased Blood creatinine increased Body temperature increased
Injury, poisoning and procedural complications	-	-	Blister Overdose

Laboratory Abnormalities observed with Xeloda *Monotherapy:* Table 5 lists laboratory abnormalities of all grades observed with Xeloda monotherapy in three major trials in adjuvant treatment for colon cancer and for metastatic colorectal cancer. Each laboratory abnormality has been added to the appropriate frequency

grouping according to the overall incidence from a pooled analysis of the safety data from these three major clinical studies in colorectal cancer.

Table 5: Laboratory abnormalities observed in patients treated with Xeloda mono-therapy

Grade of Abnormality	**Very Common (≥ 1/10)**	**Common (≥ 1/100 - < 1/10)**	**Uncommon (≥ 1/1 000 - < 1/100)**
Patients with grade 1 to 4 abnormality	Decreased haemoglobin Decreased neutrophils/granulocytes Decreased platelets Decreased lymphocytes Decreased sodium Decreased potassium Decreased calcium Increased bilirubin Increased alkaline phosphatase Increased ALT (SGPT) Increased AST (SGOT)	Increased calcium	-
Patients with grade 3/4	Decreased lymphocytes Increased bilirubin	Decreased haemoglobin Decreased neutrophils/granulocytes Decreased platelets Decreased calcium Increased alkaline phosphatase Increased ALT (SGPT)	Decreased sodium Decreased potassium Increased calcium Increased AST (SGOT)

Grade of Abnormality	**Very Common (≥ 1/10)**	**Common (≥ 1/100 - < 1/10)**	**Uncommon (≥ 1/1 000 - < 1/100)**
Patients with grade 4	-	Decreased neutrophils/granulocytes Decreased lymphocytes Decreased calcium Increased bilirubin	Decreased haemoglobin Decreased platelets Decreased sodium Decreased potassium Increased calcium Increased alkaline phosphatase Increased ALT (SGPT) Increased AST (SGOT)

Xeloda in combination therapy:

Tables 6, 7, and 8 list those side effects reported in patients treated with Xeloda in combination with another agent that were seen **in addition to** those seen with Xeloda monotherapy (see Table 4) or seen at **a higher frequency grouping** compared to Xeloda monotherapy (see Table 4). Table 9 lists those side effects reported in patients treated with Xeloda in combination with two agents (oxaliplatin and bevacizumab) that were seen **in addition to** those seen with Xeloda monotherapy and those seen with Xeloda in combination with oxaliplatin (see Table 8) or seen at **a higher frequency grouping** compared to Xeloda monotherapy and Xeloda in combination with oxaliplatin (see Table 8).

Each adverse drug reaction has been added to the appropriate frequency grouping according to the incidence seen in the major clinical trial (for combination with cisplatin, with docetaxel, and with oxaliplatin and bevacizumab) or in the pooled safety analysis (for combination with oxaliplatin).

Uncommon side effects reported for the combination therapy of Xeloda with the combination agent are consistent with the side effects reported for Xeloda monotherapy or reported for monotherapy with the

combination agent (in literature and/or respective summary of product characteristics).

Xeloda in combination with cisplatin:

Safety data for Xeloda in combination with cisplatin has been obtained from > 150 patients. Table 6 lists side effects associated with the use of Xeloda in combination with cisplatin in the major clinical trial in gastric cancer.

The incidence of hand-foot syndrome for Xeloda plus cisplatin was 22 % (all grades) and 4 % (grade 3) in study ML17032.

Table 6. Summary of related side effects reported in patients treated with Xeloda in combination with cisplatin **in addition to** those seen with Xeloda monotherapy or seen at **a higher frequency grouping** compared to Xeloda monotherapy.

Body System	**Very common (≥ 1/10) All Grades**	**Common (≥ 1/100 - < 1/10) All Grades**
Infections and infestations	-	Herpes zoster, Urinary tract infection
Blood and lymphatic system disorders	Neutropenia Leucopenia Anaemia	Thrombocytopenia, Bone-marrow depression
Metabolism and nutrition disorders	-	Hypokalaemia, Hyponatraemia
Psychiatric disorders	-	Sleep disorder
Nervous system disorders	-	Neuropathy, Peripheral sensory neuropathy, Hypoaesthesia
Ear and labyrinth disorders	-	Tinnitus,

Body System	**Very common** **(≥ 1/10)** **All Grades**	**Common** **(≥ 1/100 - < 1/10)** **All Grades**
		Hypoacusis
Gastrointestinal disorders	-	Upper gastrointestinal haemorrhage, Mouth ulceration, Gastritis
Hepatobiliary disorders	-	Hepatic function abnormal
Skin and subcutaneous tissue disorders	-	Hyperhidrosis
Musculoskeletal and connective tissue disorders	-	Myalgia
General disorders and administration site conditions	-	Mucosal inflammation
Investigations	-	Creatinine renal clearance decreased

Xeloda in combination with docetaxel:

Safety data for Xeloda in combination with docetaxel has been obtained from > 250 patients. Table 7 lists side effects associated with the use of Xeloda in combination with docetaxel in the major clinical trial in metastatic breast cancer.

Table 7: Summary of related side effects reported in patients treated with Xeloda in combination with docetaxel **in addition to** those seen with Xeloda monotherapy or seen at **a higher frequency grouping** compared to Xeloda monotherapy

Body System	**Very common** **(≥ 1/10)** **All Grades**	**Common** **(≥ 1/100 - < 1/10)** **All Grades**
Infections and infestations	-	Oral candidiasis
Blood and lymphatic system disorders	Neutropenic fever (Grade 3 - 4)	-
Metabolism and nutrition disorders	Appetite decreased	-
Nervous system disorders	Taste disturbance Paraesthesia	Peripheral neuropathy
Eye disorders	Lacrimation increased	-
Vascular disorders	Lower limb oedema	
Respiratory, thoracic and mediastinal system disorders	Sore throat	-
Gastrointestinal disorders	Constipation Dyspepsia	-
Skin and Subcutaneous Disorders	Alopecia Nail disorder	Rash erythematous, Nail discolouration, Onycholysis
Musculoskeletal and connective tissue disorders	Myalgia Arthralgia	-
General disorders and administration site	Pyrexia Weakness	Pain in limb, Pain

Xeloda in combination with oxaliplatin:

Safety data for Xeloda in combination with oxaliplatin has been obtained from > 900 patients. Table 8 lists

side effects associated with the use of Xeloda in combination with oxaliplatin from a pooled analysis of the safety data from two major clinical trials in first- and second-line treatment of metastatic colorectal cancer.

Table 8: Summary of related side effects reported in patients treated with Xeloda in combination with oxaliplatin for the first-line and second-line treatment of metastatic colorectal cancer. The side effects shown are those that were seen **in addition to** those seen with Xeloda monotherapy or seen at **a higher frequency grouping** compared to Xeloda monotherapy

Body System	**Very common** **(≥ 1/10)** **All Grades**	**Common** **(≥ 1/100 - < 1/10)** **All Grades**
Infections and infestations	-	Urinary tract infection, Upper respiratory tract infection
Blood and lymphatic system disorders	Neutropenia, Thrombocytopenia, Anaemia	Leucopenia
Immune system disorders	-	Hypersensitivity
Metabolism and nutrition disorders	-	Hypokalaemia, Hypomagnesaemia Hypocalcaemia
Psychiatric disorders	-	Anxiety
Nervous system disorders	Paraesthesia, Neuropathy peripheral, Peripheral sensory neuropathy, Dysgeusia, Neuropathy, Dysaesthesia	Hypoaesthesia, Neurotoxicity, Tremor, Polyneuropathy, Neuralgia
Eye disorders	-	Vision blurred, Dry eye, Visual disturbance

Body System	**Very common** **(≥ 1/10)** **All Grades**	**Common** **(≥ 1/100 - < 1/10)** **All Grades**
Vascular disorders	-	Flushing, Hypertension, Hypotension
Respiratory, thoracic and mediastinal system disorders	Dysaesthesia pharynx	Hiccups, Pharyngolaryngeal pain Dysphonia
Gastrointestinal disorders	Constipation	Oral dysaesthesia, Abdominal distension, Gastro-oesophageal reflux disease, Oral pain, Dysphagia, Paraesthesia oral, Rectal haemorrhage, Abdominal pain lower
Skin and Subcutaneous Disorders	-	Hyperhydrosis, Urticaria
Musculoskeletal and connective tissue disorders	-	Pain in jaw, Muscle spasms, Myalgia, Trismus, Muscular weakness
Renal and urinary disorder	-	Haematuria
General disorders and administration site	Pyrexia	Temperature intolerance, Chills, Chest pain

Xeloda in combination with oxaliplatin and bevacizumab:

Safety data for Xeloda in combination with oxaliplatin and bevacizumab has been obtained from > 350 patients. Table 9 lists side effects associated with the use of Xeloda in combination with oxaliplatin and bevacizumab in a clinical trial in the first-line treatment of metastatic colorectal cancer.

Table 9: Summary of related side effects reported in patients who received Xeloda in combination with oxaliplatin and bevacizumab for the first-line treatment of metastatic colorectal cancer. The side effects shown

are those that were seen **in addition to** those seen with Xeloda monotherapy and Xeloda in combination with oxaliplatin or seen at **a higher frequency grouping** compared to Xeloda monotherapy and Xeloda in combination with oxaliplatin.

Body System	**Very common** **(≥ 1/10)** **All Grades**	**Common** **(≥ 1/100 - < 1/10)** **All Grades**
Infections and infestations	-	Rhinitis, Influenza
Blood and lymphatic system disorders	-	Febrile neutropenia
Metabolism and nutrition disorders	-	Hyperglycaemia
Nervous system disorders	Headache	-
Cardiac disorders	-	Atrial fibrillation, Myocardial ischaemia
Vascular disorders	Hypertension	Deep vein thrombosis, Hypertensive crisis
Respiratory, thoracic and mediastinal system disorders	-	Pulmonary embolism
Gastrointestinal disorders	-	Gastritis
Skin and Subcutaneous Disorders	-	Night sweats
Musculoskeletal and connective tissue disorders	Pain in extremity	-
Renal and urinary disorder	-	Proteinuria
General disorders and administration site	-	Pain, Influenza-like illness

Body System	**Very common** **(≥ 1/10)** **All Grades**	**Common** **(≥ 1/100 - < 1/10)** **All Grades**
Investigations	-	Blood pressure increased
Injury, poisoning and procedural complications	-	Contusion

Xeloda in combination with irinotecan:

Side effects reported in patients treated with Xeloda in combination with irinotecan **in addition** to those seen with Xeloda monotherapy or seen at **a higher frequency grouping** compared to Xeloda monotherapy include: *Very common, all grade side effects*: thrombosis/embolism; *Common, all grade side effects:* hypersensitivity reaction, cardiac ischaemia/infarction; *Common, grade 3 and grade 4 side effects*: febrile neutropenia.

Xeloda in combination with irinotecan and bevacizumab:

Grade 3 and Grade 4 side effects reported in patients treated with Xeloda in combination with irinotecan and bevacizumab **in addition** to those seen with Xeloda monotherapy or seen at **a higher frequency grouping** compared to Xeloda monotherapy include: *Common, grade 3 and grade 4 side effects:* neutropenia, thrombosis/embolism, hypertension, and cardiac ischaemia/ infarction.

Xeloda in combination with epirubicin and oxaliplatin:

Grade 3 and Grade 4 side effects reported in patients treated with Xeloda in combination with epirubicin and oxaliplatin **in addition to** those seen with Xeloda monotherapy or seen at **a higher frequency grouping** compared to Xeloda monotherapy include: *Very common, grade 3 and grade 4 side effects*: leucopenia, neutropenia, lethargy; *Common, grade 3 and grade 4 side effects:* anaemia, thrombocytopenia, febrile neutropenia, peripheral neuropathy, infection, fever, thromboembolism.

Xeloda in combination with epirubicin and cisplatin:

Grade 3 and Grade 4 side effects reported in patients treated with Xeloda in combination with epirubicin and cisplatin **in addition to** those seen with Xeloda monotherapy or seen at **a higher frequency grouping** compared to Xeloda monotherapy include: *Very common, grade 3 and grade 4 side effects*: leucopenia, neutropenia, anaemia, lethargy, thromboembolism; *Common, grade 3 and grade 4 side effects:* thrombocytopenia, febrile neutropenia, peripheral neuropathy, infection, fever. *Very rare side effects (≥ 1/10 000):* hepatic failure and cholestatic hepatitis.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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

IDENTIFICATION

Xeloda 150: A light peach biconvex film-coated oblong-shaped tablet with **Xeloda** engraved on one face and **150** engraved on the reverse.

Xeloda 500: A peach biconvex film-coated oblong-shaped tablet with **Xeloda** engraved on one face and **500** engraved on the reverse.

STORAGE INSTRUCTIONS

Xeloda 150 should be stored at or below 25 ºC.

Xeloda 500 should be stored at or below 30 ºC.

This medicine should not be used after the expiry date shown on the pack.

KEEP OUT OF REACH OF CHILDREN.

PRESENTATION

Xeloda 150: 60 film-coated tablets in a plastic bottle or blister pack.

Xeloda 500: 120 film-coated tablets in a plastic bottle or blister pack.

REGISTRATION NUMBERS

Xeloda 150: 33/26/0198

Xeloda 500: 33/26/0199

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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