APPROVED PROFESSIONAL INFORMATION (Clean copy)

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

REBUTRIX 150 mg film-coated tablet

REBUTRIX 500 mg film-coated tablet

WARNING

Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy such as warfarin should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important REBUTRIX-Warfarin interaction was demonstrated in a clinical pharmacology trial. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking REBUTRIX 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 REBUTRIX was introduced. These events occurred within several days and up to several months after initiating REBUTRIX therapy and, in a few cases, within one month after stopping REBUTRIX 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.

2. QUALITATIVE AND QUANTITIVE COMPOSITION:

REBUTRIX 150 mg:

Each film coated tablet contains capecitabine 150 mg. Contains sugar: 19.99 mg lactose.

REBUTRIX 500 mg:

Each film coated tablet contains capecitabine 500 mg. Contains sugar: 66.65 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

REBUTRIX 150 mg:

Light peach coloured biconvex, oblong shaped film coated tablets, debossed with 150 on the one side and plain on the other side.

REBUTRIX 500 mg:

Peach coloured biconvex, oblong shaped film coated tablets, debossed with 500 on the one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast Cancer

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

Metastatic colorectal cancer: **REBUTRIX** 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: REBUTRIX 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

REBUTRIX should only be prescribed by a qualified medical practitioner experienced in the

utilization of antineoplastic medicines. **REBUTRIX** tablets should be swallowed with water within 30 minutes after a meal. Treatment should be discontinued if progressive disease or intolerable toxicity is observed.

Adults

Monotherapy – Colon, colorectal and breast cancer

The recommended monotherapy dose of **REBUTRIX** 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 **REBUTRIX 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 **REBUTRIX.** 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 **REBUTRIX.**

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 **REBUTRIX** plus cisplatin combination.

Breast Cancer: In combination with docetaxel for locally advanced or metastatic breast cancer, the recommended dose of **REBUTRIX** is 1 250 mg/m^2 twice daily for 14 days followed by a 7 day rest period, combined with docetaxel at 75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks. Pre-medication with an oral corticosteroid such as dexamethasone according to the docetaxel prescribing information should be started prior to docetaxel administration for patients receiving the **REBUTRIX** plus docetaxel combination.

REBUTRIX 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 **REBUTRIX** 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
1,127 – 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 **REBUTRIX** 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)**

	Dose per administration (mg)	**150 mg**	**500 mg**	**Dose per administration (mg)**	**Dose per administration (mg)**
≤ 1,26	1 150	1	2	800	600
1,127 – 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 **REBUTRIX** administration may be managed by symptomatic treatment and/or modification of the **REBUTRIX** dose (treatment interruption or dose reduction).

Dosage modifications are not recommended for Grade 1 events. Therapy with **REBUTRIX** should be interrupted upon the occurrence of a Grade 2 or 3 adverse experiences. Once the adverse event has resolved or decreased in intensity to Grade 1, then **REBUTRIX** 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 **REBUTRIX** should be informed of the need to interrupt treatment immediately if moderate or worse toxicity occurs.

Doses of **REBUTRIX** 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 4.4 and 4.8. The following table shows the recommended dose modifications following toxicity with **REBUTRIX.**

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

Toxicity NCIC ~~g~~Grades*	**Dose changes within a treatment cycle**	**Dose adjustment for next cycle/dose (% of starting dose)**
• ***Grade 1***	Maintain dose level	Maintain dose level
• ***Grade 2***		
1st appearance	Interrupt until resolved to Grade 0 – 1	100 %
2nd appearance	Interrupt until resolved to Grade 0 – 1	75 %
3rd appearance	Interrupt until resolved to Grade 0 – 1	50 %
4th appearance	Discontinue treatment permanently	
• ***Grade 3***		
1st appearance	Interrupt until resolved to Grade 0 – 1	75 %
2nd appearance	Interrupt until resolved to Grade 0 – 1	50 %
3rd appearance	Discontinue treatment permanently	
• ***Grade 4***		
1st appearance	Discontinue permanently or If medical practitioner deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0 - 1	50 %
2nd appearance	Discontinue treatment permanently	

* 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 4.4 and 4.8.

Haematology: Patients with baseline neutrophil counts of $\leq$ 1,5 x 10^9/L and/or thrombocyte counts of < 100 x 10^9/L should not be treated with the **REBUTRIX** . If unscheduled laboratory assessments during

a treatment cycle show Grade 3 or 4 haematologic toxicity, treatment with **REBUTRIX** should be interrupted.

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

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

At the beginning of a treatment cycle, if a treatment delay is indicated for either **REBUTRIX** 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 **REBUTRIX**, **REBUTRIX** should be continued and the dose of the other medicine(s) should be adjusted according to the appropriate prescribing information. If other medicines have to be discontinued permanently, **REBUTRIX** treatment can be resumed when the requirements for restarting are met, This advice is applicable to all indications and to all special populations,

Dose modifications for toxicity when REBUTRIX is used continuously in combination with other medicines:

Dose modifications for toxicity when **REBUTRIX** is used continuously in combination with other medicine(s) should be made according to Table 3 above for **REBUTRIX** and according to the appropriate prescribing 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 Sections 4.3 and 4.4).

Patients with renal impairment: **REBUTRIX** is contra-indicated 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 mg/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 recommendation for patients with moderate renal impairment apply both to monotherapy and combination use. (See Section 4.8 and 5.2)

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

Elderly: No adjustment of the starting dose is needed for **REBUTRIX** monotherapy. However, severe Grade 3 or 4 treatment-related and 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 **REBUTRIX.**

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

4.3 Contra-indications

REBUTRIX is contra-indicated in:

- patients with known hypersensitivity to capecitabine or to any of its components.
- patients who have a history of severe and unexpected reactions to fluoropyrimidine therapy, or with known hypersensitivity to fluorouracil (capecitabine metabolite).
- patients with known dihydropyrimidine dehydrogenase (DPD) deficiency.
- patients with severe leukopaenia, neutropenia, or thrombocytopenia
- patients with severe hepatic impairment
- in patients with severe renal impairment (creatinine clearance below 30 ml/min)
- Pregnancy and breastfeeding (See Section 4.6)

REBUTRIX should not be administered with sorivudine or its chemically related analogues, such as brivudine. (See section 4.5). If contra-indications exist for any of the medicines in the combination regimen, that medicine should not be used.

4.4 Special warnings and precautions for use

Coagulopathy

Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely with great frequency and the anticoagulant dose should be adjusted accordingly [see Boxed Warning and Section 4.5].

Diarrhoea

Capecitabine can induce diarrhoea, sometimes severe. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. In 875 patients with either metastatic breast or colorectal cancer who received capecitabine monotherapy, the median time to first occurrence of Grade 2 to 4 diarrhoea was 34 days (range from 1 to 369 days). The median duration of Grade 3 to 4 diarrhoea was 5 days. 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 capecitabine should be immediately interrupted until the diarrhoea resolves or decreases in intensity to Grade 1 (see Section 4.2). Standard antidiarrhoeal treatments (e.g. loperamide) are recommended. (See Section 4.8)

Necrotising enterocolitis (typhlitis) has been reported.

Cardiotoxicity

The cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse reactions may be more common in patients with a prior history of coronary artery disease.

Dihydropyrimidine Dehydrogenase Deficiency

Patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by capecitabine (e.g., mucositis, diarrhoea, neutropenia, and neurotoxicity). Patients with partial DPD activity (See Section 4.3) may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by capecitabine.

Withhold or permanently discontinue capecitabine based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No capecitabine dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test.

Dehydration and Renal Failure

Dehydration has been observed and may cause acute renal failure which can be fatal. Patients with pre-existing compromised renal function or who are receiving concomitant capecitabine with known

nephrotoxic medicines are at higher risk. Patients with anorexia, asthenia, nausea, vomiting or diarrhoea may rapidly become dehydrated. Monitor patients when capecitabine is administered to prevent and correct dehydration at the onset. If Grade 2 (or higher) dehydration occurs, capecitabine treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications should be applied for the precipitating adverse event as necessary [see Section 4.2].

Patients with moderate renal impairment at baseline require dose reduction [see Section 4.2 and 5.2]. Patients with mild and moderate renal impairment at baseline should be carefully monitored for adverse reactions. Prompt interruption of therapy with subsequent dose adjustments is recommended if a patient develops a Grade 2 to 4 adverse event as outlined in Table 2 [see Section 4.2 and 5.2].

Mucocutaneous and Dermatologic Toxicity

Severe mucocutaneous reactions, some with fatal outcome, such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN) can occur in patients treated with capecitabine [see Section 4.8]. Capecitabine should be permanently discontinued in patients who experience a severe mucocutaneous reaction possibly attributable to capecitabine treatment.

Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) is a cutaneous toxicity. Median time to onset was 79 days (range from 11 to 360 days) with a severity range of Grades 1 to 3 for patients receiving capecitabine monotherapy in the metastatic setting. Grade 1 is characterized by any of the following: numbness, dysesthesia/paresthesia, tingling, painless swelling or 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 causes the patient to be unable to work or perform activities of daily living. Persistent or severe hand-and-foot syndrome (Grade 2 and above) can eventually lead to loss of fingerprints which could impact patient identification. If Grade 2 or 3 hand-and-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to Grade 1.

Following Grade 3 hand-and-foot syndrome, subsequent doses of capecitabine should be decreased [see section 4.2].

Hyperbilirubinemia

If medicine-related Grade 3 to 4 elevations in bilirubin, or medicinerelated elevations in hepatic aminotransferases (ALT,AST) occur, administration of capecitabine should be immediately interrupted until the hyperbilirubinemia decreases to ≤3.0 X ULN or hepatic aminotransferases decreases to ≤2.5 x ULN. (see recommended dose modifications under Section 4.2).

Haematologic

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 capecitabine. If unscheduled laboratory assessments during a treatment cycle show Grade 3 or 4 hematologic toxicity, treatment with capecitabine should be interrupted. (See Section 4.2)

Elderly Patients

Patients ≥80 years old may experience a greater incidence of Grade 3 or 4 adverse reactions.

Hepatic Insufficiency

Patients with mild to moderate hepatic dysfunction due to liver metastases should be carefully monitored when capecitabine is administered. The effect of severe hepatic dysfunction on the disposition of capecitabine is not known [see Section 4.3 and 5.2].

Paediatric Use

The safety and effectiveness of **REBUTRIX** in paediatric patients has not been established.

Lactose:

As this medicinal product contains anhydrous lactose as an excipient, patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Anticoagulants

Altered coagulation parameters and/or bleeding have been reported in patients taking **REBUTRIX** concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon [see Boxed Warning]. In a medicine interaction study with single-dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin [See Section 5.2]. The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites.

Sorivudine and analogues

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

Phenytoin

The level of phenytoin should be carefully monitored in patients taking **REBUTRIX** and phenytoin dose may need to be reduced. Postmarketing reports indicate that some patients receiving **REBUTRIX** and phenytoin had toxicity associated with elevated phenytoin levels. Formal medicine interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by **REBUTRIX** and/or its metabolites.

Leucovorin

The concentration of 5-fluorouracil is increased and its toxicity may be enhanced by leucovorin. Deaths from severe enterocolitis, diarrhoea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil.

CYP2C9 substrates

Other than warfarin, no formal medicine interaction studies between **REBUTRIX** and other CYP2C9 substrates have been conducted. Care should be exercised when **REBUTRIX** is coadministered with CYP2C9 substrates.

Allopurinol

Concomitant use with allopurinol may decrease concentration of **REBUTRIX** active metabolites [See Section 5.2], which may decrease **REBUTRIX** efficacy. Avoid the use of allopurinol during treatment with **REBUTRIX**.

Interferon Alpha

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 **REBUTRIX** was combined with interflora aplha-2a (3MIU//m^2 per day) compared to 3000 mg/m^2 when **REBUTRIX** was used alone.

Antacids

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

Radiotherapy

The MTD of capecitabine alone using the intermittent regimen is 3000 mg/m2 per day, whereas, when combined with radiotherapy for rectal cancer, the MTD of capecitabine is 2000 mg/m2 per day using

either a continuous schedule or given daily Monday through Friday during a 6-week course of radiotherapy.

Oxaliplatin

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

Bevacizumab

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

Food Interaction

Food was shown to reduce both the rate and extent of absorption of **REBUTRIX** [See Section 5.2]. In all clinical trials, patients were instructed to administer **REBUTRIX** within 30 minutes after a meal. It is recommended that **REBUTRIX be** administered with food [See Section 4.2].

4.6 Fertility, pregnancy and lactation

Pregnancy

REBUTRIX is contraindicated during pregnancy (See Section 4.3)

Based on findings in animal reproduction studies and its mechanism of action, **REBUTRIX** can cause foetal harm when administered to a pregnant woman [see Section 5.2]. Limited available human data are not sufficient to inform the medicine-associated risk during pregnancy. In animal reproduction studies, administration of **REBUTRIX** to pregnant animals during the period of organogenesis caused embryo lethality and teratogenicity in mice and embryo lethality in monkeys at 0.2 and 0.6 times the exposure (AUC) in patients receiving the recommended dose respectively [see Section 5.3]. Apprise pregnant women of the potential risk to a foetus.

Lactation

There is no information regarding the presence of **REBUTRIX** in human milk, or on its effects on milk production or the breast-fed infant. Capecitabine metabolites were present in the milk of lactating mice [see Data]. Because of the potential for serious adverse reactions from capecitabine exposure in breast-fed infants, advise women not to breastfeed during treatment with **REBUTRIX** and for 2 weeks after the final dose. (See Section 4.3)

Fertility

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating **REBUTRIX.**

Contraception

Females

REBUTRIX can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the final dose of **REBUTRIX**.

Males

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

Infertility

Based on animal studies, **REBUTRIX** may impair fertility in females and males of reproductive potential.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable Effects

a. Summary of the safety profile

The overall safety profile of **REBUTRIX** is based on data from over 3000 patients treated with **REBUTRIX** as monotherapy or capecitabine in combination with different chemotherapy regimens in multiple indications. The safety profiles of **REBUTRIX monotherapy** for the metastatic breast cancer, metastatic colorectal cancer and adjuvant colon cancer populations are comparable.

The most commonly 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 preexisting compromised renal function, and thrombosis/embolism.

b. Tabulated list of adverse reactions

ADRs considered by the investigator to be possibly, probably, or remotely related to the administration of capecitabine are listed in table 4 for capecitabine given as monotherapy and in table 5 for capecitabine given in combination with different chemotherapy regimens in multiple indications. The following headings are used to rank the ADRs by frequency. Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Capecitabine Monotherapy:

Table 4 lists ADRs associated with the use of capecitabine monotherapy based on a pooled analysis of safety data from three major studies.

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, Gastroenteritis, Fungal infection, Herpes Infection, Tooth abscess	
Neoplasm 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	
Metabolism and nutrition disorders	Anorexia Dehydration, Weight decreased	Diabetes, Hypokalaemia, Appetite disorder, Malnutrition, Hypertriglyceridaemia,	
Psychiatric disorders	- Insomnia, Depression	Confusional state, Panic attack, Depressed mood, Libido decreased	

Nervous system disorders	- Headache, Lethargy Dizziness, Parasthesia Dysgeusia	Aphasia, Memory impairment, Ataxia, Syncope, Balance disorder, Sensory disorder, Neuropathy peripheral	Toxic leukoencephalopathy (very rare)
Eye disorders	- Lacrimation increased, Conjunctivitis, Eye irritation	Visual acuity reduced, Diplopia	Lacrimal duct stenosis (rare), Corneal disorders(rare), keratitis (rare), punctate keratitis (rare)
Ear and labyrinth disorders	- -	Vertigo, Ear pain	
Cardiac disorders	- -	Angina unstable, Angina pectoris, Myocardial ischaemia/infarction, Atrial fibrillation, Arrhythmia, Tachycardia, Sinus tachycardia, Palpitations	Ventricular fibrillation (rare), QT prolongation (rare), Torsade de pointes (rare), Bradycardia (rare), Vasospasm (rare)
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, Loose stools	Intestinal obstruction, Ascites, Enteritis, Gastritis, Dysphagia, Abdominal pain lower, Oesophagitis, Abdominal discomfort, Gastrooesophageal reflux disease, Colitis, Blood in stool	
Hepatobiliary disorders	- Hyperbilirubinemia, Liver function test abnormalities	Jaundice	Hepatic failure (rare), Cholestatic hepatitis (rare)
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	Blister, Skin ulcer, Rash, Urticaria, Photosensitivity reaction, Palmar erythema, Swelling face, Purpura, Radiation recall syndrome	Cutaneous lupus erythematosus (rare), Severe skin reactions such as Stevens-Johnson Syndrome and toxic Epidermal Necrolysis (very rare) (see section 4.4.)

	disorder, Nail disorder		
Muskuloskeletal 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, non cardiac 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)

Capecitabine in combination therapy:

Table 5 lists ADRs associated with the use of capecitabine in combination with different chemotherapy regimens in multiple indications based on safety data from over 3000 patients. ADRs are added to the appropriate frequency grouping (frequent or less frequent) 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 capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy (see table 4). Uncommon 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 summary of product characteristics).

Some of the ADRs are reactions commonly seen 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 5 Summary of related ADRs reported in patients treated with capecitabine in combination treatment in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy

Body System	***Frequent*** ***All Grades***	***Frequency unknown*** **(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, Taste disturbance Neurotoxicity, Tremor, Neuralgia, Hypersensitivity reaction, Hypoaesthesia	
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	
Gastrointestinal disorders	Constipation, Dyspepsia Upper gastrointestinal haemorrhage, Mouth ulceration, Gastritis, Abdominal distension, Gastroesophageal 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 Hyperhidrosis, Rash erythematous, Urticaria, Night sweats, 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 clearance decreased, Dysuria	Acute renal failure secondary to dehydration
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	

+ 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.

4.9 Overdosage

The manifestations of acute overdose would include nausea, vomiting, diarrhoea, gastrointestinal irritation and bleeding, and bone marrow depression. Medical management of overdose should include customary supportive medical interventions aimed at correcting the presenting clinical manifestations. Although no clinical experience using dialysis as a treatment for **REBUTRIX** overdose has been

reported, dialysis may be of benefit in reducing circulating concentrations of 5'-DFUR, a low–molecular-weight metabolite of the parent compound.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A26 - Cytostatic agents

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

Enzymes convert capecitabine to 5-fluorouracil (5-FU) *in vivo*. Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). 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 2'-deoxyuridylate. 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.

5.2 Pharmacokinetics 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 extensively converted to the metabolites 5'- deoxy-5-fluorocytidine (5'-DFCR) and 5'-deoxy-5-fluorouridine (5'-DFUR). Administration with food decreases the rate of capecitabine absorption, but only results in a minor effect on the AUC of 5'- DFUR, and on the AUC of the subsequent metabolite 5-FU. At the dose of 1 250 mg/m^2 on day 14 with

administration after food intake, the peak plasma concentrations (C_{max} in µg/mλ) 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/mλ were 7, 75, 7,24, 24,6, 2,03 and 36,3.

Protein binding:

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

Metabolism:

Capecitabine is first metabolised by hepatic carboxylesterase to 5'-deoxy-5- fluorocytidine (5'-DFCR), which is then converted to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase, principally located in the liver and tumour tissues. Further catalytic activation of 5'- DFUR then occurs by thymidine phosphorylase (dThdPase) to form 5-FU. Formation of 5-FU occurs preferentially at the tumor site by the tumour associated angiogenic factor dThdPase. The metabolites of capecitabine become cytotoxic after conversion to 5-FU and anabolites of 5-FU. 5-FU is further catabolised to the inactive metabolites dihydro-5-fluoruracil (FUH2), 5-fluoroureidopropionic acid (FUPA) and α-fluoro-β-alanine (FBAL) via dihydropyrimidine dehydrogenase (DPD), which is rate limiting. **Elimination:** The elimination half-life ($t_{1/2}$ in hours) of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 0,85, 1,11, 0,66, 0,76 and 3,23 respectively. The pharmacokinetics of capecitabine have been evaluated over a dose range of 502 – 3 514 mg/m^2/day. The parameters of capecitabine, 5'-DFCR and 5'-DFUR measured on days 1 and 14 were similar. The AUC of 5-FU was 30 - 35 % higher on day 14, but did not increase subsequently (day 22). At therapeutic doses, the pharmacokinetics of capecitabine and its metabolites were dose proportional; except for 5-FU. After oral administration capecitabine metabolites are primarily recovered in the urine. 95,5 % of administered capecitabine dose is recovered in urine. Faecal excretion is minimal (2,6 %). The major metabolite excreted in urine is FBAL, which represents 57 % of the administered dose. About 3 % of the administered dose is excreted in urine as unchanged active ingredient, capecitabine. The interpatient variability in C_{max} and AUC of 5-FU was greater than 85 %. Combination therapy: Phase I studies evaluating the effect of

REBUTRIX on the pharmacokinetics of either docetaxel or paclitaxel and vice versa showed no effect

by **REBUTRIX** on the pharmacokinetics of docetaxel or paclitaxel (C_{max} and AUC) and no effect by docetaxel or paclitaxel on the pharmacokinetics of 5'-DFUR (the most important metabolite of capecitabine). **Pharmacokinetics in special populations:**

Gender, presence or absence of liver metastasis at baseline, Karnofsky Performance Status, total bilirubin, serum albumin, ASAT and ALAT had no statistically significant effect on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL in patients with colorectal cancer. Patients with hepatic impairment due to liver metastases: No clinically significant effect on the bioactivation and pharmacokinetics of capecitabine was observed in cancer patients with mildly to moderately impaired liver function due to liver metastases. There are no pharmacokinetic data in patients with severe hepatic impairment. (See 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 Section 4.2, 4.3 and 4.4)

6 Pharmaceutical particulars

6.1 List of excipients

The other ingredients of **REBUTRIX** are cellulose microcrystalline, croscarmellose sodium, ferric oxide red, ferric oxide yellow, hypromellose, lactose anhydrous, magnesium stearate, talc and titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

two years

6.4 Special precautions for storage

Do not store above 30 °C.

Do not remove blister from carton until required for use.

6.5 Nature and contents of container

Blister pack:

PVC/PVdC with aluminium foil:

Tablets are packed in clear 250 micrometer PVC film coated with 90 g/m2 PVdC as the forming material and 25 micrometer aluminium foil with 7 g/m2 heat seal lacquer as the lidding material.

For 150 mg:

Pack size: 60's - Each carton contains 6 blisters of 10 tablets each.

For 500 mg:

Pack size: 120's - Each carton contains 12 blisters of 10 tablets each.

6.6 Special precautions for disposal and other handling

Procedures for safe handling of cytotoxic medicines should be followed.

7. Holder of certificate of registration

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. Registration number

Rebutrix 150 mg : 53/26/0102

Rebutrix 500 mg : 53/26/0103

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 15 December 2020

10. Date of revision of the text

Not applicable