Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CAXETA 150 Film-coated tablets

CAXETA 500 Film-coated tablets

WARNING:

CAXETA-Warfarin Interaction:

Patients receiving concomitant CAXETA 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 CAXETA-warfarin interaction was reported in a clinical pharmacology trial. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking CAXETA concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Post-marketing reports have been reported for clinically significant increases in prothrombin time (PT) and INR in patients who were stabilised on anticoagulants at the time CAXETA was introduced. These events occurred within several days and up to several months after initiating CAXETA therapy and, in a few cases, within one month after stopping CAXETA. These events reported 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.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CAXETA 150

Each film-coated tablet contains 150 mg capecitabine.

Contains sugar: lactose anhydrous 29,526 mg per tablet.

CAXETA 500

Each film-coated tablet contains 500 mg capecitabine.

Contains sugar: lactose anhydrous 143,408 mg per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

CAXETA 150

Light peach coloured, oval shaped, biconvex film-coated tablets debossed with "150" on one side and plain on other side.

CAXETA 500

Peach coloured, oval shaped, biconvex film-coated tablets debossed with "500" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast Cancer

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

Metastatic breast cancer (Monotherapy): **CAXETA** 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: **CAXETA** is indicated as adjuvant treatment after surgery, of patients with Dukes C colon cancer.

Metastatic colorectal cancer: **CAXETA** 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:

CAXETA 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.

4.2 Posology and method of administration

CAXETA should only be prescribed by a qualified medical practitioner experienced in the utilisation of antineoplastic medicines. **CAXETA** tablets is for oral use only and should be swallowed with water within 30 minutes after a meal. **CAXETA** tablets should not be crushed or cut (see section 4.8).Treatment should be discontinued if progressive disease or intolerable toxicity is observed.

Adults

Monotherapy - Colon, colorectal and breast cancer

The recommended monotherapy dose of **CAXETA** is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 14 days followed by a 7 day rest period.

Adjuvant treatment in patients with Stage III colon cancer is recommended for a maximum of six months.

Combination therapy - ***Colorectal and Gastric cancer:***

In combination treatment, the starting dose of **CAXETA** should be reduced to 1000 mg/m^2 when administered twice daily for 14 days followed by a 7 day rest period. For **CAXETA** Dose Reduction Schedule, please refer to Table 1 below.

The inclusion of biological medicines in a combination regimen has no effect on the starting dose of **CAXETA**.

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 **CAXETA** plus cisplatin combination.

Breast Cancer:

In combination with docetaxel for locally advanced or metastatic breast cancer, the recommended dose of **CAXETA** is 1250 mg/m^2 twice daily for 14 days followed by a 7 day rest period, combined with docetaxel at 75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks. Pre-medication with an oral corticosteroid such as

dexamethasone according to the docetaxel prescribing information should be started prior to docetaxel administration for patients receiving the **CAXETA** plus docetaxel combination.

CAXETA 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 **CAXETA** of 1 250 mg/m^2

Table1: 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 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	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 **CAXETA** 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 administration (mg)	**150 mg**	**500 mg**	**Dose per administration (mg)**	**Dose per administration (mg)**
≤1,26	1 150	1	2	800	600
1,27 – 1,38	1 300	2	2	1000	600
1,39 – 1,52	1 450	3	2	1100	750
1,53 – 1,66	1 600	4	2	1200	800
1,67 – 1,78	1 750	5	2	1300	800

1,79 – 1,92	1 800	2	3	1400	900
1,93 – 2,06	2 000	-	4	1500	1 000
2,07 – 2,18	2 150	1	4	1600	1 050
≥2,19	2 300	2	4	1750	1 100

Dose adjustments during treatment

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

Dosage modifications are not recommended for Grade 1 events. Therapy with **CAXETA** should be interrupted upon the occurrence of a Grade 2 or 3 adverse drug reaction (ADR). Once the adverse event has resolved or decreased in intensity to Grade 1, then **CAXETA** therapy may be restarted at full dose or adjusted according to the table below. If a Grade 4 ADR 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 **CAXETA** should be informed of the need to interrupt treatment immediately if moderate or worse toxicity occurs.

Doses of **CAXETA** 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 section 4.8).

The following table shows the recommended dose modifications following toxicity with **CAXETA**.

Table 3: CAXETA dose reduction schedule (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		75 %
-3rd appearance		50 %
-4th appearance	Discontinue treatment permanently	Not applicable
• ***Grade 3***		
-1st appearance	Interrupt until resolved to grade 0-1	75 %
-2nd appearance		50 %
-3rd appearance	Discontinue treatment permanently	Not applicable
• ***Grade 4***		
-1st appearance	Discontinue permanently *or* If 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 permanently	Not applicable

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

For hand-foot syndrome and hyperbilirubinaemia, (see section 4.8).

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 **CAXETA**. If unscheduled laboratory assessments during a treatment cycle reported for grade 3 or 4 haematologic toxicity, treatment with **CAXETA** should be interrupted.

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

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

During a treatment cycle for those toxicities considered by the treating medical practitioner not to be related to **CAXETA**, **CAXETA** should be continued and the dose of the other medicine should be adjusted according to the appropriate prescribing information.

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

Dose modifications for toxicity when CAXETA is used continuously in combination with other medicines:
Dose modifications for toxicity when **CAXETA** is used continuously in combination with other medicines should be made according to Table 3 above for **CAXETA** and according to the appropriate prescribing information for the other a medicine(s).

Special Populations

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 section 4.8).

Renal impairment

CAXETA is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min) (See section 4.3).

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 1250 mg/m^2 is recommended. In patients with moderate renal impairment at baseline, no dose reduction is required for a starting dose of 1000 mg/m^2. In patients with mild renal impairment (creatinine

clearance 51 - 80 mL/min), 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 sections 4.3 and 4.8).

Elderly population

No adjustment of the starting dose is needed for **CAXETA** 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.

When **CAXETA** was used in combination with other antineoplastic medicines, elderly patients (≥ 65 years) experienced more Grade 3 and Grade 4 ADRs and ADRs that led to discontinuation, than younger patients.

Careful monitoring of elderly patients is advisable for treatment with **CAXETA.**

In combination with docetaxel, an increased incidence of grade 3 or 4 treatment-related adverse reactions and treatment-related serious adverse reactions were reported in patients 60 years of age or more.

For patients 60 years of age or more treated with the combination of **CAXETA** plus docetaxel, a starting dose reduction of **CAXETA** to 75 % (950 mg/m^2 twice daily) is recommended. If no toxicity reported in patients ≥ 60 years of age treated with a reduced **CAXETA** starting dose in combination with docetaxel, the dose of **CAXETA** 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 **CAXETA** with irinotecan, a starting dose reduction of **CAXETA** to 800 mg/m^2 twice daily is recommended.

Paediatric population

The safety and efficacy of **CAXETA** for children below 18 years of age have not yet been reported. No reported data available.

4.3 Contraindications

CAXETA is contraindicated in:

- patients with known hypersensitivity to capecitabine or to any of the excipients of **CAXETA** listed in section 6.1;

- 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);
- pregnancy and lactation (see section 4.6).

CAXETA should not be administered with sorivudine or its chemically related analogues, such as brivudine (see Section 4.5).

If contraindications exist for any of the medicines in the combination regimen, that medicine should not be used.

4.4 Special warnings and precautions for use

Patients treated with **CAXETA** 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.

CAXETA-Warfarin interaction – see boxed warning at the beginning of this professional information.

Care should be exercised when **CAXETA** is co-administered with medicines, which are metabolised by cytochrome P450 2C9 such as for example warfarin or phenytoin. Patients receiving concomitant **CAXETA** and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely and the anticoagulant dose adjusted accordingly. Patients taking phenytoin concomitantly with **CAXETA** should be regularly monitored for increased phenytoin plasma concentrations (see section 4.5).

Diarrhoea

CAXETA can induce diarrhoea, which can sometimes be severe. In patients receiving **CAXETA** 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 **CAXETA** should be immediately interrupted until the diarrhoea resolves or decreases in intensity to Grade 1. Following Grade 3 or 4 diarrhoea, subsequent doses of **CAXETA** should be decreased. See Section 4.2 Standard anti-diarrhoeal treatments (e.g. loperamide) need to be instituted immediately. Dose reduction should be applied as necessary (see section 4.2).

Geriatric patients

Careful monitoring of elderly patients is advisable (See section 4).

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 **CAXETA** 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, **CAXETA** treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications applied should be applied for the precipitating adverse event as necessary (See section 4.2).

Hand-foot syndrome:

CAXETA can induce hand-foot syndrome (palmar-plantar erythrodysaesthesia or chemotherapy induced acral erythema) which is a cutaneous toxicity (for patients receiving **CAXETA** 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 **CAXETA** should be interrupted until the event resolves or decreases in intensity to grade 1. Following Grade 3 hand-and-foot syndrome, subsequent doses of **CAXETA** should be decreased (See section 4.2).

Cardiotoxicity

Caution is advised in patients with a history of heart disease.

The spectrum of cardiotoxicity reported with **CAXETA** 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. Cardiac arrhythmias (including ventricular fibrillation, torsade de pointes, and bradycardia), angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving capecitabine. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris (see section 4.8).

Renal insufficiency

CAXETA is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min). Medical practitioners should exercise caution when **CAXETA** is administered to patients with impaired renal function. As reported 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 **CAXETA** monotherapy and **CAXETA** 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 section 4.2 and section 4.3.

The rapid destruction of large numbers of cells during **CAXETA** treatment and the consequent release of breakdown products may also lead to problems with hyperuricaemia and acute renal failure due to uric acid nephropathy (tumour lysis syndrome).

Hyperbilirubinemia

CAXETA can induce hyperbilirubinemia. The risk of hyperbilirubinaemia with concurrent increases in alkaline phosphatase and/or transaminases is higher in patients with mild to moderate hepatic function impairment due

to hepatic metastases. Administration of capecitabine should be interrupted if treatment-related elevations in bilirubin of > 3,0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of > 2,5 x ULN occur. Treatment may be resumed when bilirubin decreases to ≤ 3,0 x ULN or hepatic aminotransferases decreases to ≤ 2,5 x ULN.

Immunosuppression, bone marrow depression and infection:

Immunosuppression and bone marrow depression are features of **CAXETA** and may be associated with an increased risk of infections due to pathogenic or opportunistic microorganisms and the reduced capability to cope with them.

CAXETA should not be given to patients with acute infections and a dose reduction or withdrawal of treatment is recommended if an infection develops and until the infection is controlled.

Great caution is advised in patients with existing bone marrow depression and dosage adjustments is recommended. Patients with existing bone marrow depression or cancer are predisposed to coagulopathy.

Treatment with **CAXETA** can result in anaemia, neutropenia, thrombocytopenia, pancytopenia or thrombocytopenic purpura.

Routine measurements of blood cell counts and haemoglobin concentrations should be done to help prevent the onset of bone marrow depression.

Hepatic insufficiency

Patients with hepatic impairment should be carefully monitored when **CAXETA** is administered. However, the effect of hepatic impairment not due to liver metastases or severe hepatic impairment on the disposition of **CAXETA** is not known. (See section 4.2).

CAXETA has been associated with hepatic failure and cholestatic jaundice.

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 (See Section 4.3). DPD deficiency related toxicity usually occurs during the first cycle treatment or after dose increase.

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

- lacrimal duct stenosis NOS

- hepatic failure and cholestatic hepatitis

Complete DPD deficiency

Complete DPD deficiency is rare (0,01 - 0,5 % of Caucasians). Patients with complete DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated with **CAXETA** (see section 4.3).

Partial DPD deficiency

Partial DPD deficiency is estimated to affect 3 - 9 % of the Caucasian population. Patients with partial DPD deficiency are at increased risk of severe and potentially life-threatening toxicity. A reduced starting dose should be considered to limit this toxicity. DPD deficiency should be considered as a parameter to be taken into account in conjunction with other routine measures for dose reduction. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.

Testing for DPD deficiency

Phenotype and/or genotype testing prior to the initiation of treatment with **CAXETA** is recommended despite uncertainties regarding optimal pre-treatment testing methodologies. Consideration should be given to applicable clinical guidelines.

Genotypic characterisation of DPD deficiency

Pre-treatment testing for rare mutations of the DPYD gene can identify patients with DPD deficiency. The four DPYD variants c.1905+1G>A [also known as DPYD*2A], c.1679T>G [DPYD*13], c.2846A>T and c.1236G>A/HapB3 can cause complete absence or reduction of DPD enzymatic activity. Other rare variants may also be associated with an increased risk of severe or life-threatening toxicity. Certain homozygous and compound heterozygous mutations in the DPYD gene locus (e.g. combinations of the four variants with at least one allele of c.1905+1G>A or c.1679T>G) are known to cause complete or near complete absence of DPD enzymatic activity. Patients with certain heterozygous DPYD variants (including c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants) have increased risk of severe toxicity when treated with fluoropyrimidines. The frequency of the heterozygous c.1905+1G>A genotype in the DPYD gene in Caucasian patients is around 1 %, 1,1 % for c.2846A>T, 2.6-6.3% for c.1236G>A/HapB3 variants and 0,07 to 0,1 % for c.1679T>G. Data on the frequency of the four DPYD variants in other populations than Caucasian is limited. At the present, the four DPYD variants (c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3) are considered virtually absent in populations of African (-American) or Asian origin.

Phenotypic characterisation of DPD deficiency

For phenotypic characterisation of DPD deficiency, the measurement of pre-therapeutic blood levels of the endogenous DPD substrate uracil (U) in plasma is recommended. Elevated pre-treatment uracil concentrations are associated with an increased risk of toxicity. Despite uncertainties on uracil thresholds defining complete and partial DPD deficiency, a blood uracil level ≥ 16 ng/mL and < 150 ng/mL should be considered indicative of partial DPD deficiency and associated with an increased risk for fluoropyrimidine toxicity. A blood uracil level ≥ 150 ng/mL should be considered indicative of complete DPD deficiency and associated with a risk for life-threatening or fatal fluoropyrimidine toxicity.

Dose limiting toxicities

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

Hypo- or hypercalcaemia

Hypo- or hypercalcaemia has been reported during capecitabine treatment. Caution must be exercised in patients with pre-existing hypo- or hypercalcaemia (see section 4.8).

Cytotoxic medication or radiation therapy:

Caution is advised with **CAXETA** treatment in patients who have previously received cytotoxic medication or radiation treatment.

Chicken pox or herpes zoster:

Caution is advised with **CAXETA** in patients who have or recently had chicken pox or herpes zoster infections, as they are at risk of developing generalised disease.

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 section 4.8).

Diabetes mellitus or electrolyte disturbances

Caution must be exercised in patients with diabetes mellitus or electrolyte disturbances, as these may be aggravated during **CAXETA** treatment.

Brivudine and sorivudine

Brivudine or sorivudine must not be administered concomitantly with **CAXETA**. Fatal cases have been reported following this drug interaction. There must be at least a 4-week waiting period between end of treatment with brivudine or sorivudine and start of **CAXETA** therapy. Treatment with brivudine or sorivudine can be started 24 hours after the last dose of **CAXETA** (see sections 4.3 and 4.5). In the event of accidental administration of brivudine or sorivudine to patients being treated with capecitabine, effective measures should be taken to reduce the toxicity of capecitabine. Immediate admission to hospital is recommended. All measures should be initiated to prevent systemic infections and dehydration.

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

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

Elderly:

Elderly patients should be carefully monitored during treatment with **CAXETA**.

Lactose

CAXETA contains lactose. Patients with the rare hereditary problems of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **CAXETA**.

CAXETA tablets should not be crushed or cut. In case of exposure of either patient or caregiver to crushed or cut **CAXETA** tablets adverse drug reactions could occur (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Warfarin

See boxed warning.

Phenytoin

Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin. Dose of phenytoin may need to be reduced with concomitant use. 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 professional information). Patients taking phenytoin concomitantly with **CAXETA** should be regularly monitored for increased phenytoin plasma concentrations.

Food interaction

In all reported clinical trials, patients were instructed to take capecitabine within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that **CAXETA** be administered with food. Administration with food reported to decrease the rate of capecitabine absorption. (See section 5.2).

Antacid

The effect of an aluminium hydroxide and magnesium hydroxide-containing antacid on the pharmacokinetics of capecitabine was reported to be investigated in cancer patients. There was a small increase reported 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).

Sorivudine or brivudine and analogues

A clinically significant interaction between sorivudine or brivudine and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase by sorivudine or brivudine has been described in the literature. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, **CAXETA** should not be administered with sorivudine or its chemically related analogues, such as brivudine. (See section 4.3 and Section 4.4).

There must be at least a 4-week waiting period between end of treatment with brivudine or sorivudine and start of **CAXETA** therapy. Treatment with brivudine can be started 24 hours after the last dose of **CAXETA**.

Allopurinol

Interactions with allopurinol have been reported for 5-FU; with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with **CAXETA** 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 capecitabine was 2000 mg/m^2 per day when combined with interferon alpha-2a (3 MIU/m^2 per day) compared to 3000 mg/m^2 per day when capecitabine was used alone.

Radiotherapy

Additive bone marrow depression can occur, including severe dermatitis and/or mucositis. Dosage reduction is recommended when two or more bone marrow depressants, including radiation therapy, are used concomitantly or consecutively. The MTD of capecitabine alone using the intermittent regimen is 3000 mg/m^2 per day, whereas, when combined with radiotherapy for rectal cancer, the MTD of capecitabine is 2000 mg/m^2 per day using either a continuous schedule or given daily Monday through Friday during a 6-week course of radiotherapy.

Oxaliplatin

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

Bevacizumab

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

Folinic acid / (leucovorin) folic acid

A combination study with capecitabine and folinic acid reported that folinic acid has no major effect on the pharmacokinetics of capecitabine and its metabolites. However, folinic acid has an effect on the pharmacodynamics of capecitabine and its toxicity may be enhanced by folinic acid: the maximum tolerated dose (MTD) of capecitabine alone using the intermittent regimen is 3000 mg/m^2 per day whereas it is only 2000 mg/m^2 per day when capecitabine was combined with folinic acid (30 mg orally bid). The enhanced toxicity may be relevant when switching from 5- FU/LV to a capecitabine regimen. This may also be relevant with folic acid supplementation for folate deficiency due to the similarity between folinic acid and folic acid.

Vaccines:

CAXETA may reduce the response to vaccines and there is a possibility of generalised infection with live vaccines. Use with live vaccines is generally not recommended. An estimation of the interval between the discontinuation of **CAXETA** and restoration of the ability of the patient to respond to a vaccine depends on the intensity of treatment and is estimated to vary from 3 months to 1 year. Vaccination of people in close contact with the patient is also not recommended and should be postponed if possible.

Erlotinib:

Exposure to erlotinib may be increased by concomitant **CAXETA** use.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Female

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

Male

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

Pregnancy

There are no studies in pregnant women using capecitabine; however, it should be assumed that capecitabine may cause foetal harm if administered to pregnant women.

In reproductive toxicity studies in animals, capecitabine administration has been reported to cause embryolethality and teratogenicity. These findings are expected effects of fluoropyrimidine derivatives. **CAXETA** is contraindicated during pregnancy (see section 4.3). If **CAXETA** is used during pregnancy, or if the patient becomes pregnant while receiving **CAXETA**, the patient must be apprised of the potential hazard to the foetus.

Breastfeeding

It is not known whether capecitabine is excreted in human milk. No studies have been reported to assess the impact of capecitabine on milk production or its presence in human breast milk. In lactating mice, considerable amounts of capecitabine and its metabolites were reported to be present in milk.

As the potential for harm to the nursing infant is unknown, breastfeeding should be discontinued while receiving treatment with **CAXETA** and for 2 weeks after the final dose (see section 4.3).

Fertility

There is no reported data on capecitabine and impact on fertility. However, in animal studies effects on fertility were reported.

4.7 Effects on the ability to drive and use machines

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

Patients should be advised not to drive a vehicle or operate machinery until they know how **CAXETA** affects them.

4.8 Undesirable effects

Summary of the safety profile

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

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

Capecitabine Monotherapy:

Table 4 below lists ADRs associated with the use of capecitabine monotherapy.

Table 4: Summary of related ADRs reported in patients treated with capecitabine monotherapy

Body System	**Frequent** ***All grades***	**Less frequent** ***Severe and/or Life-threatening (grade 3-4) or considered medically relevant,***	**Frequency unknown** **Post-marketing Experience**
Infections and infestations	Herpes viral infection, Nasopharyngitis, Lower respiratory tract infection	Sepsis, Urinary tract infection, Cellulitis, Tonsillitis, Pharyngitis, Oral candidiasis, Influenza, Bronchitis, Bronchopneumonia, Pneumonia, Gastroenteritis, Fungal infection, Herpes infection, Infection, Viral infection, Tooth abscess	
Neoplasm benign, malignant and unspecified	-	Lipoma	
Blood and lymphatic system disorders	Neutropenia, Anaemia, Lymphopenia, Thrombocytopenia	Febrile neutropenia, Pancytopenia, Granulocytopenia, Thrombocytopenia, Leukopenia, Haemolytic anaemia, International Normalised Ratio (INR) Increased/Prothrombin time	

		prolonged, Lymphoedema	
Immune system disorders	-	Hypersensitivity, Anaphylaxis	Angioedema (rare)
Metabolism and nutrition disorders	Anorexia, Dehydration, Weight decreased	Diabetes, Hypokalaemia, Appetite disorder, Malnutrition, , Hypomagnesaemia, Cachexia, Thirst	Hypertriglyceridaemia
Psychiatric disorders	Insomnia, Depression	Confusional state, Panic attack, Depressed mood, Libido decreased, Dysarthria, Hoarseness, Irritability	
Nervous system disorders	Headache, Lethargy, Dizziness, Parasthesia, Dysgeusia	Aphasia, Memory impairment, Ataxia, Syncope, Balance disorder, Sensory disorder, Neuropathy peripheral, Cerebrovascular incident, Encephalopathy, Loss of consciousness, Abnormal coordination, Sedation, Tremor, Difficulty walking	Toxic leukoencephalopathy
Eye disorders	Lacrimation increased, Conjunctivitis, Eye irritation	Visual acuity reduced, Diplopia, Keratoconjunctivitis, Ocular toxicity, Dacryostenosis, Photophobia	Lacrimal duct stenosis, Corneal disorders including keratitis and punctate keratitis
Ear and labyrinth	-	Vertigo, Ear pain	

disorders			
Cardiac disorders	-	Angina unstable, Angina pectoris, Myocardial ischaemia/infarction, Atrial fibrillation, Dysrythmia, Tachycardia, Sinus tachycardia, Palpitations, Cardiomyopathy, Cardiotoxicity, Extrasystoles, Myocarditis, Ventricular extrasystoles, Pericardial effusion, Chest pain, Electrocardiogram (ECG) changes	Ventricular fibrillation, QT prolongation, Torsade de pointes, Bradycardia, Vasospasm
Vascular disorders	Thrombophlebitis, Epistaxis	Deep vein thrombosis, Hypertension, Petechiae, Hypotension, Hot flush, Peripheral coldness, Coagulation disorder, Collapse, Haemorrhage	
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Epistaxis, Cough, Rhinorrhoea, Nasopharyngitis	Tonsillitis, Pharyngitis, Pulmonary embolism, Pneumothorax, Haemoptysis, Asthma, Dyspnoea exertional, Exertional dyspnoea, Bronchospasm, Respiratory	

		distress, Laryngitis	
Gastrointestinal disorders	Diarrhoea, Vomiting, Nausea, Stomatitis, Abdominal pain, Gastrointestinal haemorrhage, Constipation, Upper abdominal pain, Dyspepsia, Flatulence, Dry mouth, Loose stools	Gastroenteritis, Intestinal obstruction, Ascites, Enteritis, Gastritis, Dysphagia, Abdominal pain lower, Oesophagitis, Abdominal discomfort, Gastro-oesophageal reflux disease, Colitis, Blood in stool, Gastric ulcer, Gastrointestinal tract toxicity, Ileus, Toxic dilation of intestines, Abdominal distension, Gastrointestinal motility disorder, Proctalgia, Mucositis, Oral ulceration	
Hepatobiliary disorders	Hyperbilirubinemia, Liver function test abnormalities	Jaundice, Hepatic fibrosis, Hepatitis	Hepatic failure, Cholestatic hepatitis
Skin and subcutaneous tissue disorders	Palmar-plantar erythro-dysaesthesia syndrome**, Rash, Alopecia, Erythema, Dry skin, Pruritus, Skin hyper-pigmentation, Rash macular, Skin desquamation, Dermatitis, Pigmentation disorder, Nail disorder	Petechiae, Blister, Skin ulcer, Rash, Urticaria, Photosensitivity reaction, Palmar erythema, Swelling face, Purpura, Radiation recall syndrome, Increased sweating, Erythema multiforme	Cutaneous lupus erythematosus, Severe skin reactions such as Stevens-Johnson Syndrome and toxic Epidermal Necrolysis

Muskuloskeletal and connective tissue disorders	Pain in extremity, Back pain, Arthralgia	Joint swelling, Bone pain, Facial pain, Musculoskeletal stiffness, Muscular weakness, Arthritis, Myalgia	
Renal and urinary disorders	-	Urinary tract infection, Hydronephrosis, Urinary incontinence, Haematuria, Nocturia, Renal impairment, Blood creatinine increased	Acute renal failure secondary to dehydration
Reproductive system and breast disorders	-	Decreased libido, Vaginal haemorrhage	
General disorders and administration site conditions	Lethargy, Fatigue, Asthenia, Pyrexia, Oedema peripheral, Malaise, Non-cardiac Chest pain	Oedema, Chills, Influenza like illness, Rigors, Body temperature increased, Chest mass, Fibrosis	
Investigations	Decreased weight, Liver function test abnormalities, Decreased haemoglobin	Blood in stools, Increased INR, Increased blood creatinine, Increased body temperature, Increased weight	
Injury and poisoning		Blister, Overdose, radiation recall syndrome	
Post-marketing experience			

** Based on the post-marketing experience, persistent or severe palmar-plantar erythrodysaesthesia syndrome can eventually lead to loss of fingerprints.

Laboratory abnormalities reported with capecitabine monotherapy

Table below lists laboratory abnormalities of all grades reported with capecitabine monotherapy in 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 reported safety data from these major clinical studies in colorectal cancer.

Table 5: Laboratory abnormalities reported in patients treated with capecitabine mono-therapy

Grade of Abnormality	**Frequent**	**Less frequent**
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)

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)

Capecitabine in combination therapy

Table below lists adverse drug reactions (ADRs) associated with the use of capecitabine in combination with different chemotherapy regimens in multiple indications based on reported safety data from patients. ADRs are added to the appropriate frequency grouping (frequent and less frequent) according to the highest incidence reported in any of the major clinical trials and are only added when they were reported **in addition to** those reported with capecitabine monotherapy or reported at **a higher frequency grouping** compared to capecitabine monotherapy (see table above). Less frequent ADRs reported for capecitabine in combination therapy are consistent with the ADRs reported for capecitabine monotherapy or reported for monotherapy with the combination medicinal product (in literature and/or respective package inserts).

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

Table 6: Summary of related ADRs reported in patients treated with capecitabine in combination treatment in addition to those reported with capecitabine monotherapy or reported at a higher frequency grouping compared to capecitabine monotherapy.

Body System	**Frequent** ***All grades***	**Less frequent** **(Post-Marketing Experience)**
Infections and infestations	Herpes zoster, Urinary tract infection, Oral candidiasis, Upper respiratory tract infection, Rhinitis, Influenza, [+]Infection, Oral herpes	
Blood and lymphatic system disorders	[+]Neutropenia, [+]Leucopenia, [+]Anaemia, [+]Neutropenic fever, Thrombocytopenia, Bone marrow depression, [+]Febrile Neutropenia	
Immune system disorders	Hypersensitivity	
Metabolism and nutrition disorders	Appetite decreased, Hypokalaemia, Hyponatraemia, Hypomagnesaemia, Hypocalcaemia, Hyperglycaemia	
Psychiatric disorders	Sleep disorder, Anxiety	
Nervous system disorders	Paraesthesia, Dysaesthesia, Peripheral neuropathy, Peripheral sensory neuropathy, Dysgeusia, Headache, Neurotoxicity, Tremor, Neuralgia, Hypersensitivity reaction, Hypoaesthesia, Taste disturbance, Neuropathy, Polyneuropathy	
Eye disorders	Lacrimation increased, Visual disorders, Dry eye, Eye pain, Visual impairment, Vision blurred	
Ear and labyrinth disorders	Tinnitus, Hypoacusis	

Cardiac disorders	Atrial fibrillation, Cardiac ischaemia/infarction	
Vascular disorders	Lower limb oedema, Hypertension, [+]Embolism and thrombosis, Flushing, Hypotension, Hypertensive crisis, Hot flush, Phlebitis	
Respiratory, thoracic and mediastinal system disorders	Sore throat, Dysaesthesia pharynx, Hiccups, Pharyngolaryngeal pain, Dysphonia, Pulmonary embolism	
Gastrointestinal disorders	Constipation, Dyspepsia, Upper gastrointestinal haemorrhage, Mouth ulceration, Gastritis, Abdominal distension, Gastro-esophageal reflux disease, Oral pain, Dysphagia, Rectal haemorrhage, Abdominal pain lower, Oral dysaesthesia, Paraesthesia oral, Hypoaesthesia oral, Abdominal discomfort	
Hepatobiliary disorders	Hepatic function abnormal	
Skin and subcutaneous tissue disorders	Alopecia, Nail disorder, Hyperhydrosis, Rash erythematous, Urticaria, Night sweats, Palmar-plantar erythrodysaesthesia, Mucosal inflammation, Nail discolouration, Onycholysis	
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia, Pain in extremity, Pain in jaw , Muscle spasms, Trismus, Muscular weakness	
Renal and urinary disorder	Haematuria, Proteinuria, Creatinine renal	Acute renal failure secondary to

	clearance decreased, Dysuria	dehydration (rare)
General disorders and administration site conditions	Pyrexia, Weakness, +Lethargy, Temperature intolerance, Mucosal inflammation, Pain in limb, Pain, Chills, Chest pain, Influenza-like illness, +Fever, Infusion related reaction, Injection site reaction, Infusion site pain, Injection site pain	
Injury, poisoning and procedural complications	Contusion	
Investigations	Creatinine renal clearance decreased, Blood pressure increased	

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

Description of selected adverse reactions

Hand-foot syndrome (see section 4.4):

In all reported studies combined, the following covariates were statistically significantly associated with an increased risk of developing HFS: increasing capecitabine starting dose (gram), decreasing cumulative capecitabine dose (0,1*kg), increasing relative dose intensity in the first six weeks, increasing duration of study treatment (weeks), increasing age (by 10-year increments), female gender, and good ECOG performance status at baseline (0 versus ≥1).

Diarrhoea (see section 4.4):

In all reported studies combined, the following covariates were statistically significantly associated with an increased risk of developing diarrhoea: increasing capecitabine starting dose (gram), increasing duration of study treatment (weeks), increasing age (by 10 year increments), and female gender. The following covariates were statistically significantly reported to be associated with a decreased risk of developing diarrhoea:

increasing cumulative capecitabine dose (0,1*kg) and increasing relative dose intensity in the first six weeks.

Cardiotoxicity (see section 4.4):

In addition to the ADRs in above tables, the following ADRs with an incidence of less than 0,1 % were reported to be associated with the use of capecitabine monotherapy: cardiomyopathy, cardiac failure, sudden death, and ventricular extrasystoles.

Encephalopathy:

In addition to the ADRs in tables above, encephalopathy was also reported to be associated with the use of capecitabine monotherapy with an incidence of less than 0,1 %.

*Exposure to crushed or cut **CAXETA** tablets:*

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

Special populations

Elderly patients (see section 4.2):

Patients ≥ 60 years of age treated with capecitabine monotherapy and patients treated with capecitabine plus docetaxel combination therapy reported for an increase in the incidence of treatment-related grade 3 and 4 adverse reactions and treatment-related serious adverse reactions compared to patients < 60 years of age. Patients ≥ 60 years of age treated with capecitabine plus docetaxel also had more early withdrawals from treatment due to adverse reactions compared to patients < 60 years of age.

Increasing age (by 10 year increments) was statistically significantly reported to be associated with an increased risk of developing HFS and diarrhoea and with a decreased risk of developing neutropenia.

Gender

Female gender was statistically significantly reported to be associated with an increased risk of developing HFS and diarrhoea and with a decreased risk of developing neutropenia.

Patients with renal impairment (see section 4.2):

Patients treated with capecitabine monotherapy (colorectal cancer) with baseline renal impairment reported for an increase in the incidence of treatment-related grade 3 and 4 adverse reactions compared to patients with normal renal function (36 % in patients without renal impairment vs. 41 % in mild).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of **CAXETA**. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via email: pharmacovigilance.africasme@sunpharma.com or tel: +27(0) 12 643 2000.

4.9 Overdose

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. Dialysis may be effective to remove circulating 5'-DFUR, the metabolite that is the immediate precursor of fluorouracil.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A26 cytostatic (antimetabolite).

ATC code: L01BC06.

Mechanism of Action:

Capecitabine is a fluoropyrimidine carbamate and is an orally administered, tumour-activated prodrug cytotoxic medicine. Capecitabine is non-cytotoxic *in vitro.* However, *in vivo,* it is sequentially converted to the cytotoxic moiety, 5-fluorouracil (5-FU), which is further metabolised. Formation of 5-FU is catalysed preferentially at the

tumour site by the tumour associated angiogenic factor thymidine phosphorylase (dThdPase). 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 reported to be present in tumour tissues, but also in normal tissues, albeit usually at lower levels. In human cancer xenograft models capecitabine was reported a synergistic effect in combination with docetaxel, which may be related to the up-regulation 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 reported 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.

5.2 Pharmacokinetic properties

The pharmacokinetics of capecitabine have been reported over a dose range of 502 – 3514 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 reported to be similar. The reported 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 reported to be extensively converted to the metabolites 5'-deoxy-5 - fluorocytidine (5'-DFCR) and 5'-deoxy-5-fluorouridine (5 '-DFUR). Administration with food reported to decrease the rate of capecitabine absorption, but only results in a minor effect on the AUC of 5'-DFUR and on the AUC of the subsequent metabolite 5-FU.

At the dose of 1250 mg/m^2 on day 14 with administration after food intake, the reported 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 reported time to peak plasma concentrations (T_{max} in hours) were 1,50, 2,00, 2,00, 2,00 and 3,34. The reported $AUC_{0-\infty}$ 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 reported 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 reported to be 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 reported preferentially at the tumor site by the tumour associated angiogenic factor dThdPase.

The metabolites of capecitabine have been repoted to become cytotoxic after conversion to 5-FU and anabolites of 5-FU. 5-FU is further catabolised to the inactive metabolites dihydro-5-fluoruracil (FUH2), 5-fluoro-ureidopropionic acid (FUPA) and α-fluoro-β-alanine (FBAL) via dihydropyrimidine dehydrogenase (DPD), which is rate limiting.

Elimination

The reported 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 reported over a dose range of 502 – 3514 mg/m^2/day. The parameters of capecitabine, 5'-DFCR and 5'-DFUR reported on days 1 and 14 were similar. The AUC of 5-FU was reported to be 30 - 35 % higher on day 14, but did not increase subsequently (day 22). At therapeutic doses, the pharmacokinetics of capecitabine and its metabolites were reported to be dose proportional; except for 5-FU. After oral administration capecitabine metabolites are primarily

reported to be recovered in the urine. 95,5 % of administered capecitabine dose is reported to be recovered in urine. Faecal excretion is reported to be minimal (2,6 %). The major metabolite reported to be excreted in urine is FBAL, which represents 57 % of the administered dose. About 3 % of the administered dose is reported to be excreted in urine as unchanged active ingredient, capecitabine. The reported interpatient variability in C_{max} and AUC of 5-FU was greater than 85 %.

Combination therapy

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

Pharmacokinetics in special populations:

Gender, presence or absence of liver metastasis at baseline, Karnofsky Performance Status, total bilirubin, serum albumin, ASAT and ALAT had not been reported for 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 reported in cancer patients with mildly to moderately impaired liver function due to liver metastases. There are no pharmacokinetic data reported in patients with severe hepatic impairment (See Section 4.3).

Patients with renal impairment

Based on a pharmacokinetic study in cancer patients with mild to severe renal impairment, there is no reported evidence of an effect of creatinine clearance on the pharmacokinetics of intact active ingredient, capecitabine, and 5-FU. Creatinine clearance was reported 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 section 4.3).

Elderly

Based on the population pharmacokinetic analysis, which included patients with a wide range of ages (27 to 86 years) and included patients greater or equal to 65, age no influence on the pharmacokinetics of 5'-DFUA and 5-

FU have been reported. The AUC of FBAL is reported to be 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.

Ethnic factors

Following oral administration of 825 mg/m^2 capecitabine twice daily for 14 days, in Japanese patients about 36 % lower C_{max} and 24 % lower AUC for capecitabine have been reported in comparison to Caucasian patients. Japanese patients had also about 25% lower C_{max} and 34 % lower AUC have been reported for FBAL in comparison to Caucasian patients. The clinical relevance of these differences is reported to be unknown. No significant differences in the exposure to other metabolites (5'-DFCR, 5'-DFUR, and 5-FU) have been reported.

5.3 Preclinical safety data

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

No evidence of carcinogenicity by capecitabine have been reported in a two-year mouse carcinogenicity study.

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

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

Capecitabine was not reported to be mutagenic *in vitro* to bacteria (Ames test) or mammalian cells (Chinese hamster V79/HPRT gene mutation assay). However, similar to other nucleoside analogues (i.e., 5-FU),

capecitabine was clastogenic in human lymphocytes (*in vitro*) and a positive trend have been reported in mouse bone marrow micronucleus tests (*in vivo*).

6. Pharmaceutical particulars

6.1 List of excipients

Croscarmellose sodium, hypromellose, lactose anhydrous, microcrystalline cellulose, magnesium stearate, opadry II pink 30F540003 (150 mg), opadry II orange 30F530001 (500 mg), purified water, and talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in the original package until required for use.

6.5 Nature and contents of container

CAXETA 150:

Blister Pack 60's: 6 blisters of 10 tablets packaged in the Aluminum/Aluminum blister consists of Triple Layer laminate made up of 25 OPA/45 AL/ 60 PVC forming material film and Push through aluminum foil with 6-8 g heat seal lacquer lidding foil.

Bottle Pack 60's: 60 Tablets packaged in 30 mL HDPE bottles, closed with 33 mm child resistant polypropylene caps (CRC) with FS5-4 induction liner, one 2 g silica gel canister is kept in each bottle.

CAXETA 500:

Blister Pack 120's: 12 blisters of 10 tablets packaged in the Aluminum/Aluminum blister consists of Triple Layer laminate made up of 25 OPA/45 AL/ 60 PVC forming material film and Push through aluminum foil with 6-8 g heat seal lacquer lidding foil.

Bottle Pack 120's: 120 Tablets packaged in 150 mL HDPE bottles, closed with 38 mm child resistant polypropylene caps (CRC) with FS5-4 induction liner, two 2 g silica gel canisters are kept in each bottle.

6.6 Special precautions for disposal and other handling

Procedures for safe handling and disposal of cytotoxic medicines should be followed.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road, Stormill, Ext.1,

Roodepoort, 1724

South Africa

Tel: +27(0) 12 643 2000

8. Marketing authorisation number(s)

CAXETA 150: 47/26/1287

CAXETA 500: 47/26/1288

9. Date of first authorisation/renewal of the authorisation

16 February 2021

10. Date of revision of the text

17 February 2026