Proposed professional information for CAPCITURAS 150 mg and 500 mg

WARNING

Patients receiving concomitant capecitabine and oral coumarin derivative anticoagulant therapy should have their anticoagulant response (international normalised ration [INR] or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important capecitabine-warfarin interaction was demonstrated in a clinical pharmacology trial. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine 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 was introduced. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. These events occurred in patients with and without liver metastases. Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy.

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CAPCITURAS 150 mg film-coated tablets

CAPCITURAS 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Excipients with known effect:

Contains sugar.

CAPCITURAS 150 mg: Each film-coated tablet contains 7,5 mg anhydrous lactose.

CAPCITURAS 500 mg: Each film-coated tablet contains 25,0 mg anhydrous lactose.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

CAPCITURAS 150 mg: Light pink coloured, capsule shaped, biconvex film-coated tablet debossed with CAP on one side and 150 on the other side.

CAPCITURAS 500 mg: Dark pink coloured, capsule shaped, biconvex film coated tablet debossed with CAP on one side and 500 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast Cancer

Metastatic breast cancer (combination therapy): CAPCITURAS 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): CAPCITURAS 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: CAPCITURAS is indicated as adjuvant treatment after surgery, of patients with Dukes C colon cancer.

Metastatic colorectal cancer: CAPCITURAS 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: CAPCITURAS 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

CAPCITURAS should only be prescribed by a qualified medical practitioner experienced in the utilisation of antineoplastic medicines. Treatment should be discontinued if progressive disease or intolerable toxicity is observed.

Posology:

Adults

Monotherapy - colon, colorectal and breast cancer

The recommended monotherapy dose of CAPCITURAS is 1 250 mg/m^2 administered twice daily (morning and evening; equivalent to 2 500 mg/m^2 total daily dose) for 14 days followed by a 7-day rest period.

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

Combination therapy

Colorectal and gastric cancer: In combination treatment, the starting dose of CAPCITURAS should be reduced to 1 000 mg/m^2 when administered twice daily for 14 days followed by a 7-day rest period.

For the CAPCITURAS Dose Reduction Schedule, please refer to Table 1.

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

Premedication to maintain adequate hydration and anti-emesis according to the cisplatin professional information (PI) should be started prior to cisplatin administration for patients receiving the CAPCITURAS plus cisplatin combination.

Breast cancer: In combination with docetaxel for locally advanced or metastatic breast cancer, the recommended dose of CAPCITURAS 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. Premedication with an oral corticosteroid, such as dexamethasone according to the docetaxel professional information, should be started prior to docetaxel administration for patients receiving the CAPCITURAS plus docetaxel combination.

CAPCITURAS dose is calculated according to body surface area (BSA).

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

Table 1: Dose level 1 250 mg/m^2 (twice daily)					
Body Surface Area (m^2)	**Full dose 1 250 mg/m^2**	**Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be 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 CAPCITURAS 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	1 000	600
1,39 – 1,52	1 450	3	2	1 100	750
1,53 – 1,66	1 600	4	2	1 200	800
1,67 – 1,78	1 750	5	2	1 300	800
1,79 – 1,92	1 800	2	3	1 400	900
1,93 – 2,06	2 000	-	4	1 500	1 000
2,07 – 2,18	2 150	1	4	1 600	1 050
≥ 2,19	2 300	2	4	1 750	1 100

Dose adjustments during treatment

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

Dosage modifications are not recommended for grade 1 events. Therapy with CAPCITURAS should be interrupted upon the occurrence of a grade 2 or 3 adverse experience. Once the adverse event has resolved or decreased in intensity to grade 1, then CAPCITURAS therapy may be restarted at full dose or adjusted according to the table below. If a grade 4 experience occurs, therapy should be discontinued or interrupted until resolved or decreased to grade 1, and therapy can then be restarted at 50 % of the original dose.
Patients taking CAPCITURAS should be informed of the need to interrupt treatment immediately if moderate or worse toxicity occurs.

Doses of CAPCITURAS 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 CAPCITURAS.

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

Toxicity **NCIC grades***	**Dose changes within a treatment cycle**	**Dose adjustment for next cycle/dose (% of starting dose)**
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to grade 0 – 1	100 %
2nd appearance	Interrupt until resolved to grade 0 – 1	75 %

3rd appearance	Interrupt until resolved to grade 0 – 1	50 %
4th appearance	Discontinue treatment permanently	
Grade 3		
1st appearance	Interrupt until resolved to grade 0 – 1	75 %
2nd appearance	Interrupt until resolved to grade 0 – 1	50 %
3rd appearance	Discontinue treatment permanently	
Grade 4		
1st appearance	Discontinue permanently *or* If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0 – 1	50 %
2nd appearance	Discontinue treatment permanently	

*According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) Common Toxicity Criteria (version 1) or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 3.0. For hand-foot syndrome and hyperbilirubinaemia, see section 4.8.

Haematology:

Patients with baseline neutrophil counts of < 1,5 x 109/L and/or thrombocyte counts of < 100 x 109/L should not be treated with CAPCITURAS. If unscheduled laboratory assessments during a treatment cycle show grade 3 or 4 haematologic toxicity, treatment with CAPCITURAS should be interrupted.

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

At the beginning of a treatment cycle, if a treatment delay is indicated for either CAPCITURAS 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 physician not to be related to CAPCITURAS, CAPCITURAS should be continued and the dose of the other medicine should be adjusted according to the appropriate professional information.

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

Dose modifications for toxicity when CAPCITURAS is used continuously in combination with other medicines: Dose modifications for toxicity when CAPCITURAS is used continuously in combination with other medicines should be made according to Table 3 above for CAPCITURAS and according to the appropriate professional information for the other medicine(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 section 4.8.

Patients with renal impairment

CAPCITURAS 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 1 250 mg/m^2 is recommended. In patients with moderate renal impairment at baseline, no dose reduction is required for a starting dose of 1 000 mg/m^2. In patients with mild renal impairment (creatinine clearance 51 –80 mL/min), no adjustment

in starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3 or 4 adverse event, with subsequent dose adjustment as outlined in the table above. The dose adjustment recommendations for patients with moderate renal impairment apply both to monotherapy and combination use. See sections 4.3 and 5.2.

Elderly

No adjustment of the starting dose is needed for CAPCITURAS 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 CAPCITURAS:

- 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 CAPCITURAS plus docetaxel, a starting dose reduction of CAPCITURAS 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 CAPCITURAS starting dose in combination with docetaxel, the dose of CAPCITURAS 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 CAPCITURAS with irinotecan, a starting dose reduction of CAPCITURAS to 800 mg/m2 twice daily is recommended.

Children

Safety and efficacy in children have not been established.

Method of administration

CAPCITURAS tablets should be swallowed with water within 30 minutes after a meal.

4.3 Contraindications

CAPCITURAS is contraindicated in:

- Hypersensitivity to capecitabine or to any of the excipients (see section 6.1).
- A history of severe and unexpected reactions to fluoropyrimidine therapy, or with known hypersensitivity to fluorouracil (capecitabine metabolite).
- Known dihydropyrimidine dehydrogenase (DPD) deficiency.
- Severe leukopenia, neutropenia, or thrombocytopenia.
- Severe hepatic impairment.
- Severe renal impairment (creatinine clearance below 30 mL/min).
- Co-administration with sorivudine or its chemically related analogues, such as brivudine (see section 4.5).
- Pregnancy and lactation.

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

Dose limiting toxicities

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.

Diarrhoea

CAPCITURAS can induce diarrhoea, which can sometimes be severe. In patients receiving capecitabine 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 4,5 days. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. 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 CAPCITURAS should be immediately interrupted until the diarrhoea resolves or decreases in intensity to grade 1. Following grade 3 or 4 diarrhoea, subsequent doses of CAPCITURAS should be decreased (see section 4.2).

Standard antidiarrhoeal treatments (e.g. loperamide) need to be instituted immediately.

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 CAPCITURAS is given concomitantly with known nephrotoxic medicines. Acute renal failure secondary to dehydration might be potentially fatal. If grade 2 (or higher) dehydration occurs, CAPCITURAS 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

CAPCITURAS can induce hand-foot syndrome (also known as hand-foot skin reaction or palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema). Grade 1 hand- foot syndrome is defined as numbness, dysesthesia/paraesthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt the patient's normal activities.

Grade 2 hand-foot syndrome is painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living.

Grade 3 hand-foot syndrome is moist desquamation, ulceration, blistering and severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. Persistent or severe hand-foot syndrome (grade 2 and above) can eventually lead to loss of fingerprints which could impact patient identification. If grade 2 or 3 hand-foot syndrome occurs, administration of CAPCITURAS should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-foot syndrome, subsequent doses of CAPCITURAS should be decreased (see section 4.2). When CAPCITURAS 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 CAPCITURAS.

Cardiotoxicity

Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias (including ventricular fibrillation, torsades de pointes and bradycardia), heart failure and cardiomyopathy, cardiogenic shock, sudden death and electrocardiographic changes (including very rare cases of QT prolongation). These adverse reactions may be more common in patients with a prior history of coronary artery disease. Caution must be exercised in patients with history of significant cardiac disease, dysrhythmias and angina pectoris (see section 4.8).

Hypo- or hypercalcaemia

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

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 CAPCITURAS treatment.

Coumarin-derivative anticoagulation

Patients receiving concomitant CAPCITURAS and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely and the anticoagulant dose adjusted accordingly (see section 4.5).

Brivudine

Brivudine must not be administered concomitantly with CAPCITURAS. Fatal cases have been reported following this medicine interaction. There must be at least a 4-week waiting period between end of treatment with brivudine and start of CAPCITURAS therapy. Treatment with brivudine can be started 24 hours after the last dose of CAPCITURAS (see section 4.3 and 4.5). In the event of accidental administration of brivudine to patients being treated with CAPCITURAS, 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.

Hepatic impairment

Patients with hepatic impairment should be carefully monitored when CAPCITURAS is administered. However, the effect of hepatic impairment not due to liver metastases or severe hepatic impairment on the disposition of CAPCITURAS is not known. See section 4.2.
CAPCITURAS can induce hyperbilirubinemia. Administration of CAPCITURAS should be interrupted if treatment-related elevations in bilirubin of > 3,0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of > 2,5 x ULN occur. Treatment with CAPCITURAS monotherapy may be resumed when bilirubin decreases to ≤ 3,0 x ULN or hepatic aminotransferases decrease to ≤ 2,5 x ULN.

Renal impairment

CAPCITURAS is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min). Medical practitioners should exercise caution when CAPCITURAS is administered to patients with impaired renal function. As seen with 5-fluorouracil (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 CAPCITURAS monotherapy and CAPCITURAS 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. See sections 4.3 and section 5.2.

Dihydropyrimidine dehydrogenase (DPD) deficiency

DPD activity is rate limiting in the catabolism of 5-fluorouracil (see section 5.2). Patients with DPD deficiency are therefore at increased risk of fluoropyrimidines-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. DPD-deficiency related toxicity usually occurs during the first cycle of treatment or after dose increase.

- Patients with DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated with CAPCITURAS (see section 4.3).

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 initiated as clinically appropriate.

Severe skin reactions

CAPCITURAS can induce severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. CAPCITURAS should be permanently discontinued in patients who experience a severe skin reaction during treatment.

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

CAPCITURAS contains lactose

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

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Sorivudine and analogues

A clinically significant interaction between brivudine and fluoropyrimidines (e.g. capecitabine, 5-Fluorouracil, tegafur), resulting from the inhibition of dihydropyrimidine dehydrogenase by brivudine, has been described. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, CAPCITURAS should not be administered with sorivudine or its chemically related analogues, such as brivudine (see section 4.3 and 4.4). There must be at least a 4-week waiting period between end of treatment with brivudine and start of CAPCITURAS therapy. Treatment with brivudine can be started 24 hours after the last dose of CAPCITURAS.

Cytochrome (CYP) P450 2C9 substrates

Other than warfarin, no formal interaction studies between capecitabine and other CYP2C9 substrates have been conducted. Care should be exercised when CAPCITURAS is co-administered with 2C9 substrates (e.g. phenytoin). See also interaction with coumarin-derivative anticoagulants below, and section 4.4.

Coumarin-derivative anticoagulants

Altered coagulation parameters and/or bleeding have been reported in patients taking CAPCITURAS concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These reactions occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. In a clinical pharmacokinetic interaction study, after a single 20 mg dose of warfarin, capecitabine treatment increased the area under the curve (AUC) of S-warfarin by 57 % with a 91 % increase in INR value. Since metabolism of R-warfarin was not affected, these results indicate that CAPCITURAS down-regulates isozyme 2C9, but has no effect on isozymes 1A2 and 3A4. Patients taking coumarin-derivative anticoagulants concomitantly with CAPCITURAS should be monitored regularly for alterations in their coagulation parameters (prothrombin time 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 CAPCITURAS with phenytoin. Patients taking phenytoin concomitantly with CAPCITURAS should be regularly monitored for increased phenytoin plasma concentrations.

Folinic acid (leucovorin)

A combination study with capecitabine and folinic acid indicated that folinic acid has no major effect on the pharmacokinetics of CAPCITURAS and its metabolites. However, folinic acid has an effect on the pharmacodynamics of CAPCITURAS and its toxicity may be enhanced by folinic acid: the maximum tolerated dose (MTD) of capecitabine alone using the intermittent regimen is 3 000 mg/m^2 per day whereas it is only 2 000 mg/m^2 per day when CAPCITURAS 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.

Antacid

The effect of an aluminium hydroxide and magnesium hydroxide-containing antacid on the pharmacokinetics of CAPCITURAS 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).

Allopurinol

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

Interferon alpha

The (maximum tolerated dose) MTD of capecitabine was 2 000 mg/m^2 per day when combined with interferon alpha-2a (3 MIU/m^2 per day) compared to 3 000 mg/m^2 per day when CAPCITURAS was used alone.

Radiotherapy

The MTD of CAPCITURAS alone using the intermittent regimen is 3 000 mg/m^2 per day, whereas, when combined with radiotherapy for rectal cancer, the MTD of CAPCITURAS is 2 000 mg/m^2 per day using either a continuous schedule or given daily Monday through Friday during a 6-week course of radiotherapy.

Oxaliplatin

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

Bevacizumab

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

Food interaction

Since current safety and efficacy data are based upon administration with food, it is recommended that CAPCITURAS be administered with food. Administration with food decreases the rate of capecitabine absorption (see section 4.2 and 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAPCITURAS. If the patient becomes pregnant while receiving CAPCITURAS, 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 CAPCITURAS.
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 CAPCITURAS.

Pregnancy

There are no studies in pregnant women using capecitabine; however, it should be assumed that CAPCITURAS may cause foetal harm if administered to pregnant women. In reproductive toxicity studies in animals, capecitabine administration caused embryolethality and teratogenicity. These findings are expected effects of fluoropyrimidine derivatives. CAPCITURAS should not be used during pregnancy (see section 4.3).

Breastfeeding

It is not known whether CAPCITURAS is excreted in human breast milk. No studies have been conducted to assess the impact of capecitabine on milk production or its presence in human breast milk. In lactating mice, considerable amounts of capecitabine and its metabolites were found in milk. As the potential for harm to the nursing infant is unknown, breastfeeding should be discontinued while receiving treatment with CAPCITURAS and for 2 weeks after the final dose (see section 4.3).

Fertility

There is no data on CAPCITURAS and impact on fertility.

4.7 Effects on ability to drive and use machines

CAPCITURAS causes side effects, such as dizziness, fatigue and nausea and may affect the ability to drive and use machinery. Caution is advised before driving a vehicle or operating machinery until the effects of CAPCITURAS are known.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of CAPCITURAS is based on data from over 3 000 patients treated with capecitabine as monotherapy, or capecitabine in combination with different chemotherapy regimens in multiple indications. The safety profiles of CAPCITURAS monotherapy for metastatic breast cancer, metastatic colorectal cancer and adjuvant colon cancer populations are comparable.

The most commonly reported and/or clinically relevant treatment-related adverse reactions 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.

Tabulated summary of adverse reactions

Adverse reactions considered by the investigator to be possibly, probably, or remotely related to the administration of capecitabine are listed in table 4 for CAPCITURAS given as monotherapy and in table 5 for CAPCITURAS given in combination with different chemotherapy regimens in multiple indications.

CAPCITURAS monotherapy

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

System organ class	**Frequent** ***All grades***	**Less frequent** ***Severe and/or life threatening (grade 3-4) or considered medically relevant***	**Less frequent** ***Post-marketing experience***
Infections and infestations	herpes viral infection, nasopharyngitis, lower respiratory tract infection	sepsis, urinary tract infection, cellulitis, tonsillitis, pharyngitis, oral candidiasis, influenza, gastroenteritis, fungal infection, infection, tooth abscess	
Neoplasms benign, malignant and unspecified		lipoma	
Blood and lymphatic system disorders	neutropenia, anaemia	febrile neutropenia, pancytopenia,	

		granulocytopenia, thrombocytopenia, leukopenia, haemolytic anaemia, international normalised ratio (INR) increased/ prothrombin time prolonged	
Immune system disorders		hypersensitivity	angioedema
Metabolism and nutrition disorders	anorexia, dehydration, weight decreased	diabetes, hypokalaemia, appetite disorder, malnutrition, hypertriglyceri-daemia	
Psychiatric disorders	insomnia, depression	confusional state, panic attack, depressed mood, libido decreased	
Nervous system disorders	headache, lethargy dizziness, paraesthesia dysgeusia	aphasia, memory impairment, ataxia, syncope, balance disorder, sensory disorder, neuropathy peripheral	toxic leukoencephalo-pathy
Eye disorders	lacrimation increased, conjunctivitis, eye irritation	visual acuity reduced, diplopia	lacrimal duct stenosis, corneal disorders, keratitis, punctate keratitis
Ear and labyrinth disorders		vertigo, ear pain	
Cardiac disorders		angina unstable, angina pectoris, myocardial	ventricular fibrillation, QT prolongation,

		ischaemia/ infarction, atrial fibrillation, dysrhythmia, tachycardia, sinus tachycardia, palpitations	torsades de pointes, bradycardia, vasospasm
Vascular disorders	thrombophlebitis	deep vein thrombosis, hypertension, petechiae, hypotension, hot flush, peripheral coldness	
Respiratory, thoracic and mediastinal disorders	dyspnoea, epistaxis, cough, rhinorrhoea	pulmonary embolism, pneumothorax, haemoptysis, asthma, dyspnoea exertional	
Gastrointestinal disorders	diarrhoea, vomiting, nausea, stomatitis, abdominal pain, gastrointestinal haemorrhage, constipation, upper abdominal pain, dyspepsia, flatulence, dry mouth	intestinal obstruction,ascites, enteritis, gastritis, dysphagia, abdominal pain lower, oesophagitis, abdominal discomfort, gastro-oesophageal reflux disease, colitis, blood in stool	
Hepatobiliary disorders	hyperbilirubin-aemia, liver function test abnormalities	jaundice	hepatic failure, cholestatic hepatitis

Skin and subcutaneous tissue disorders	palmar-plantar erythrodysaesthe-sia syndrome**, rash, alopecia, erythema, dry skin, pruritus, skin hyperpigmentation, rash macular, skin desquamation, dermatitis, pigmentation disorder, nail disorder	blister, skin ulcer, rash, urticaria, photosensitivity reaction, palmar erythema, swelling face, purpura, radiation recall syndrome	cutaneous lupus erythematosus, severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4.)
Musculoskeletal and connective tissue disorders	pain in extremity, back pain, arthralgia	joint swelling, bone pain, facial pain, musculoskeletal stiffness, muscular weakness	
Renal and urinary disorders		hydronephrosis, urinary incontinence, haematuria, nocturia, blood creatinine increased	
Reproductive system and breast disorders		vaginal haemorrhage	
General disorders and administration site conditions	fatigue, asthenia, pyrexia, oedema peripheral, malaise, chest pain	oedema, chills, influenza like illness, rigors, body temperature increased	

**Based on the post-marketing experience, persistent or severe palmar-plantar erythrodysaesthesia syndrome can eventually lead to loss of fingerprints (see section 4.4).

CAPCITURAS in combination therapy

Table 5 lists adverse reactions associated with the use of CAPCITURAS in combination with different chemotherapy regimens in multiple indications. Adverse reactions are added to the appropriate frequency grouping according to the highest incidence seen in any of the major clinical trials and are only added when they were seen **in addition** to those seen with CAPCITURAS monotherapy or seen at **a higher frequency grouping** compared to CAPCITURAS monotherapy (see table 4). Less frequent adverse reactions reported for CAPCITURAS in combination therapy are consistent with the adverse reactions reported for CAPCITURAS monotherapy or reported for monotherapy with the combination medicine (in literature and/or respective Professional Information).

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

Table 5 Summary of related adverse reactions reported in patients treated with CAPCITURAS in combination treatment in addition to those seen with CAPCITURAS monotherapy or seen at a higher frequency grouping compared to CAPCITURAS monotherapy.

System organ class	**Frequent** ***All grades***	**Less frequent** ***Post-marketing experience***
Infections and infestations	herpes zoster[1], urinary tract infection[1, 3], oral candidiasis[2], upper respiratory tract infection[3], rhinitis[4], influenza[4], infection[+7, 8], oral herpes	
Blood and lymphatic system disorders	neutropenia[+1, 3, 6, 7, 8], leucopenia[+1, 3, 7, 8], anaemia[+1, 3, 7, 8], neutropenic fever[+2],	

	thrombocytopenia[1, 3, 7, 8], bone marrow depression[1], febrile neutropenia[+4, 5, 7, 8]	
Immune system disorders	hypersensitivity[3]	
Metabolism and nutrition disorders	appetite decreased[2], hypokalaemia[1, 3], hyponatraemia[1], hypomagnesaemia[3], hypocalcaemia[3], hyperglycaemia[4]	
Psychiatric disorders	sleep disorder[1], anxiety[3]	
Nervous system disorders	paraesthesia[2, 3], dysaesthesia[3], peripheral neuropathy[1, 2, 3, 7, 8], peripheral sensory neuropathy[1, 3], dysgeusia[2, 3], headache[4], neurotoxicity[3], tremor[3], neuralgia[3], hypersensitivity reaction[5], hypoaesthesia[1, 3]	
Eye disorders	lacrimation increased[2], visual disorders, dry eye[3], eye pain, visual impairment[3], vision blurred[3]	
Ear and labyrinth disorders	tinnitus[1], hypoacusis[1]	
Cardiac disorders	atrial fibrillation[4], cardiac ischaemia/ infarction[4, 5, 6]	
Vascular disorders	lower limb oedema[2], hypertension[3, 4, 6], embolism and thrombosis[+4, 5, 6, 7, 8], flushing[3], hypotension[3], hypertensive crisis[4], hot flush, phlebitis	
Respiratory, thoracic and mediastinal system disorders	sore throat[2], dysaesthesia pharynx[3], hiccups[3], pharyngolaryngeal pain[3], dysphonia[3]	
Gastrointestinal disorders	constipation[2, 3], dyspepsia[2], upper gastrointestinal haemorrhage[1], mouth ulceration[1], gastritis[1, 4], abdominal distension[3], gastroesophageal reflux disease[3], oral pain[3], dysphagia[3], rectal	

	haemorrhage[3], abdominal pain lower[3], oral dysaesthesia[3], paraesthesia oral[3], hypoaesthesia oral, abdominal discomfort	
Hepatobiliary disorders	hepatic function abnormal[1]	
Skin and subcutaneous tissue disorders	alopecia[2], nail disorder[2], hyperhidrosis[1, 3], rash erythematous[2], urticaria[3], night sweats[4]	
Musculoskeletal and connective tissue disorders	myalgia[1, 2, 3], arthralgia[2], pain in extremity[4], pain in jaw[3], muscle spasms[3], trismus[3], muscular weakness[3]	
Renal and urinary disorders	haematuria[3], proteinuria[4], creatinine renal clearance decreased[1], dysuria	acute renal failure secondary to dehydration
General disorders and administration site conditions	pyrexia[2, 3, 7, 8], weakness[2], lethargy[+7, 8], temperature intolerance[3], mucosal inflammation[1], pain in limb[2], pain[2, 4], chills[3], chest pain[3], influenza-like illness[4], fever[+], infusion related reaction, injection site reaction, infusion site pain, injection site pain	
Injury, poisoning and procedural complications	contusion[4]	

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

[1] Side effects associated with the use of CAPCITURAS in combination with cisplatin in a major clinical trial in gastric cancer.

[2] Side effects associated with the use of CAPCITURAS in combination with docetaxel in a major clinical trial in metastatic breast cancer.

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

[4] Side effects associated with the use of CAPCITURAS in combination with oxaliplatin and bevacizumab in a clinical trial in the first-line treatment of metastatic colorectal cancer.

[5] Side effects reported in patients treated with CAPCITURAS in combination with irinotecan.

[6] Grade 3 and grade 4 side effects reported in patients treated with CAPCITURAS in combination with irinotecan and bevacizumab.

[7] Grade 3 and grade 4 side effects reported in patients treated with CAPCITURAS in combination with epirubicin and oxaliplatin.

[8] Grade 3 and grade 4 side effects reported in patients treated with CAPCITURAS in combination with epirubicin and cisplatin.

Less frequent side effects: hepatic failure and cholestatic hepatitis.

Exposure to crushed or cut CAPCITURAS tablets:

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of CAPCITURAS is important. It allows continued monitoring of the benefit/risk balance of CAPCITURAS. Health care 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.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 - Cytostatic agents

Pharmacotherapeutic group: Cytostatic (antimetabolite)

ATC code: L01BC06

Capecitabine is a fluoropyrimidine carbamate and is an orally administered, tumour-activated and tumour-selective prodrug cytotoxic agent. Capecitabine is non-cytotoxic *in vitro*. However, *in vivo*, it is sequentially converted to the cytotoxic moiety, 5-fluorouracil (5-FU), which is further metabolised. Formation of 5-FU is catalysed preferentially at the tumor site by the tumour associated angiogenic factor thymidine phosphorylase (dThdPase). Both normal and tumour cells metabolise 5-FU to 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine-triphosphate (FUTP). The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found in tumour tissues, but also in normal tissues, albeit usually at lower levels. In human cancer xenograft models capecitabine demonstrated a synergistic effect in combination with docetaxel, which may be related to the upregulation of thymidine phosphorylase by docetaxel.

These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N^{5-10}-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from uracil. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA,

so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error
can interfere with RNA processing and protein synthesis.

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

5.2 Pharmacokinetic properties

The pharmacokinetics of capecitabine have been evaluated over a dose range of 502 – 3 514 mg/m^2/day. The parameters of capecitabine, 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'- deoxy-5-fluorouridine (5'-DFUR) measured on days 1 and 14 were similar. The AUC of 5-FU was 30 % – 35 % higher on day 14. Capecitabine dose reduction decreases systemic exposure to 5-FU more than dose-proportionally, due to non-linear pharmacokinetics for the active metabolite.

Absorption

After oral administration, capecitabine is rapidly and extensively absorbed, followed by extensive conversion to the metabolites, 5'-DFCR and 5'-DFUR. Administration with food decreases the rate of capecitabine absorption, but only results in a minor effect on the area under the curve (AUC) of 5'-DFUR, and on the AUC of the subsequent metabolite 5-FU.
At the dose of 1 250 mg/m^2 on day 14 with administration after food intake, the peak plasma concentrations (C_{max} in µg/mL) for capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 4,67, 3,05, 12,1, 0,95 and 5,46 respectively. The time to peak plasma concentrations (T_{max} in hours)

were 1,50, 2,00, 2,00, 2,00 and 3,34. The $AUC_{0-\infty}$ values in µg·h/mL were 7,75, 7,24, 24,6, 2,03 and 36,3.

Distribution

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

Biotransformation

Capecitabine is first metabolised by hepatic carboxylesterase to 5'-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumour tissues. Further catalytic activation of 5'-DFUR then occurs by thymidine phosphorylase (ThyPase). The enzymes involved in the catalytic activation are found in tumour tissues but also in normal tissues, albeit usually at lower levels. The sequential enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations within tumour tissues. In the case of colorectal tumours, 5-FU generation appears to be in large part localised in tumour stromal cells. Following oral administration of capecitabine to patients with colorectal cancer, the ratio of 5-FU concentration in colorectal tumours to adjacent tissues was 3,2 (ranged from 0,9 to 8,0). The ratio of 5-FU concentration in tumour to plasma was 21,4 (ranged from 3,9 to 59,9, n=8) whereas the ratio in healthy tissues to plasma was 8,9 (ranged from 3,0 to 25,8, n=8). Thymidine phosphorylase activity was measured and found to be 4 times greater in primary colorectal tumour than in adjacent normal tissue. According to immunohistochemical studies, thymidine phosphorylase appears to be in large part localised in tumour stromal cells.

5-FU is further catabolised by the enzyme dihydropyrimidine dehydrogenase (DPD) to the much less toxic dihydro-5-fluorouracil (FUH_2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureidopropionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β-alanine (FBAL) which is cleared in the urine. Dihydropyrimidine dehydrogenase (DPD) activity is

the rate limiting step. Deficiency of DPD may lead to increased toxicity of capecitabine (see section 4.3 and 4.4).

Elimination

The elimination half-life ($t_{1/2}$ in hours) of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 0,85, 1,11, 0,66, 0,76 and 3,23 respectively. Capecitabine and its metabolites are predominantly excreted in urine; 95,5 % of administered capecitabine dose is recovered in urine. 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 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.

Special populations

Gender, presence or absence of liver metastasis at baseline, Karnofsky Performance Status, total bilirubin, serum albumin, ASAT and ALAT had no statistically significant effect on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL in patients with colorectal cancer.

Patients with hepatic impairment due to liver metastases

No clinically significant effect on the bioactivation and pharmacokinetics of capecitabine was observed in cancer patients with mildly to moderately impaired liver function due to liver metastases. There are no pharmacokinetic data in patients with severe hepatic impairment. See section 4.2.

Patients with renal impairment

Based on a pharmacokinetic study in cancer patients with mild to severe renal impairment, there is no evidence of an effect of creatinine clearance on the pharmacokinetics of intact active ingredient, capecitabine, and 5-FU. Creatinine clearance was found to influence the systemic exposure to 5'-DFUR (35 % increase in AUC when creatinine clearance decreases by 50 %) and to FBAL (114 % increase in AUC when creatinine clearance decreases by 50 %). FBAL is a metabolite without antiproliferative activity; 5'-DFUR is the direct precursor of 5-FU. See sections 4.2, 4.3 and 4.4.

Elderly

Based on the population pharmacokinetic analysis, which included patients with a wide range of ages (27 to 86 years) and included 234 (46 %) patients greater or equal to 65, age has no influence on the pharmacokinetics of 5'-DFUR and 5-FU. The AUC of FBAL increased with age (20 % increase in age results in a 15 % increase in the AUC of FBAL). This increase is likely due to a change in renal function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Anhydrous lactose

Croscarmellose sodium

Hypromellose

Magnesium Stearate

Microcrystalline cellulose

Tablet coating:

Hypromellose

Iron oxide red (E172)

Iron oxide yellow (E172)

Talc

Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister in the outer carton until required for use.

6.5 Nature and contents of container

Clear PVC/PVdC/aluminium foil blister strips placed in an outer carton.

Pack size:

CAPCITURAS 150 mg: 60 tablets

CAPCITURAS 500 mg: 60 or 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The procedures for safe handling of cytotoxic medicines should be followed. Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Alturas Healthcare (Pty) Ltd

Unit 18a, First floor, Key Largo Shopping Centre

Corner of North Rand and Trichard Road

Boksburg, Gauteng

1459

8. REGISTRATION NUMBERS

CAPCITURAS 150 mg: Will be allocated by SAHPRA upon registration.

CAPCITURAS 500 mg: Will be allocated by SAHPRA upon registration.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated by SAHPRA upon registration.

10. DATE OF REVISION OF THE TEXT

Not yet revised.