Applicant : Eurolab (Pty) Ltd
Proprietary name : Pecaset 150 mg & 500 mg
Dosage form and strength : Tablet
: Capecitabine 150 mg & 500 mg
Date of submission : 12 December 2024
Approval date: : 22 April 2025

CLEAN PROFESSIONAL INFORMATION

WARNING:

Patients receiving oral coumarin-derivative anticoagulant therapy concomitantly with **PECASET,** should have their anticoagulant response i.e. international normalised ratio (INR) or prothrombin time (PT), frequently monitored, in order to adjust the anticoagulant dosage accordingly. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking **PECASET** concomitantly with warfarin. Clinically significant increase in PT and INR can occur within several days and up to several months after the initiation of **PECASET** treatment, as well as after **PECASET** treatment has been stopped. These events can occur in patients with or without liver metastases. Age > 60 years and a diagnosis of cancer independently predispose the patients to an increased risk of coagulopathy.

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

PECASET 150 (film-coated tablets)

PECASET 500 (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Excipients with known effect: lactose anhydrous

Contains sugar: lactose anhydrous (see section 4.4)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

PECASET 150: Light peach coloured, oblong shaped, biconvex, film-coated tablet, debossed with '150' on one side and plain on other side.

PECASET 500: Peach coloured, oblong shaped, biconvex, film-coated tablet, debossed with '500' on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Breast cancer:

Metastatic breast cancer (combination therapy):

PECASET 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):

PECASET 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:

PECASET is indicated as adjuvant treatment after surgery, of patients with Dukes' C colon cancer.

Metastatic colorectal cancer:

PECASET 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:

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

4.2 Posology and method of administration

PECASET should only be prescribed by a qualified medical practitioner experienced in the utilisation of antineoplastic medicine. **PECASET** film-coated 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 **PECASET** 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 6 months.

Combination therapy:

Colorectal and gastric cancer:

In combination treatment, the starting dose of **PECASET** 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 **PECASET** dose reduction schedule, please refer to ***Table 1***. The inclusion of biological agents in a combination regimen has no effect on the starting dose of **PECASET**.

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

Breast cancer:

In combination with docetaxel, for locally advanced or metastatic breast cancer, the recommended dose of **PECASET** 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 prescribing information, should be started prior to docetaxel administration for patients receiving the **PECASET** plus docetaxel combination. **PECASET** 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 PECASET of 1 250 mg/m^2**

Dose level 1 250 mg/m^2 (twice daily)					
Body Surface Area (m^2)	**Full dose 1250 mg/m^2**	**Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)**		**Reduced dose (75 %) 950 mg/m^2**	**Reduced dose (50 %) 625 mg/m^2**
	Dose per administration (mg)	**150 mg**	**500 mg**	**Dose per administration (mg)**	**Dose per administration (mg)**
≤ 1,26	1500	-	3	1150	800
1,27 – 1,38	1650	1	3	1300	800
1,39 – 1,52	1800	2	3	1450	950
1,53 – 1,66	2000	-	4	1500	1000
1,67 – 1,78	2150	1	4	1650	1000
1,79 - 1,92	2300	2	4	1800	1150

1,93 – 2,06	2500	-	5	1950	1300
2,07 – 2,18	2650	1	5	2000	1300
≥ 2,19	2800	2	5	2150	1450

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

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

Dose adjustments during treatment:

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

Dose modifications are not recommended for Grade 1 events.

Treatment with **PECASET** 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, **PECASET** treatment may be restarted at full dose or adjusted according to ***Table 3*** below. If a Grade 4 experience occurs, treatment should be discontinued or interrupted until resolved or decreased to Grade 1, and treatment can be restarted at 50 % of the original dose.

Patients taking **PECASET** should be informed of the need to interrupt treatment immediately if moderate or worse toxicity occurs. Doses of **PECASET** 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. ***Table 3*** shows the recommended dose modifications following toxicity with **PECASET**.

Table 3: **PECASET 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 palmar-plantar erythrodysaesthesia and hyperbilirubinaemia, see section 4.4.

Haematology:

Patients with baseline neutrophil counts of < 1,5 x 10^9/l and/or thrombocyte counts of < 100 x 10^9/l should not be treated with **PECASET**. If unscheduled laboratory assessments during a treatment cycle show Grade 3 or 4 haematologic toxicity, treatment with **PECASET** should be interrupted.

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

Dose modifications for toxicity when **PECASET** is used as a 3 weekly cycle in combination with other medicine should be made according to ***Table 3*** above for **PECASET**, and according to the appropriate prescribing information for the medicine(s) used. At the beginning of a treatment cycle, if a treatment delay is indicated for either **PECASET** 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 **PECASET**, **PECASET** should be continued and the dose of the other medicine should be adjusted according to the appropriate prescribing information. If the other medicine(s) has(ve) to be discontinued permanently, **PECASET** treatment can be resumed when the requirements for restarting **PECASET** are met. This advice is applicable to all indications and to all special populations.

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

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

Dosing in special populations:

Patients with hepatic impairment due to liver metastases:

No starting dose adjustment is necessary in patients with mild to moderate liver impairment due to liver metastases. However, such patients should be carefully monitored. Data is not available on patients with severe liver impairment (see section 4.4).

Patients with renal impairment:

PECASET is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.3). The incidence of Grade 3 or 4 adverse events 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, a dose reduction of 75 % for a starting dose of 1 250 mg/m^2 is recommended. In patients with moderate renal impairment, 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 interruption of treatment 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.

Children:

Safety and efficacy in children have not been established.

Elderly:

No adjustment in the starting dose is needed for **PECASET** monotherapy. However, severe Grade 3 or 4 treatment related adverse events are more frequent in patients > 60 years of age compared to younger patients. Careful monitoring of elderly patients is recommended.

For treatment with **PECASET**:

In combination with docetaxel, an increased incidence of Grade 3 or 4 treatment related adverse reactions and treatment related serious adverse reactions are observed in patients > 60 years of age.

For patients ≥ 60 years of age, treated with the combination of **PECASET** plus docetaxel, a starting dose reduction of **PECASET** 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 **PECASET** starting dose in combination with docetaxel, the dose of **PECASET** may be cautiously increased to 1 250 mg/m^2 twice daily.

For patients ≥ 65 years of age, treated with the combination of **PECASET** plus irinotecan, a starting dose reduction of **PECASET** to 800 mg/m^2 twice daily is recommended.

4.3 Contraindications

Hypersensitivity to capecitabine or any of the other ingredients of **PECASET** (see **COMPOSITION**).

Hypersensitivity to fluorouracil (capecitabine metabolite), or a history of severe and unexpected reactions to fluoropyrimidine treatment.

Dihydropyrimidine dehydrogenase (DPD) deficiency.

Severe leukopenia, neutropenia or thrombocytopenia.

Severe hepatic impairment.

Severe renal impairment (creatinine clearance < 30 ml/min).

Concomitant administration with sorivudine or its chemically related analogues, such as brivudine (see section 4.5). If contraindications exist for any of the medicines in the combination regimen, that medicine should not be used.

Pregnancy and lactation (see **PREGNANCY AND LACTATION**).

4.4 Special warnings and precautions for use

Patients should be carefully monitored for toxicity. Most adverse events are reversible and do not require permanent discontinuation of **PECASET**, although doses may have to be withheld or reduced.

Coumarin-derivative anticoagulation

Warfarin interaction:

See boxed warning above.

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

hospital is recommended. All measures should be initiated to prevent systemic infections and dehydration.

Diarrhoea:

PECASET can produce diarrhoea, which can sometimes be severe and lead to dehydration (see **SIDE EFFECTS**). **PECASET** should be used with care in patients who are weak or malnourished. Patients with severe diarrhoea should be closely monitored and given fluid and electrolyte replacement if they become dehydrated. Standard antidiarrhoeal treatments (e.g. loperamide) should be instituted immediately. If National Cancer Institute (NCI) Grade 2, 3 or 4 diarrhoea occurs, treatment with **PECASET** should be interrupted until the diarrhoea resolves or decreases in intensity.

Grade 2 diarrhoea is defined as an increase of 4 to 6 stools per day, or nocturnal stools.

Grade 3 diarrhoea is defined as an increase of 7 to 9 stools per day or incontinence and malabsorption.

Grade 4 diarrhoea is defined as an increase of ≥ 10 stools per day, grossly bloody diarrhoea or the need for parenteral fluid support.

Dose reduction should be applied as necessary (see section 4.2).

Dehydration:

Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhoea may rapidly become dehydrated. Dehydration may cause acute renal failure, especially in patients with pre-existing compromised renal function or when capecitabine is given concomitantly with known nephrotoxic medicinal products. Acute renal failure secondary to dehydration might be potentially fatal. If grade 2 (or higher) dehydration occurs, capecitabine 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).

Palmar-plantar erythrodysaesthesia (PPE):

PECASET can cause a cutaneous toxicity known as palmar-plantar erythrodysaesthesia (hand-foot syndrome or chemotherapy induced acral erythema), with severity range of Grades 1 - 3. This may result in severe discomfort that interferes with the ability of the patient to work or perform daily tasks. Immediate medical attention is required for such reactions.

Grade 1 PPE is defined as numbness, dysaesthesia, paraesthesia, tingling erythema of the hands and/or feet and/or discomfort which does not disrupt normal daily activities.

Grade 2 PPE is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting normal daily activities.

Grade 3 PPE is defined as 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 normal daily activities.

The use of **PECASET** should be interrupted if Grade 2 or 3 PPE occurs, until the event resolves or decreases in intensity to Grade 1.

Subsequent doses of **PECASET** should be decreased following Grade 3 hand-foot syndrome (see **section 4.2**).

Cardiotoxicity:

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

PECASET may cause cardiotoxicity, including myocardial infarction, angina, dysrhythmias, cardiac arrest, cardiac failure and electrocardiographic changes, which may be more common in patients with a history of coronary artery disease. Cardiac arrhythmias (including ventricular fibrillation, torsade de pointes, and bradycardia), angina pectoris,myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving capecitabine Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris (see section 4.8).

Hypo- or hypercalcaemia:

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

Immunosuppression, bone marrow depression and infection:

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

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

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

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

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

Renal impairment:

PECASET is contraindicated in patients with severe renal impairment (see section 4.3).

Caution is advised in patients with impaired renal function. Grade 3 - 4 adverse events are higher in patients with moderate renal impairment (creatinine clearance 30 - 50 ml/min) and a dose reduction of 75 % of the starting dose is recommended in these patients. The dosage adjustment applies to both **PECASET** monotherapy and combination treatment.

Patients should be carefully monitored and if Grade 2, 3 or 4 adverse events develop during treatment with **PECASET**, dosage adjustment or treatment interruption is recommended (see **section 4.2**).

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

Hepatic impairment:

Caution is recommended in patients with hepatic impairment as blood concentrations and AUC values for capecitabine treatment may be increased. The effect of hepatic impairment not due to liver metastases or severe hepatic impairment on the disposition of **PECASET** is not known. **PECASET** has been associated with hepatic failure and cholestatic jaundice.

Dihydropyrimidine dehydrogenase (DPD) deficiency:

Patients with DPD deficiency must not take Pecaset (see contraindications, section 4.3). 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 treatment or after dose increase.

Complete DPD deficiency

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

Partial DPD deficiency

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

Testing for DPD deficiency

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

Genotypic characterisation of DPD deficiency

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

Phenotypic characterisation of DPD deficiency

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

should be considered indicative of complete DPD deficiency and associated with a risk for life-threatening or fatal fluoropyrimidine toxicity.

Hyperbilirubinaemia:

PECASET can induce hyperbilirubinaemia.

The risk of hyperbilirubinaemia with concurrent increases in alkaline phosphatase and/or transaminases is higher in patients with mild to moderate hepatic function impairment due to hepatic metastases. Treatment with **PECASET** should be interrupted if treatment-related elevations of bilirubin increase > 3,0 x upper limit of normal (ULN) or treatment-related elevations in hepatic aminotransferases (alanine transaminase (ALT), aspartate aminotransferase (AST) increase > 2,5 x ULN. Treatment may be resumed once bilirubin levels decrease ≤ 3,0 x ULN or hepatic aminotransferases decrease ≤ 2,5 x ULN.

Dihydropyramidine dehydrogenase (DPD) deficiency:

PECASET is contraindicated in patients with DPD deficiency (see section 4.3).

PECASET can cause stomatitis, diarrhoea, neutropenia and neurotoxicity, which has been attributed to a deficiency of DPD activity. A link between decreased levels of DPD and increased, potentially fatal toxic effects of 5-fluorouracil can therefore not be excluded.

Cytotoxic medication or radiation therapy:

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

Chicken pox or herpes zoster:

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

Diabetes mellitus or electrolyte disturbances:

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

Ophthalmologic complications:

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

Severe skin reactions:

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

Elderly:

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

Lactose intolerance*:*

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

4.5 Interaction with other medicines and other forms of interaction

Warfarin:

See boxed warning above.

Sorivudine and analogues:

Due to the inhibition of DPD by sorivudine, a clinically significant interaction occurs between sorivudine and the capecitabine metabolite 5-FU. This interaction causes increased fluoropyrimidine toxicity and is potentially fatal. **PECASET** should not be administered with sorivudine or any related analogues such as brivudine (see **CONTRAINDICATIONS**).

Phenytoin

Formal interaction studies of phenytoin with **PECASET** have not been conducted. The mechanism of interaction between **PECASET** and phenytoin is presumed to be inhibition of the CYP2C9 isoenzyme system by capecitabine. Plasma concentration and associated clinical symptoms of toxicity may increase as a result of concomitant use with **PECASET**. Dose of phenytoin may need to be reduced with concomitant use. Patients should be regularly monitored for increased phenytoin plasma concentrations.

Food:

Current safety and efficacy data is based upon the administration of **PECASET** after food, therefore it is recommended that **PECASET** be taken after food. Administration of **PECASET** with food decreases the absorption of capecitabine. See section 5.2.

Antacid:

The administration of aluminium and magnesium containing antacids immediately after **PECASET** produces a small increase in capecitabine blood concentrations and the metabolite 5'-DFCR. No effect on other metabolites (5'-DFUR, 5-FU and FBAL) was noted.

Leucovorin (folinic acid):

Leucovorin has no effect on the pharmacokinetics of capecitabine. However, concurrent use may increase the therapeutic and toxic effects of fluorouracil as a result of increased concentrations. Fatalities as a result of severe enterocolitis, diarrhoea and dehydration have been reported in elderly patients who receive **PECASET** and leucovorin concomitantly.

Allopurinol:

Concomitant use of **PECASET** with allopurinol should be avoided as an interaction between allopurinol and 5-FU is possible, and may cause decreased efficacy of 5-FU.

Cytochrome P450:

Caution is advised during co-administration of **PECASET** and isoenzymes 1A2, 2C9 and 3A4 due to a possible interaction (see boxed warning above) with CYP2C9 substrate (warfarin).

Interferon alpha:

The maximum tolerated dose of **PECASET** is reduced when used concomitantly with interferon alpha.

Radiation therapy or bone marrow depressants:

Additive bone marrow depression can occur, including severe dermatitis and/or mucositis. Dosage reduction is recommended when two or more bone marrow depressants, including radiation therapy, are used concomitantly or consecutively. The maximum tolerated dose (MTD) of **PECASET** is reduced during radiotherapy for the treatment of rectal cancer, using either a continuous schedule or given daily Monday to Friday during a 6 week course of radiotherapy.

Oxaliplatin and bevacizumab:

No clinical significant difference in the exposure of **PECASET** or its metabolites, free platinum or total platinum occurred during concomitant treatment with oxaliplatin or in combination with oxaliplatin and bevacizumab. Bevacizumab does not alter the pharmacokinetics of **PECASET** or its metabolites in the presence of oxaliplatin.

Vaccines:

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

Erlotinib:

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Male patients treated with **PECASET** should be advised to use highly effective contraception, until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites plus an additional 3 months after exposure (i.e. five half-lives after the last dose, plus 60-75 days for sperm production plus 10-14 days for the transport to epididymis).

Female patients and female sexual partners of male patients receiving **PECASET**, should be advised to avoid becoming pregnant and to use highly effective contraception, until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites plus an additional 6 months after exposure (i.e. five half-lives after the last dose, plus 6 months which covers the growth and maturation phase of folliculogenesis).

PECASET is contraindicated in pregnancy and lactation.

Pregnancy

PECASET may be mutagenic and teratogenic, and use during pregnancy, especially the first trimester, may lead to foetal abortion, stunting or malformation.

Lactation

It is not known if **PECASET** is excreted into breast milk and should not be taken during breastfeeding, due to the potential risk to the nursing infant.

4.7 Effects on ability to drive and use machines

PECASET can cause side effects such as dizziness, syncope, confusion or vision problems. Patients should be advised not to drive a vehicle or operate machinery until they know how **PECASET** affects them.

4.8 Undesirable effects

PECASET monotherapy:

The safety profiles for metastatic breast cancer, metastatic colorectal cancer and colon cancer are comparable.

Infections and infestations:

Frequent: Herpes simplex, nasopharyngitis, lower respiratory tract infection

Less frequent: Sepsis, cellulitis, oral candidiasis, influenza, fungal infection, herpes infection, infection, tooth abscess, bronchitis, bronchopneumonia, pneumonia, viral infection

Neoplasms benign and malignant (including cysts and polyps):

Less frequent: Lipoma

Blood and the lymphatic system disorders:

Frequent: Neutropenia, anaemia, lymphopenia, thrombocytopenia

Less frequent: Febrile neutropenia, pancytopenia, granulocytopenia, leukopenia, haemolytic anaemia, thrombocytopenic purpura, lymphoedema

Immune system disorders:

Less frequent: Hypersensitivity, anaphylaxis

Metabolism and nutrition disorders:

Frequent: Anorexia, dehydration, decreased appetite

Less frequent: Diabetes mellitus, hypokalaemia, appetite disorder, malnutrition, hypertriglyceridaemia, hypomagnesaemia, cachexia, thirst

Psychiatric disorders:

Frequent: Insomnia, depression

Less frequent: Confusional state, panic attack, dysarthria, hoarseness, irritability

Nervous system disorders:

Frequent: Headache, dizziness, paraesthesia, dysgeusia

Less frequent: Aphasia, memory impairment, ataxia, balance disorder, sensory disorder, peripheral neuropathy, cerebrovascular incident, encephalopathy, loss of consciousness, abnormal coordination, sedation, tremor, difficulty walking

Eye disorders:

Frequent: Increased lacrimation, increased conjunctivitis, eye irritation

Less frequent: Reduced visual acuity, diplopia, keratoconjunctivitis, ocular toxicity, dacryostenosis, photophobia

Ear and labyrinth disorders:

Less frequent: Vertigo, ear pain

Cardiac disorders:

Less frequent: Unstable angina, angina pectoris, myocardial ischaemia, atrial fibrillation, dysrhythmia, tachycardia, sinus tachycardia, palpitations, bradycardia, cardiomyopathy, cardiotoxicity, extrasystoles, myocarditis, ventricular extrasystoles, pericardial effusion, chest pain, electrocardiogram (ECG) changes

Vascular disorders:

Frequent: Thrombophlebitis, epistaxis

Less frequent: Syncope, deep vein thrombosis, hypertension, hypotension, hot flushes, peripheral coldness, coagulation disorder, collapse, haemorrhage

Respiratory, thoracic and mediastinal disorders:

Frequent: Nasopharyngitis, dyspnoea, cough, rhinorrhoea

Less frequent: Tonsillitis, pharyngitis, pulmonary embolism, pneumothorax, haemoptysis, asthma, exertional dyspnoea, bronchospasm, respiratory distress, laryngitis

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, stomatitis, abdominal pain, gastrointestinal haemorrhage, constipation, upper abdominal pain, dyspepsia, flatulence, dry mouth, loose stools

Less frequent: Gastroenteritis, intestinal obstruction, ascites, gastritis, enteritis, dysphagia, lower abdominal pain, oesophagitis, abdominal discomfort, gastro-oesophageal reflux disease, colitis, gastric ulcer, gastrointestinal tract toxicity, ileus, toxic dilation of intestines, abdominal distension, gastrointestinal motility disorder, proctalgia, mucositis, oral ulceration

Hepatobiliary disorders:

Frequent: Hyperbilirubinaemia

Less frequent: Jaundice, cholestatic hepatitis, hepatic fibrosis, hepatitis

Frequency unknown: Hepatic failure

Skin and subcutaneous tissue disorders:

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

Less frequent: Petechiae, skin ulcer, urticaria, photosensitivity reaction, palmar erythema, purpura, facial oedema, increased sweating, erythema multiforme

Musculoskeletal, connective tissue and bone disorders:

Frequent: Pain in extremity, back pain, arthralgia

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

Renal and urinary disorders:

Less frequent: Urinary tract infection, hydronephrosis, urinary incontinence, haematuria, nocturia, renal impairment

Reproductive system and breast disorders:

Less frequent: Decreased libido, vaginal haemorrhage

General disorders and administrative site conditions:

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

Less frequent: Oedema, chills, influenza-like illness, rigors, chest mass, fibrosis

Investigations:

Frequent: Decreased weight, liver function test abnormalities, decreased haemoglobin

Less frequent: Blood in stools, increased INR, increased blood creatinine, increased body temperature, increased weight

Injury and poisoning:

Less frequent: Blister, overdose, radiation recall syndrome

Laboratory abnormalities:

Patients with Grade 1 – 4 abnormality:

Frequent: Decreased haemoglobin, decreased neutrophils/granulocytes, decreased platelets, decreased lymphocytes, decreased sodium, decreased potassium, decreased calcium, increased bilirubin, increased alkaline phosphatase, increased ALT (SGPT), increased AST (SGOT), increased calcium

Patients with Grade 3 or 4 abnormality:

Frequent: Decreased lymphocytes, increased bilirubin, decreased haemoglobin, decreased neutrophils/granulocytes, decreased platelets, decreased calcium, increased alkaline phosphatase, increased ALT (SGPT)

Less frequent: Decreased sodium, decreased potassium, increased calcium, increased AST (SGOT)

Patients with Grade 4 abnormality:

Frequent: Decreased neutrophils/granulocytes, decreased lymphocytes, decreased calcium, increased bilirubin

Less frequent: Decreased haemoglobin, decreased platelets, decreased sodium, decreased potassium, increased calcium, increased alkaline phosphatase, increased ALT (SGPT), increased AST (SGOT)

PECASET in combination with other medicines:

The following side effects occur in addition to the side effects of **PECASET** when used as monotherapy.

PECASET in combination with cisplatin:

Infections and infestations:

Frequent: Herpes zoster, urinary tract infection

Blood and the lymphatic system disorders:

Frequent: Neutropenia, leukopenia, anaemia, thrombocytopenia, bone marrow depression

Metabolism and nutrition disorders:

Frequent: Hypokalaemia, hyponatraemia

Psychiatric disorders:

Frequent: Sleep disorder

Nervous system disorders:

Frequent: Neuropathy, peripheral sensory neuropathy, hypoaesthesia

Ear and labyrinth disorders:

Frequent: Tinnitus, hypoacusis

Gastrointestinal disorders:

Frequent: Upper gastrointestinal haemorrhage, mouth ulceration, gastritis

Hepatobiliary disorders:

Frequent: Abnormal hepatic function

Skin and subcutaneous tissue disorders:

Frequent: Palmar-plantar erythrodysaesthesia, hyperhidrosis, mucosal inflammation

Musculoskeletal, connective tissue and bone disorders:

Frequent: Myalgia

Investigations:

Frequent: Decreased creatinine clearance

PECASET in combination with docetaxel:

Infections and infestations:

Frequent: Oral candidiasis

Blood and the lymphatic system disorders:

Frequent: Neutropenic fever (Grade 3 - 4)

Metabolism and nutrition disorders:

Frequent: Decreased appetite

Nervous system disorders:

Frequent: Paraesthesia, peripheral neuropathy, taste disturbances

Eye disorders:

Frequent: Increased lacrimation

Respiratory, thoracic and mediastinal disorders:

Frequent: Sore throat

Gastrointestinal disorders:

Frequent: Constipation, dyspepsia

Skin and subcutaneous tissue disorders:

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

Musculoskeletal, connective tissue and bone disorders:

Frequent: Myalgia, arthralgia, pain in limb

General disorders and administrative site conditions:

Frequent: Lower limb oedema pyrexia, weakness, pain in limb, pain

PECASET in combination with oxaliplatin:

Infections and infestations:

Frequent: Upper respiratory tract infection, urinary tract infection

Blood and the lymphatic system disorders:

Frequent: Neutropenia, thrombocytopenia, anaemia, leukopenia

Immune system disorders:

Frequent: Hypersensitivity

Metabolism and nutrition disorders:

Frequent: Hypokalaemia, hypomagnesaemia, hypocalcaemia

Psychiatric disorders:

Frequent: Anxiety

Nervous system disorders:

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

Eye disorders:

Frequent: Blurred vision, dry eyes, visual disturbances

Cardiac disorders:

Frequent: Chest pain

Vascular disorders:

Frequent: Flushing, hypertension, hypotension

Respiratory, thoracic and mediastinal disorders:

Frequent: Pharyngeal dysaesthesia, pharyngolaryngeal pain

Gastrointestinal disorders:

Frequent: Hiccups, constipation, oral dysaesthesia, abdominal distention, gastro-oesophageal reflux disease, oral pain, dysphagia, oral paraesthesia, rectal haemorrhage, lower abdominal pain

Skin and subcutaneous tissue disorders:

Frequent: Hyperhidrosis, urticaria

Musculoskeletal, connective tissue and bone disorders:

Frequent: Jaw pain, muscle spasms, myalgia, trismus, muscular weakness

Renal and urinary disorders:

Frequent: Haematuria

General disorders and administrative site conditions:

Frequent: Pyrexia, temperature intolerance, chills

PECASET in combination with oxaliplatin and bevacizumab:

Infections and infestations:

Frequent: Influenza

Blood and the lymphatic system disorders:

Frequent: Febrile neutropenia

Metabolism and nutrition disorders:

Frequent: Hyperglycaemia

Nervous system disorders:

Frequent: Headache

Cardiac disorders:

Frequent: Atrial fibrillation, myocardial ischaemia

Vascular disorders:

Frequent: Hypertension, deep vein thrombosis, hypertensive crisis

Respiratory, thoracic and mediastinal disorders:

Frequent: Rhinitis, pulmonary embolism

Gastrointestinal disorders:

Frequent: Gastritis

Skin and subcutaneous tissue disorders:

Frequent: Night sweats

Musculoskeletal, connective tissue and bone disorders:

Frequent: Pain in extremity

Renal and urinary disorders:

Frequent: Proteinuria

General disorders and administrative site conditions:

Frequent: Pain, influenza-like illness

Investigations:

Frequent: Increased blood pressure

Injury and poisoning:

Frequent: Contusion

PECASET in combination with irinotecan:

The following side effects occur frequently: thrombosis, embolism, hypersensitivity, cardiac ischaemia or infarction, and febrile neutropenia.

PECASET in combination with irinotecan and bevacizumab:

The following side effects occur frequently: neutropenia, thrombosis, embolism, hypertension and cardiac ischaemia or infarction.

PECASET in combination with epirubicin and oxaliplatin:

The following side effects occur frequently: leukopenia, neutropenia, lethargy, anaemia, thrombocytopenia, febrile neutropenia, peripheral neuropathy, infection, fever and thromboembolism.

PECASET in combination with epirubicin and cisplatin:

The following side effects occur frequently: thromboembolism, thrombocytopenia, febrile neutropenia, peripheral neuropathy, infection and fever.

The following side effects occur less frequently: hepatic failure and cholestatic hepatitis.

Reporting of suspected adverse reactions

If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Eurolab (Pty) Ltd. by email: drug-safety@eurolab.co.za. By reporting side effects, you can help provide more information on the safety of PECASET.

4.9 Overdose

In the event of overdose, side effects such as nausea, vomiting, diarrhoea, mucositis, gastrointestinal irritation and bleeding, and bone marrow depression can occur. Treatment is symptomatic and supportive.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: cytostatic agents, ATC code: L01BC06

Capecitabine is a fluoropyramidine carbamate, tumour-activated and tumour-selective prodrug cytotoxic agent, which is orally administered.

In vitro capecitabine is non-cytotoxic. However, *in vivo* capecitabine is converted to the cytotoxic moiety, 5-fluorouracil (5-FU). To exert its cytotoxic activity, 5-FU requires enzymatic conversion (ribosylation and phosphorylation) to the nucleotide form.

The formation of 5-FU is preferentially catalysed by the tumour associated angiogenic factor thymidine phosphorylase (dThdPase) at the tumour site. Thymidine phosphorylase is found in both normal and tumour tissue, albeit in lower levels, therefore 5-FU is metabolised by both normal and tumour cells to 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine-triphosphate (FUTP).

These metabolites cause cell injury by two mechanisms. Firstly, a covalently bound ternary complex is formed by FdUMP and the folate cofactor, N^{5-10}-methylenetetrahydrofolate, which binds to thymidylate synthase (TS). 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, therefore a deficiency of this compound can inhibit cell division. Secondly, during the synthesis of RNA, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP). This metabolic error can interfere with RNA processing and protein synthesis.

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

5.2 Pharmacokinetic properties

Absorption:

Capecitabine is well absorbed after oral administration and is extensively converted to the metabolites 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'deoxy-5-fluorouridine (5'DFUR).

The administration of 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 the subsequent metabolite 5-FU.

Protein binding:

In vitro capecitabine, 5'-DFCR, 5'-DFUR and 5-FU are 54 %, 10 %, 62 % and 10 % protein bound, mainly to albumin.

Metabolism:

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

After the conversion to 5-FU and anabolites, the metabolites of capecitabine become cytotoxic. 5-FU is further catabolised via dihydropyrimidine dehydrogenase (DPD), which is rate limiting, to inactive metabolites dihydro-5-fluorouracil (FUH_2), 5-fluoro-ureidopropionic acid (FUPA) and FBAL.

Elimination:

The elimination half-lives of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL are 0,85; 1,11; 0,66; 0,76 and 3,23 hours respectively. The pharmacokinetics of capecitabine and its metabolites, except 5-FU, are dose proportional.
95,5 % of the administered capecitabine dose is recovered in urine. The major metabolite excreted in urine is FBAL, which represents 57 % of the administered dose. Approximately 3 % of the administered dose is excreted as unchanged capecitabine. Faecal excretion is minimal at 2,6 %. Inter-patient variability in peak plasma concentration and AUC of 5-FU is > 85 %.

Special populations:

Hepatic impairment due to liver metastases:

No clinically significant effect on the pharmacokinetics and the bioactivation of capecitabine was noted in cancer patients with mildly to moderately impaired liver function due to liver metastases. There is no pharmacokinetic data available in patients with severe hepatic impairment (see section 4.2).

Renal impairment:

In patients with mild to severe renal impairment, there is no evidence of an effect of the creatinine clearance on the pharmacokinetics of capecitabine or 5-FU. Creatinine clearance influences 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 with antiproliferative activity and 5'-DFUR is the direct precursor of 5-FU (see 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

Other ingredients of the tablet:

Croscarmellose sodium,

ferric oxide red (colourant),

ferric oxide yellow (colourant),

hypromellose,

lactose anhydrous,

magnesium stearate,

microcrystalline cellulose,

talcum,

titanium oxide,

Contains sugar: lactose anhydrous.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blister strips in outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Clear transparent PVC/PVdC/aluminium blister strips containing 10 tablets.

Pack size: 30, 60 or 120 tablets are packed into an outer carton.

Or

Aluminium/aluminium blister strips containing 10 tablets.

Pack size: 30, 60 or 120 tablets are packed into an outer carton

6.6 Special precautions for disposal and other handling

Special handling using appropriate equipment and disposal procedures, should be taken as Pecaset is a cytotoxic medicine.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd

Woodmead Office Park,

3 Stirrup Lane, Van Reenens Avenue,

Woodmead, 2144

8. REGISTRATION NUMBER(S)

PECASET 150: 49/26/0681

PECASET 500: 49/26/0682

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 30 September 2016

10. DATE OF REVISION OF THE TEXT

Last revision: 22 April 2025