PROFESSIONAL INFORMATION for

CAPELODA 150 / 500 mg

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

CAPELODA 150 (Film-coated tablets)

CAPELODA 500 (Film-coated tablets)

COMPOSITION:

CAPELODA 150: Each film-coated tablet contains 150 mg capecitabine.

CAPELODA 500: Each film-coated tablet contains 500 mg capecitabine.

Inactive ingredients in both formulations include croscarmellose sodium, hypromellose, iron oxide red, lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

Contains sugar: Lactose Monohydrate.

WARNING:

Warfarin interaction: Patients receiving concomitant CAPELODA, and warfarin therapy should have their anticoagulant response (International Normalised Ratio {INR} or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important CAPELODA-warfarin interaction was demonstrated in a clinical pharmacology trial. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine, as in CAPELODA, 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 capecitabine, as in CAPELODA, was introduced. These events

occurred within several days and up to several months after initiating capecitabine, as in CAPELODA, therapy and, in a few cases, within one month after stopping capecitabine, as in CAPELODA. 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.

CATEGORY AND CLASS:

A 26 Cytostatic agents.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Capecitabine is a fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety, 5-fluorouracil (5-FU).

Formation of 5-FU is catalysed preferentially at the tumour 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. Firstly, FdUMP inhibits thymidylate synthase (TS), and blocks the synthesis of thymidine triphosphate (TTP), a necessary constituent of DNA. This inhibition is achieved when FdUMP and the folate cofactor, N^{5-10}-methylenetetrahydrofolate, bind to (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. Secondly, 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.

Pharmacokinetic properties:

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 a 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, respectively. The $AUC_{0-\infty}$ values in µg.h/mL were 7,75; 7,24; 24,6; 2,03; and 36,3, respectively.

Distribution:

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 tumour 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 dihydro5-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. Capecitabine and its metabolites are predominantly excreted in urine; 95,5 % of administered capecitabine dose 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.

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.

Higher response rates are seen when 5-FU or capecitabine is used in combination with other medicines (e.g. cisplatin in head and neck cancer, with oxaliplatin or irinotecan in colon cancer).

Pharmacokinetics in special populations:

Gender, presence or absence of liver metastases at baseline, Karnofsky performance status, total bilirubin, serum albumin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) 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 **"CONTRAINDICATIONS"** and **"DOSAGE AND DIRECTIONS FOR USE"**).

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 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.

Elderly:

Age has no influence on the pharmacokinetics of 5'-DFUR and 5-FU. The AUC of FBAL increased with age (20 % increase in age resulted in a 15 % increase in the AUC of FBAL). This increase is likely due to a change in renal function (see **"DOSAGE AND DIRECTIONS FOR USE"**).

INDICATIONS:

Breast cancer:

- *Metastatic breast cancer (combination therapy):*

  CAPELODA 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):*

  CAPELODA 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:*

  CAPELODA is indicated as adjuvant treatment after surgery of patients with Dukes C colon cancer.

- ***Metastatic colorectal cancer:***

  CAPELODA 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:

- CAPELODA 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:

CAPELODA is contraindicated in:

- Patients with known hypersensitivity to capecitabine or to any of the components of CAPELODA.
- 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.
- Patients with severe renal impairment (creatinine clearance below 30 mL/min).

- In combination with sorivudine or its chemically related analogues, such as brivudine (see **"INTERACTIONS"**).
- Pregnancy and lactation (see **"HUMAN REPRODUCTION"**)
- Patients with a known DPD deficiency

WARNINGS AND SPECIAL PRECAUTIONS:

CAPELODA and warfarin interaction – see initial boxed warning.

Patients treated with CAPELODA should be carefully monitored for toxicity.

Patients receiving 5- fluorouracil and its prodrugs, capecitabine and tegafur, given by oral, injection or infusion, be tested for DPD deficiency before starting treatment. A reduced starting dose be considered to limit the risk of severe toxicity for patients with partial DPD deficiency (as they are at an increased risk of severe and potentially life-threatening toxicity). Subsequent doses may be increased in the absence of serious toxicity, as the efficacy of a reduced dose has not been established.

Dose limiting toxicities

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

Diarrhoea:

Patients with severe diarrhoea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. Standard anti-diarrhoeal treatments (e.g. loperamide) may be used. 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. Grade 4 diarrhoea is 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 CAPELODA should be immediately interrupted until the diarrhoea resolves or decreases in intensity to Grade 1. Following Grade 3 or 4 diarrhoea, subsequent doses of CAPELODA should be decreased (see **"DOSAGE AND DIRECTIONS FOR USE"**). Standard anti-diarrhoeal treatments (e.g. loperamide) need to be instituted immediately (see **"SPECIAL PRECAUTIONS"**).

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 medicinal products. Acute renal failure secondary to dehydration might be potentially fatal. If grade 2 or higher dehydration occurs, capecitabine as in CAPELODA 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 modification should be applied for the precipitating adverse event as necessary. (see **“DOSAGE AND DIRECTION FOR USE”**)

Elderly patients:

Careful monitoring of elderly patients is advisable. (See **“DOSAGE AND DIRECTIONS FOR USE”**).

Cutaneous:

CAPELODA can induce hand-foot syndrome (palmar-plantar erythrodysaesthesia or chemotherapy-induced acral erythema) which is a cutaneous toxicity (for patients receiving CAPELODA monotherapy the median time to onset is 79 days) with a severity range of Grades 1 to 3 (see **"SIDE EFFECTS"**). 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-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-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-foot syndrome occurs, administration of CAPELODA should be interrupted until the event resolves or decreases in intensity to grade 1. Following Grade 3 hand-foot syndrome, subsequent doses of CAPELODA should be decreased (see **"DOSAGE AND DIRECTIONS FOR USE"**).

When capecitabine and cisplatin are used in combination, the use of vitamin B6 (pyridoxine) is not advised for symptomatic or secondary prophylactic treatment of hand-foot syndrome, because of published reports that it may decrease the efficacy of cisplatin. There is some evidence that dexpanthenol is effective for hand-foot syndrome prophylaxis in patients treated with CAPELODA.

Cardiotoxicity:

The spectrum of cardiotoxicity observed with CAPELODA includes myocardial infarction, angina, dysrhythmias, cardiac arrest, cardiac failure, and electrocardiograph changes (including cases of QT prolongation). These adverse events may be more common in patients with a prior history of coronary artery disease.

Cardiac dysrhythmias (including ventricular fibrillation, torsade de pointes, and bradycardia), angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving CAPELODA. Caution must be exercised in patients with a history of significant cardiac disease, dysrhythmias and angina pectoris.

Renal insufficiency:

CAPELODA is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min). Medical practitioners should exercise caution when CAPELODA 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 CAPELODA monotherapy and CAPELODA 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 **"Pharmacokinetics: Special populations"**, **"CONTRAINDICATIONS"** and **"Dosing in special populations"**).

Hyperbilirubinemia:

CAPELODA can induce hyperbilirubinemia. Administration of CAPELODA 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 (see **"DOSING AND DIRECTIONS FOR USE"**).

Hepatic insufficiency:

Patients with hepatic impairment should be carefully monitored when CAPELODA is administered. However, the effect of hepatic impairment not due to liver metastases or severe hepatic impairment on the disposition of CAPELODA is not known (see **"Dosing in special populations"**).

Dihydropyrimidine dehydrogenase (DPD) deficiency:

Severe toxicity (e.g. stomatitis, diarrhoea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to a deficiency of DPD activity.

Patients with low or absent DPD activity, an enzyme involved in fluorouracil degradation, are at increased risk for severe, life-threatening, or fatal adverse reactions caused by fluorouracil.

Although DPD deficiency cannot be precisely defined, it is known that patients with certain homozygous or certain compound heterozygous mutations in the DPYD gene locus, which can cause complete or near complete absence of DPD enzymatic activity (as determined from laboratory assays), have the highest risk of life-threatening or fatal toxicity and should not be treated with CAPELODA (see **"CONTRAINDICATIONS"**). No dose has been proven safe for patients with complete absence of DPD activity.

For patients with partial DPD deficiency (such as those with heterozygous mutations in the DPYD gene) and where the benefits of CAPELODA 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 and frequent monitoring with dose adjustment according to toxicity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by specific test.

In patients with unrecognised DPD deficiency treated with CAPELODA, life-threatening toxicities manifesting as acute overdose may occur (see **"KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT"**). 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.

Hypo-or hypercalcaemia

Hypo-or hypercalcaemia has been reported during CAPELODA treatment. Caution must be exercised in patients with pre-existing hypo- or hypercalcaemia (see **"SIDE EFFECTS"**)

Central or peripheral nervous system disease

Caution must be exercised in patients with central or peripheral nervous system disease, e.g. brain metastasis or neuropathy (see **"SIDE EFFECTS"**)

Diabetes mellitus or electrolyte disturbances

Caution must be exercised in patients with diabetes mellitus or electrolyte disturbances, as these

may be aggravated during CAPELODA treatment.

Ophthalmologic complications:

Patients should be carefully monitored for ophthalmological complications such as keratitis and corneal disorders, especially if they have a prior history of eye disorders. Treatment of eye disorders should be initiated as clinically appropriate.

Severe skin reactions:

CAPELODA can induce severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. CAPELODA should be permanently discontinued in patients who experience a severe skin reaction during treatment.

Effects on ability to drive and use machines:

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

Lactose Intolerance:

CAPELODA contains lactose, which may influence the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary problems of galactose tolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take CAPELODA.

INTERACTIONS:

Warfarin:

Altered coagulation parameters and bleeding have occurred in patients taking capecitabine as in CAPELODA concomitantly with warfarin or phenprocoumon (see initial boxed warning).

These reactions occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. Patients taking warfarin concomitantly with capecitabine as in CAPELODA should be monitored regularly

for alterations in their coagulation parameters (PT or INR) and the anticoagulant dose adjusted accordingly.

Phenytoin:

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

Food interaction:

Since current safety and efficacy data are based upon administration with food, it is recommended that CAPELODA be administered with food. Administration with food decreases the rate of capecitabine absorption (see **"Pharmacokinetics"**).

Antacids:

The effect of an aluminium hydroxide and magnesium hydroxide-containing antacid on the pharmacokinetics of capecitabine, as in CAPELODA, 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 maximum tolerated dose (MTD) of capecitabine as in CAPELODA is reduced when it is given with either folinic acid or interferon alfa.

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,

CAPELODA should not be administered with sorivudine or its chemically related analogues, such as brivudine (see **"CONTRAINDICATIONS"**).

There must be at least a 4-week waiting period between end of treatment with sorivudine or its chemically related analogues, such as brivudine, and start of CAPELODA therapy.

Allopurinol:

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

Radiotherapy:

The MTD of CAPELODA alone using the intermittent regimen is 3 000 mg/m2 per day, whereas, when combined with radiotherapy for rectal cancer, the MTD of CAPELODA is 2 000 mg/m2 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 as in CAPELODA or its metabolites, free platinum or total platinum occurred when capecitabine as in CAPELODA 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 as in CAPELODA or its metabolites in the presence of oxaliplatin.

HUMAN REPRODUCTION:

Pregnancy:

CAPELODA is contraindicated in pregnancy (see **"CONTRAINDICATIONS"**).

Woman of childbearing Potential:

As teratogenicity has been demonstrated, women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAPELODA.

If the patient becomes pregnant while receiving CAPELODA, the potential hazard to the foetus must be explained. An effective method of contraception should be used during treatment.

Lactation:

It is not known whether CAPELODA is excreted in human milk. it is recommended that breast-feeding should be discontinued while receiving treatment with CAPELODA.

DOSAGE AND DIRECTIONS FOR USE:

CAPELODA should only be prescribed by a qualified doctor experienced in the utilisation of antineoplastic medicines. CAPELODA tablets should be swallowed with water within 30 minutes after a meal.

Careful monitoring during the first cycle of treatment is recommended for all patients.

Treatment should be discontinued if progressive disease or intolerable toxicity is observed. Standard and reduced dose calculations according to body surface area for starting doses of CAPELODA of 1250 mg/m^2 and 1000 mg/m^2 are provided in tables 1 and 2, respectively.

Adults:

Monotherapy:

Colon, colorectal and breast cancer:

The recommended monotherapy dose of CAPELODA 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 total of 6 months

Combination therapy:

Colorectal and gastric cancer:

In combination treatment, the recommended starting dose of CAPELODA should be reduced to 1000 mg/m^2 when administered twice daily for 14 days followed by a 7-day rest period. For the CAPELODA Dose reduction Schedule, please refer to Table 1. The inclusion of bevacizumab in a combination regimen has no effect on the starting dose of CAPELODA.

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

Breast cancer

In combination with docetaxel for locally advanced or metastatic breast cancer, the recommended dose of CAPELODA 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 professional information should be started prior to docetaxel administration for patients receiving the CAPELODA plus docetaxel combination.

CAPELODA dose is calculated according to body surface area:

Table 1: Standard and reduced dose calculations according to body surface area for starting doses of CAPELODA of 1250 mg/m^2

Dose level 1250 mg/m^2 (twice daily)					
Body Surface Area (m^2)	Full Dose 1250 mg/m^2	Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)		Reduced dose (75 %) 950 mg/m^2	Reduced dose (50 %) 625 mg/m^2
	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤ 1,26	1500	-	3	1150	800
1,27 – 1,38	1650	1	3	1300	800

1,39 – 1,52	1800	2	3	1450	950
1,53 – 1,66	2000	-	4	1500	1000
1,67 – 1,78	2150	1	4	1650	1000
1,79 – 1,92	2300	2	4	1800	1150
1,93 – 2,06	2500	-	5	1950	1300
2,07 – 2,18	2650	1	5	2000	1300
≥ 2,19	2800	2	5	2150	1450

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

Dose level 1000 mg/m^2 (twice daily)					
Body Surface Area (m^2)	Full Dose 1000 mg/m^2	Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)		Reduced dose (75 %) 750 mg/m^2	Reduced dose (50 %) 500 mg/m^2
	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤ 1,26	1150	1	2	800	600
1,27 – 1,38	1300	2	2	1000	600
1,39 – 1,52	1450	3	2	1100	750
1,53 – 1,66	1600	4	2	1200	800
1,67 – 1,78	1750	5	2	1300	800
1,79 – 1,92	1800	2	3	1400	900
1,93 – 2,06	2000	-	4	1500	1000
2,07 – 2,18	2150	1	4	1600	1050
≥ 2,19	2300	2	4	1750	1100

Dose adjustments during treatment:

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

Dosage modification are not recommended for grade 1 events. Therapy with CAPELODA should be interrupted upon the occurrence of Grade 2 or 3 adverse experiences. Once the adverse event has resolved or decreased in intensity to Grade 1, CAPELODA therapy may be re-started 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 be restarted at 50 % of the original dose.

Patients taking CAPELODA should be informed of the need to interrupt treatment immediately if

moderate or severe toxicity occurs. Doses of CAPELODA 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 AND SPECIAL PRECAUTIONS"**.

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

Table 3: CAPELODA 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 medical practitioner deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0 – 1	50 %
2nd appearance	Discontinue treatment permanently	Not applicable

* 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 **"WARNINGS and SPECIAL PRECAUTIONS"**

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 CAPELODA. If unscheduled laboratory assessments during a treatment cycle show that the neutrophil count drops below 1,0 x 10^9/L or that the platelet count drops below 75 x 10^9/L, treatment with capecitabine should be interrupted.

Dose modifications for toxicity when CAPELODA is used as a 3-weekly cycle in combination with other medicinal products:

Dose modifications for toxicity when CAPELODA is used as a 3-weekly cycle in combination with other medicinal products should be made according to table 3 above for CAPELODA and according to the appropriate professional information for the other medicinal product(s).

At the beginning of a treatment cycle, if a treatment delay is indicated for either CAPELODA or the other medicinal product(s), then administration of all therapy should be delayed until the requirements for restarting all medicinal products are met.

During a treatment cycle for those toxicities considered by the treating doctor not to be related to CAPELODA, CAPELODA should be continued and the dose of the other medicinal product should be adjusted according to the appropriate Professional Information.

If the other medicinal product(s) have to be discontinued permanently, CAPELODA treatment can be resumed when the requirements for restarting CAPELODA are met. This advice is applicable to all indications and to all special populations.

Dose modifications for toxicity when CAPELODA is used continuously in combination with other medicinal products:

Dose modifications for toxicity when CAPELODA is used continuously in combination with other medicinal products should be made according to table 3 above for CAPELODA and according to the appropriate professional information for the other medicinal product(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 "**WARNINGS AND SPECIAL PRECAUTIONS**").

Patients with renal impairment:

CAPELODA 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 side effect, 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**", "**WARNING AND SPECIAL PRECAUTIONS**" and "**CONTRAINDICATIONS**").

Children:

Safety and efficacy in children have not been established.

Elderly:

No adjustment of the starting dose is needed for CAPELODA 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 CAPELODA

- 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 CAPELODA plus docetaxel, a starting dose reduction of CAPELODA 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 CAPELODA starting dose in combination with docetaxel, the dose of CAPELODA 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 CAPELODA with irinotecan, a starting dose reduction of CAPELODA to 800 mg/m^2 twice daily is recommended.

SIDE EFFECTS

CAPELODA Monotherapy

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

The following side effects are reported in patients treated with CAPELODA monotherapy used as adjuvant treatment of colon cancer and metastatic colorectal cancer:

Infections and infestations:

Frequent: Herpes simplex or other herpes viral infections, nasopharyngitis, lower respiratory tract infection.

Less frequent: Sepsis, urinary tract infection, cellulitis, tonsillitis, pharyngitis, oral candidiasis, influenza, gastroenteritis, fungal infection, Herpes infection, tooth abscess

Neoplasms benign and malignant (including cysts and polyps):

Less frequent: Lipoma

Blood and lymphatic system disorders:

Frequent: Neutropenia, anaemia

Less frequent: Febrile neutropenia, pancytopenia, granulocytopenia, thrombocytopenia, leukopenia, haemolytic anaemia, International Normalised Ratio (INR) increased/ Prothrombin time prolonged, thromboembolism and bone-marrow depression

Immune system disorders:

Less frequent: Hypersensitivity

Metabolism and nutrition disorders:

Frequent: Anorexia, dehydration, decreased weight

Less frequent: Hypertriglyceridemia, hypokalaemia, diabetes, malnutrition, appetite disorder, hypo- or hypercalcaemia

Psychiatric disorders:

Frequent: Insomnia, depression.

Less frequent: Confusional state, sedation, panic attack, depressed mood, decreased libido

Nervous system disorders:

Frequent: Dysgeusia, dizziness, headache, paraesthesia, lethargy,

Less frequent: Aphasia, memory impairment, ataxia, syncope, balance disorder, sensory disorder, neuropathy peripheral, toxic leukoencephalopathy

encephalopathy

Eye disorders:

Frequent: Conjunctivitis, increased lacrimation, eye irritation

Less frequent: Keratoconjunctivitis, decreased visual acuity, diplopia, lacrimal duct stenosis, corneal disorders, keratitis, punctate keratitis

Ear and labyrinth disorders:

Less frequent: Vertigo, ear pain

Cardiac disorders:

Less frequent: Angina pectoris, unstable angina, myocardial infarction/ ischaemia, tachycardia, arrhythmia, atrial fibrillation, sinus tachycardia, ventricular fibrillation, bradycardia, palpitations, QT prolongation, torsade de pointes, vasospasm, cardiotoxicity without chest pain

Vascular disorders:

Frequent: Thrombophlebitis

Less frequent: Deep vein thrombosis, hypotension, hypertension, hot flushes, petechiae, peripheral coldness

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea, epistaxis, cough, rhinorrhoea.

Less frequent: Asthma, haemoptysis, pulmonary embolism, pneumothorax, exertional dyspnoea

Gastrointestinal disorders:

Frequent: Diarrhoea, stomatitis, vomiting, nausea, abdominal pain, constipation,

upper abdominal pain, dyspepsia, flatulence, dry mouth, loose stools, gastrointestinal haemorrhage,

Less frequent: Oesophagitis, colitis, intestinal obstruction, ascites, enteritis, dysphagia, lower abdominal pain, abdominal discomfort, gastro-oesophageal reflux disease, blood in stool, gastritis

Hepato-biliary disorders:

Frequent: Hyperbilirubinemia, liver function test abnormalities

Less frequent: Jaundice, hepatic failure, cholestatic hepatitis

Skin and subcutaneous tissue disorders:

Frequent Palmar-plantar erythrodysaesthesia syndrome, dermatitis, dry skin, rash, macular rash, erythema, skin hyperpigmentation, nail disorders, pruritus, skin pigmentation disorder, alopecia, skin desquamation.

Less frequent: Photosensitivity reactions, radiation recall syndrome, blister, skin ulcer, Palmer erythema, swelling face, purpura, urticaria, cutaneous lupus erythematosus, severe skin reactions such as Stevens-Johnson Syndrome and toxic Epidermal Necrolysis, vitiligo

Musculoskeletal, connective tissue and bone disorders:

Frequent: Pain in extremity, back pain, arthralgia

Less frequent: Joint swelling, bone pain, facial pain, musculoskeletal stiffness, muscular weakness

Renal and urinary disorders:

Less frequent: Hydronephrosis, urinary incontinence, haematuria, nocturia, increased blood creatinine

Reproductive system and breast disorders:

Less frequent: Vaginal haemorrhage.

General disorders and administration site conditions:

More Frequent: Fatigue, asthenia

Frequent: Lethargy, pyrexia, peripheral oedema, malaise, non-cardiac chest pain

Less frequent: Oedema, chills, influenza-like illness, rigors increased body temperature

Investigations:

Frequent: Decreased Weight decreased, liver function test abnormalities

Less Frequent: Blood in stool, international normalised ratio increased, Blood creatinine increased, body temperature increased

Injury and poisoning:

Less frequent: Blister, overdose

CAPELODA in combination therapy*:*

The side effects associated with CAPELODA monotherapy could also occur when CAPELODA is used in combination with different chemotherapy medicines.

The most common treatment-related side effects of CAPELODA in combination therapy, are as follows

CAPELODA in combination with cisplatin:

The following side-effects are reported in patients treated with CAPELODA in combination with cisplatin in addition to those seen with CAPELODA monotherapy or seen at a higher frequency grouping compared to CAPELODA monotherapy:

Infections and infestations:

Frequent: Herpes zoster, urinary tract infection

Blood and lymphatic system disorders:

Frequent: Neutropenia, leucopenia, anaemia

Less Frequent: Bone marrow depression, thrombocytopenia

Metabolism and nutrition disorders:

Frequent: Hypokalaemia, hyponatraemia

Psychiatric disorders:

Frequent: Sleep disorder

Nervous system disorders:

Frequent: Neuropathy, peripheral sensory neuropathy, hypoaesthesia,

Ear and labyrinth disorders:

Frequent: Tinnitus, hypoacusis

Gastrointestinal disorders:

Frequent: Upper gastrointestinal haemorrhage, mouth ulceration, gastritis,

Hepatobiliary disorders:

Frequent: Abnormal hepatic function

Skin and subcutaneous tissue disorders:

Frequent: Hyperhidrosis

Musculoskeletal, connective tissue and bone disorders:

Frequent: Myalgia

General disorders and administration disorder:

Frequent: Mucosal inflammation

Investigations:

Frequent: Decreased Creatinine renal clearance

CAPELODA in combination with docetaxel:

The following side-effects are reported in patients treated with CAPELODA in combination with docetaxel in addition to those seen with CAPELODA monotherapy or seen at a higher frequency grouping compared to CAPELODA monotherapy:

Infections and infestations:

Frequent: Oral candidiasis

Blood and lymphatic system disorders:

Frequent: Neutropenic fever

Metabolism and nutrition disorders:

Frequent: Decreased appetite

Nervous system disorders:

Frequent: Taste disturbance, paraesthesia, peripheral neuropathy

Eye disorders:

Frequent: Increased lacrimation

Vascular disorders:

Frequent Lower limb oedema

Respiratory, thoracic and mediastinal disorders:

Frequent: Sore throat

Gastrointestinal disorders:

Frequent: Constipation, dyspepsia

Skin and subcutaneous tissue disorders:

Frequent: Alopecia, nail disorder, erythematous rash, nail discolouration, onycholysis

Musculoskeletal, connective tissue and bone disorders:

Frequent: Myalgia, arthralgia

General disorders and administration disorder:

Frequent: Pyrexia, weakness, pain in limb, pain

CAPELODA in combination with oxaliplatin:

The following side-effects are reported in patients treated with CAPELODA in combination with oxaliplatin for the first line and second line treatment of metastatic colorectal cancer, in addition to those seen with CAPELODA monotherapy or seen at a higher frequency grouping compared to CAPELODA monotherapy:

Infections and infestations:

Frequent: Urinary tract infection, upper respiratory tract infection

Blood and lymphatic system disorders:

Frequent: Neutropenia, leukopenia, anaemia, thrombocytopenia

Immune system disorders:

Frequent: Hypersensitivity

Metabolism and nutrition disorders:

Frequent: Hypokalaemia, hypomagnesaemia, hypocalcaemia

Psychiatric disorders:

Frequent: Anxiety

Nervous system disorders:

Frequent: Paraesthesia, dysaesthesia, peripheral neuropathy, peripheral sensory neuropathy, dysgeusia, neurotoxicity, tremor, neuralgia, hypoaesthesia, polyneuropathy

Eye disorders:

Frequent: Visual disturbance, dry eye, blurred vision

Vascular disorders:

Frequent Hypertension, flushing, hypotension.

Respiratory, thoracic and mediastinal disorders:

Frequent: Dysaesthesia pharynx, hiccups, pharyngolaryngeal pain, dysphonia.

Gastrointestinal disorders:

Frequent: Constipation, gastro-oesophageal reflux disease, oral pain, dysphagia, rectal haemorrhage, lower abdominal pain, oral dysaesthesia, abdominal distension

Skin and subcutaneous tissue disorders:

Frequent: Hyperhidrosis, urticaria

Musculoskeletal, connective tissue and bone disorders:

Frequent: Pain in jaw, muscle spasms, myalgia, trismus, muscular weakness.

Renal and urinary disorders:

Frequent: Haematuria

General disorders and administration disorder:

Frequent: Pyrexia, temperature intolerance, chills, chest pain,

CAPELODA in combination with oxaliplatin and bevacizumab:

The following side-effects are reported in patients treated with CAPELODA in combination with oxaliplatin and bevacizumab for the first line treatment of metastatic colorectal cancer, in addition to those seen with CAPELODA monotherapy and CAPELODA in combination with oxaliplatin or seen at a higher frequency grouping compared to CAPELODA monotherapy and CAPELODA in combination with oxaliplatin:

Infections and infestations:

Frequent: Rhinitis, influenza

Blood and lymphatic system disorders:

Frequent: Febrile neutropenia.

Metabolism and nutrition disorders:

Frequent: Hyperglycaemia

Nervous system disorders:

Frequent: Headache

Cardiac disorders:

Frequent: Atrial fibrillation, myocardial ischaemia

Vascular disorders:

Frequent Hypertensive crisis, deep vein thrombosis, hypertension

Respiratory, thoracic and mediastinal disorders:

Frequent: Pulmonary embolism

Gastrointestinal disorders:

Frequent: Gastritis

Skin and subcutaneous tissue disorders:

Frequent: Night sweats

Musculoskeletal, connective tissue and bone disorders:

Frequent: Pain in extremity

Renal and urinary disorders:

Frequent: Proteinuria

General disorders and administration disorder:

Frequent: Pain, Influenza-like illness

Investigations:

Frequent: Increased blood pressure

Injury and poisoning

Frequent: Contusion

CAPELODA in combination with irinotecan:

Side-effects reported in patients treated with CAPELODA in combination with irinotecan, in addition to those seen with CAPELODA monotherapy or seen at a higher frequency grouping compared to CAPELODA monotherapy include:

Frequent, all grades side effects: thrombosis/embolism, hypersensitivity reaction, cardiac ischemia/infarction; *grade 3 and grade 4 side effects:* febrile neutropenia

CAPELODA in combination with irinotecan and bevacizumab:

Grade 3 and grade 4 side effects reported in patients treated with CAPELODA in combination with irinotecan and bevacizumab, in addition to those seen with CAPELODA monotherapy or seen at a higher frequency grouping compared to CAPELODA monotherapy include:

Frequent, grade 3 and grade 4 side effects: neutropenia, thrombosis/embolism hypertension and cardiac ischemia/infarction

CAPELODA in combination with epirubicin and oxaliplatin:

Grade 3 and Grade 4 side-effects reported in patients treated with CAPELODA in combination with epirubicin and oxaliplatin, in addition to those seen with CAPELODA monotherapy or seen at a higher frequency grouping compared to CAPELODA monotherapy include:

Frequent, grade 3 and grade 4 side effects: leukopenia, neutropenia, lethargy, anaemia, thrombocytopenia, febrile neutropenia, peripheral neuropathy, infection, fever, thromboembolism

CAPELODA in combination with epirubicin and cisplatin:

Grade 3 and Grade 4 side-effects reported in patients treated with CAPELODA in combination with epirubicin and cisplatin, in addition to those seen with CAPELODA monotherapy or seen at a higher frequency grouping compared to CAPELODA monotherapy include:

Frequent, grade 3 and grade 4 side effects: leukopenia, neutropenia, anaemia, lethargy, thromboembolism, thrombocytopenia, febrile neutropenia, peripheral neuropathy, infection, fever

Less Frequent side effects: hepatic failure and cholestatic hepatitis

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See **"SIDE EFFECTS AND SPECIAL PRECAUTIONS"**.

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:

CAPELODA 150: Pink-coloured, capsule-shaped, biconvex, film-coated tablet with 150 debossed on one side and plain on the other side.

CAPELODA 500: Pink-coloured, capsule-shaped, biconvex, film-coated tablet with 500 debossed on one side and plain on the other side.

PRESENTATION:

CAPELODA 150: Carton containing 60 film-coated tablets packed in clear PVC/ PVdC film and plain aluminium foil blister strips of 10 tablets each.

CAPELODA 500: Carton containing 120 film-coated tablets packed in clear PVC/ PVdC film and plain aluminium foil blister strips of 10 tablets each.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Keep the tablets in the blister pack and the blisters in the outer carton until required for use.

Do not use after the expiry date stated on the packaging material.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

CAPELODA 150: 47/26/0363

CAPELODA 500: 47/26/0364

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

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