

PRODUCT MONOGRAPH

 CAPRELSA[®]

Vandetanib tablets

100 and 300 mg

Receptor tyrosine kinase inhibitor

Sanofi Genzyme, a division of sanofi-aventis
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CAPRELSA®

Vandetanib tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet/100 mg, 300 mg	None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

CAPRELSA (vandetanib) monotherapy is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in adult patients with unresectable locally advanced or metastatic disease. CAPRELSA use should be carefully considered based on a risk:benefit assessment in patients with indolent, asymptomatic or slowly progressive disease because of the significant treatment-related risks.

CAPRELSA should only be prescribed by a qualified physician who has completed the certification with the **CAPRELSA Restricted Distribution Program** and who is experienced in the use of antineoplastic therapy and in the treatment of medullary thyroid cancer.

Marketing authorization was based on a primary efficacy endpoint of progression-free survival (PFS) at 2 years (RECIST criteria assessed by independent central review) (See CLINICAL TRIALS). An overall survival benefit has not been established.

CAPRELSA Restricted Distribution Program

CAPRELSA is only available through a controlled program referred to as the CAPRELSA Restricted Distribution Program. Under this program, only prescribers and pharmacies that have completed the certification and are registered with the program are able to prescribe and dispense, respectively, CAPRELSA. Only-patients who are enrolled and meet all of the requirements of the CAPRELSA Restricted Distribution Program can receive CAPRELSA. For further information about the program, please call 1 (800) 589-6215 or visit www.caprelsa.ca/rdp.

Geriatrics (> 65 years of age): No adjustment in starting dose is required for elderly patients (over 65 years old). There is limited data for patients over the age of 75.

Pediatrics (< 18 years of age): CAPRELSA is not indicated for use in pediatric patients, as safety and efficacy of CAPRELSA in children have not been established.

CONTRAINDICATIONS

CAPRELSA (vandetanib) is contraindicated in patients with:

- Congenital long QT syndrome or with a persistent Fridericia-corrected electrocardiogram interval (QTcF) of ≥ 500 ms (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS).
- Uncorrected hypokalemia, hypomagnesemia or hypocalcemia.
- Uncontrolled hypertension.
- Known hypersensitivity to the active substance, vandetanib, or to any of its excipients. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

CAPRELSA (vandetanib) should only be prescribed by a qualified physician who has completed the certification with the CAPRELSA Restricted Distribution Program and who is experienced in the use of antineoplastic therapy and in the treatment of medullary thyroid cancer.

- CAPRELSA can prolong the QTcF interval. Torsade de Pointes and sudden death have been reported in patients receiving CAPRELSA. CAPRELSA results in a QTcF interval increase from baseline of greater than 35 ms. Due to the long half-life of 19 days of vandetanib, ECG QTcF intervals should be measured at baseline, 2-4 weeks and 8-12 weeks during treatment, and every three months thereafter, as well as following dose adjustments. Machine-read QTcF interval measurements may not be accurate. Consultation with a cardiologist should be considered when assessing the QTcF intervals to ensure appropriate treatment decisions. CAPRELSA must not be used in patients with uncorrected hypokalemia, hypomagnesemia, hypocalcemia, or long QT syndrome. Monitoring for these electrolytes should be conducted at baseline, 2-4 weeks, 8-12 weeks and every three months thereafter, and following dose adjustments. Given the long half-life of 19

days, adverse reactions including QTcF interval prolongation may not resolve quickly (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS).

- Heart failure (fatal) (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS)
- Hypertension (Grade 4) or Hypertensive Crisis (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS)

Cardiovascular

Patients with congenital long QT syndrome, significant cardiac events or history of cardiac disease (e.g., ventricular arrhythmia, recent myocardial infarction), or uncontrolled hypertension were excluded from studies with CAPRELSA; therefore, the safety of CAPRELSA in these patients is not known (see ADVERSE REACTIONS).

QTcF Interval Prolongation and Torsade de Pointes

Nonclinical data indicate that vandetanib has the potential to prolong cardiac ventricular repolarization (QTcF interval) (see TOXICOLOGY).

In pooled monotherapy trials with CAPRELSA (n=1839 patients), Torsade de Pointes and sudden death have been reported (uncommon frequency $\geq 0.1\%$ to $<1\%$). Ventricular tachycardia and ventricular fibrillation have been reported with an uncommon frequency in patients administered CAPRELSA 300 mg daily.

Prolongation of the electrocardiogram (ECG) QTcF interval has been observed in patients receiving CAPRELSA (see ADVERSE REACTIONS). At a daily oral dose of 300 mg in patients with medullary thyroid cancer, adverse events of QTcF interval prolongation were reported in the phase III study, ZETA (Study 58) in 14% of CAPRELSA-treated patients versus 1% in the placebo arm. Based on the exposure-response relationship, the mean (90% CI) QTcF change from baseline (Δ QTcF) was 35 (33-36) ms for the 300-mg dose. The Δ QTcF remained above 30 ms for the duration of the trial (up to 2 years). In addition, 36% of patients experienced greater than 60 ms increase in Δ QTcF and 7% of patients had QTcF greater than 500 ms. QTcF interval prolongation appears to be dose-dependent.

CAPRELSA treatment should not be started in patients whose QTcF interval is confirmed to be ≥ 500 ms. CAPRELSA should not be given to patients who have a history of Torsade de Pointes unless all risk factors that contributed to Torsade have been corrected. Due to the 19 day half-life, a QTcF interval prolongation may not resolve quickly.

Machine-read QTcF interval measurements may not be accurate. Consultation with a cardiologist should be considered when assessing the QTcF intervals to ensure appropriate treatment decisions.

Levels of serum potassium, calcium, magnesium and thyroid stimulating hormone (TSH) should be obtained at baseline, at 2-4 weeks and 8-12 weeks after starting treatment with

CAPRELSA and every 3 months thereafter, and also following dose adjustments. Blood tests should also be obtained as clinically indicated during this period and afterwards. Serum potassium level should be maintained at 4mEq/L or higher (high normal range) and serum magnesium and serum calcium should be kept within normal range to reduce the risk of ECG QTcF interval prolongation.

CAPRELSA may be administered with drugs known to prolong the QTcF interval if there is no appropriate alternative therapy. If such drugs are given to patients already receiving CAPRELSA, ECG monitoring of the QTcF interval as appropriate to the pharmacokinetics of the added drug should be performed.

In the event of a QTcF interval ≥ 500 ms, patients should interrupt dosing until QTcF returns to less than 450 ms, then resume at a reduced dose. The 300 mg daily dose can be reduced to 200 mg (two 100 mg tablets), and then to 100 mg if necessary (see DOSAGE AND ADMINISTRATION).

Heart Failure

Fatal heart failure has been observed in patients who received CAPRELSA. Discontinuation of CAPRELSA may be necessary in patients with heart failure. Heart failure may not be reversible on stopping CAPRELSA (see ADVERSE REACTIONS).

Hypertension

Hypertension (Grade 4), including hypertensive crisis, has been observed in patients treated with CAPRELSA; patients should be monitored for hypertension and controlled as appropriate. If high blood pressure cannot be controlled, CAPRELSA should not be restarted until the blood pressure is controlled medically. Reduction in dose may be necessary (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Ischemic Cerebrovascular Events

Ischemic cerebrovascular events (some of which have been fatal) have been observed with CAPRELSA. In the randomized study in patients with medullary thyroid cancer, ischemic cerebrovascular events were observed more frequently with CAPRELSA versus placebo (1.3% versus 0%) and no deaths were reported. The safety of resuming CAPRELSA therapy after resolution of an ischemic cerebrovascular event has not been studied. Discontinue CAPRELSA in patients who experience a severe ischemic cerebrovascular event.

Endocrine and Metabolism

Hypothyroidism

In the randomized medullary thyroid cancer study where 90% of patients enrolled had prior thyroidectomy, increases in the dose of the thyroid replacement therapy were required in 49% of the patients randomized to CAPRELSA compared to 17% of patients randomized to placebo. Thyroid stimulating hormone (TSH) levels should be obtained at baseline, at 2-4 weeks and 8-12 weeks and every three months thereafter during treatment with CAPRELSA.

If signs or symptoms of hypothyroidism occur, thyroid hormone levels should be monitored and thyroid replacement therapy should be adjusted accordingly.

Gastrointestinal

Diarrhea

Diarrhea has been observed in patients treated with CAPRELSA (see ADVERSE REACTIONS). Routine anti-diarrheal agents are recommended for the treatment of diarrhea. Serum electrolytes should be monitored at baseline, at 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA and every three months thereafter. If severe diarrhea (CTCAE grade 3-4) develops, CAPRELSA should be stopped until diarrhea improves. Upon improvement, treatment with CAPRELSA should be resumed at a reduced dose (see DOSAGE AND ADMINISTRATION).

Hemorrhage

Serious hemorrhagic events, some of which were fatal, have been observed with CAPRELSA. There were no fatal bleeding events in the randomized clinical trial in patients with medullary thyroid cancer. Fatal bleeding events have occurred (frequency uncommon) while on CAPRELSA therapy in clinical monotherapy trials. Do not administer CAPRELSA to patients with a recent history of hemoptysis of $\geq \frac{1}{2}$ teaspoon of red blood. Discontinue CAPRELSA in patients with severe hemorrhage (see ADVERSE REACTIONS).

Hepatic/ Biliary and Pancreatic

Liver Transaminase Elevation

Asymptomatic increases in alanine aminotransferase (ALT) have been observed in patients receiving CAPRELSA. Therefore, periodic liver function testing (transaminases, bilirubin and alkaline phosphatase) should be considered. Dose reduction or interruption of CAPRELSA therapy should be considered if liver function changes are severe (see ACTION AND CLINICAL PHARMACOLOGY). Cases of hepatic failure including fatalities have been reported with CAPRELSA use in patients with pre-existing hepatic disease.

Neurologic

Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by a brain MRI, has been observed in the CAPRELSA program (frequency uncommon). RPLS should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function (see ADVERSE REACTIONS). Discontinuation of CAPRELSA treatment in patients with RPLS should be considered.

Ophthalmologic

Blurred vision and corneal opacities were reported more often in patients who received CAPRELSA versus patients who received placebo for medullary thyroid cancer (9% vs. 1%,

respectively for blurred vision; 5% vs. 0% for corneal opacity). Scheduled slit lamp examinations have revealed corneal opacities (vortex keratopathies) in treated patients, which can lead to halos and decreased visual acuity. It is unknown if this will improve after discontinuation. Ophthalmologic examination, including slit lamp, is recommended in patients who report visual changes (see ADVERSE REACTIONS).

Effects On Ability To Drive and Use Machines

No studies to establish the effects of CAPRELSA on ability to drive and use machinery have been conducted. However, during treatment with CAPRELSA, fatigue and blurred vision have been reported and those patients who experience these symptoms should observe caution when driving or using machines (see ADVERSE REACTIONS).

Respiratory

Interstitial Lung Disease or Pneumonitis

Interstitial Lung Disease (ILD) (Grade 3-5) or pneumonitis has been observed with CAPRELSA and deaths have been reported. Consider a diagnosis of ILD in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Advise patients to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of ILD and have few or no symptoms may continue CAPRELSA therapy while further clinical investigations are being undertaken with close monitoring at the discretion of the treating physician.

If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids and antibiotics may be indicated.

If ILD is confirmed, CAPRELSA should be permanently discontinued.

Skin Reactions and Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

Rash and other skin reactions (including exfoliative rash, photosensitivity reactions and palmar-plantar erythrodysesthesia syndrome) and severe skin reactions such as Stevens-Johnson Syndrome (fatal) and toxic epidermal necrolysis (fatal) have been observed in patients who have received CAPRELSA (see ADVERSE REACTIONS).

Mild to moderate skin reactions can usually be managed by symptomatic treatment (e.g., corticosteroids, oral antihistamines and topical antibiotics), or by dose reduction. For more severe skin reactions (such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis), referral of the patient to seek urgent medical advice is recommended. Systemic therapies e.g. steroids, may be appropriate in such cases and permanent discontinuation of CAPRELSA is recommended. (see DOSAGE AND ADMINISTRATION).

Care should be taken with sun exposure by wearing protective clothing and /or sun block and when administering CAPRELSA with drugs that cause skin toxicity. Due to the long half-life of vandetanib, protective clothing and sun block should continue for 4 months after discontinuation of CAPRELSA. In an *in vitro* assay, there is evidence of phototoxicity (see TOXICOLOGY).

Wound Healing

There is nonclinical evidence that vandetanib slows but does not prevent wound healing in animals (see TOXICOLOGY). The potential for delayed wound healing in humans has not been studied, but is a possible risk. The appropriate interval between discontinuation of CAPRELSA and subsequent elective surgery to avoid the risks of impaired wound healing has not been studied.

Special Populations

Renal Impairment

CAPRELSA exposure is increased in patients with impaired renal function (see ACTION AND CLINICAL PHARMACOLOGY). The starting dose should be reduced to 200 mg in patients with moderate and severe renal impairment. The QTcF interval should be monitored closely. There is no information available for patients with end-stage renal disease requiring dialysis (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment

CAPRELSA is not recommended for use in patients with moderate and severe hepatic impairment, as safety and efficacy have not been established (see ACTION AND CLINICAL PHARMACOLOGY).

Pregnant Women / Women of Childbearing Potential

There are no adequate and well-controlled studies in pregnant women using CAPRELSA. In nonclinical studies in rats, vandetanib was embryotoxic, fetotoxic, and teratogenic, at exposures equivalent to or lower than those expected at the recommended human dose of 300 mg/day. As expected from its pharmacological actions, vandetanib has shown significant effects on all stages of female reproduction in rats (see TOXICOLOGY).

Women of childbearing potential must be advised to use effective contraception during treatment with CAPRELSA and for at least 3 months following the last dose of CAPRELSA.

If CAPRELSA is used during pregnancy or if the patient becomes pregnant while receiving CAPRELSA, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with CAPRELSA.

Men must be advised to use an acceptable method of contraception (defined as barrier methods in conjunction with spermicides), or be surgically sterile, while receiving CAPRELSA and for 2 months after the last dose.

Nursing Women

There are no data on the use of CAPRELSA in breast feeding women. Breast feeding mothers are advised to discontinue nursing while receiving CAPRELSA therapy. Vandetanib was excreted into milk in rats and found in plasma of pups following dosing to lactating rats (see TOXICOLOGY).

Pediatrics

CAPRELSA is not indicated for use in pediatric patients, as safety and efficacy of CAPRELSA in children have not been established.

Geriatrics

No adjustment in starting dose is required for elderly patients (over 65 years old). There is limited data for patients over the age of 75.

Monitoring and Laboratory Tests

Electrocardiograms (ECGs) must be obtained at baseline, 2-4 weeks and 8-12 weeks, and every three months thereafter, and following dose adjustments (see WARNINGS AND PRECAUTIONS, DOSAGE and ADMINISTRATION). Machine-read QTcF interval measurements may not be accurate. Consultation with a cardiologist should be considered when assessing the QTcF intervals to ensure appropriate treatment decisions.

Blood tests to measure levels of serum potassium, calcium, magnesium and thyroid stimulating hormone (TSH) should be obtained at baseline, at 2-4 weeks and 8-12 weeks during treatment with CAPRELSA and every three months thereafter, and following dose adjustments. Serum potassium level should be maintained at 4mEq/L or higher (high normal range) and serum magnesium and serum calcium should be kept within normal range to reduce the risk of QTcF interval prolongation (see DOSAGE AND ADMINISTRATION).

Alanine Aminotransferase Elevations

Alanine aminotransferase (ALT) elevations occur commonly in patients treated with CAPRELSA. The majority of elevations resolve while continuing treatment with CAPRELSA, others usually resolve after a 1-2 week interruption in therapy. Periodic monitoring of ALT is recommended in patients receiving CAPRELSA (see ADVERSE REACTIONS).

Blood pressure elevation

Blood pressure measurements should be performed at baseline, 2-4 weeks and 8-12 weeks and every three months thereafter during treatment with CAPRELSA, and following dose adjustments.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Across all CAPRELSA (vandetanib) clinical studies, approximately 4000 patients have received CAPRELSA. This includes patients receiving CAPRELSA as monotherapy or in combination with chemotherapy, across a range of tumour types.

In ZETA, the randomised, double blind, pivotal phase III clinical study (Study 58) in unresectable locally advanced and metastatic medullary thyroid cancer patients, the safety analysis set included 330 patients (231 patients in the CAPRELSA arm and 99 patients in the placebo arm; 1 patient randomised to receive placebo did not receive treatment).

The most commonly reported adverse events (AEs) in the CAPRELSA arm of the ZETA study were diarrhea, rash, nausea, hypertension, headache, fatigue, acne and abdominal pain, along with decreased calcium, increased ALT and decreased glucose. These events are consistent with the known safety profile of CAPRELSA and the mechanism of action of vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) inhibition.

The most commonly reported AEs that led to CAPRELSA dose reduction were diarrhea, QTcF prolongation, and rash. Patients who dose reduced from 300 mg to 200 mg or 100 mg remained on the lower dose for a median of 23 weeks or 29 weeks, respectively.

Clinical Trial Adverse Drug Reactions

The following adverse events have been identified in the pivotal ZETA clinical study (Study 58) with patients receiving CAPRELSA monotherapy as treatment for unresectable locally advanced and metastatic medullary thyroid cancer (N=231).

Table 1 presents the adverse events reported at a very common ($\geq 10\%$) frequency in ZETA.

Table 1 Summary of patients who had at least 1 adverse event at a very common ($\geq 10\%$) frequency in the pivotal Phase III ZETA study (Study 58) for medullary thyroid cancer

Preferred term (PT)	CAPRELSA 300 mg daily N=231 ^a N (%)	Placebo N=99 ^a N (%)	CTCAE Grade 3 or higher CAPRELSA N (%)	CTCAE Grade 3 or higher Placebo N (%)
Cardiac disorders				
Electrocardiogram QT Prolonged ^b	33 (14)	1 (1)	18 (8)	1 (1)
Gastrointestinal disorders				

Preferred term (PT)	CAPRELSA 300 mg daily N=231 ^a N (%)	Placebo N=99 ^a N (%)	CTCAE Grade 3 or higher CAPRELSA N (%)	CTCAE Grade 3 or higher Placebo N (%)
Diarrhea	130 (56)	26 (26)	25 (11)	2 (2)
Nausea	77 (33)	16 (16)	2 (1)	0
Vomiting	34 (15)	7 (7)	2 (1)	0
Abdominal Pain	33 (14)	5 (5)	4 (2)	0
Dyspepsia	25 (11)	4 (4)	0	0
General disorders				
Fatigue	55 (24)	23 (23)	13 (6)	1 (1)
Asthenia	34 (15)	11 (11)	6 (3)	1 (1)
Investigations				
Weight Decreased	24 (10)	9 (9)	2 (1)	0
Metabolism and nutrition disorders				
Decreased Appetite	49 (21)	12 (12)	9 (4)	0
Hypocalcemia	25 (11)	3 (3)	4 (2)	0
Psychiatric disorders				
Insomnia	30 (13)	10 (10)	0	0
Respiratory disorders				
Nasopharyngitis	26 (11)	9 (9)	0	0
Cough	25 (11)	10 (10)	0	0
Skin and subcutaneous tissue disorders				
Rash	104 (45)	11 (11)	8 (3)	0
Acne	46 (20)	5 (5)	2 (1)	0
Dry Skin	35 (15)	5 (5)	0	0
Dermatitis Acneiform	35 (15)	2 (2)	0	0
Pruritus	25 (11)	4 (4)	3 (1)	0
Photosensitivity Reaction	31 (13)	0	4 (2)	0
Nervous system disorders				
Headache	59 (26)	9 (9)	2 (1)	0
Vascular disorders				
Hypertension	73 (32)	5 (5)	16 (7)	0

^a Number (%) of patients with adverse events (AEs), by system organ class (SOC) then in decreasing order of frequency.

Only patients who took at least 1 dose of randomized treatment are included in this table. AEs that occurred while on CAPRELSA or in the 60-day follow-up period after the last dose of CAPRELSA are included.

^b Reported as an AE, not via confirmed electrocardiogram.

Table 2 presents a summary of patients who experienced at least 1 serious adverse event with CAPRELSA during randomized treatment with a common ($\geq 1\%$ to $<10\%$) or very common ($\geq 10\%$) frequency in ZETA.

Table 2 Summary of patients who experienced at least 1 serious adverse event with CAPRELSA during randomized treatment with a frequency of $\geq 1\%$ in ZETA (Study 58)

Preferred term (PT)	CAPRELSA 300 mg daily N=231 ^a N (%)	Placebo N=99 ^a N (%)
Infections and Infestations		
Pneumonia	5 (2.2)	0 (0.0)
Urinary Tract Infection	3 (1.3)	0 (0.0)
Gastrointestinal Disorders		
Diarrhea	5 (2.2)	0 (0.0)
Abdominal Pain	3 (1.3)	0 (0.0)
Metabolism and Nutrition Disorders		
Decreased Appetite	4 (1.7)	0 (0.0)
Hypercalcemia	3 (1.3)	0 (0.0)
Vascular Disorders		
Hypertensive Crisis	4 (1.7)	0 (0.0)
Hypertension	3 (1.3)	0 (0.0)
Psychiatric Disorders		
Depression	3 (1.3)	0 (0.0)

^a Number (%) of patients with serious adverse events (SAEs), by system organ class (SOC) then in decreasing order of frequency.

Only patients who took at least 1 dose of randomized treatment are included in this table. SAEs that occurred while on CAPRELSA or in the 60-day follow-up period after the last dose of CAPRELSA are included.

Additional common adverse drug reactions include alopecia, nail disorders and tremor.

Less Common Clinical Trial Serious Adverse Drug Events (<1%)

The following serious adverse events were reported with CAPRELSA during randomized treatment with an uncommon ($\geq 0.1\%$ to $<1\%$) or rare frequency ($\leq 0.1\%$) in ZETA (Study 58):

Cardiac Disorders: Arrhythmia (0.4%), atrial fibrillation (0.4%), bradycardia (0.4%), cardiac failure acute (0.4%), pericarditis (0.4%).

Eye Disorders: Glaucoma (0.4%), vision blurred (0.4%).

Gastrointestinal Disorders: Dysphagia (0.9%), vomiting (0.9%), gastrointestinal hemorrhage (0.4%), colitis (0.4%), gastritis (0.4%), ileus (0.4%), pancreatitis (0.4%), peritonitis (0.4%), pneumatosis intestinalis (0.4%), small intestinal perforation (0.4%).

General Disorders and Administration Site Conditions: Asthenia (0.4%), fatigue (0.4%), general physical health deterioration (0.4%), chest pain (0.4%), mucosal inflammation (0.4%).

Hepatobiliary Disorders: Cholecystitis (0.4%), cholelithiasis (0.4%).

Infections and Infestations: Bronchitis (0.9%), appendicitis (0.9%), diverticulitis (0.9%), sepsis (0.9%), abdominal wall abscess (0.4%), gastroenteritis bacterial (0.4%), gastroenteritis viral (0.4%), infected bites (0.4%), laryngitis (0.4%), pyelonephritis (0.4%), staphylococcal infection (0.4%), staphylococcal sepsis (0.4%), tracheitis (0.4%).

Injury, Poisoning and Procedural Complications: Joint injury (0.4%), stent occlusion (0.4%), venomous bite (0.4%).

Metabolism and Nutrition Disorders: Dehydration (0.9%), hypocalcemia (0.9%), hypokalemia (0.9%), hypoglycaemia (0.4%), hyponatremia (0.4%), malnutrition (0.4%).

Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps): Metastasis to bone (0.4%).

Nervous System Disorders: Loss of consciousness (0.9%), transient ischemic attack (0.9%), brain edema (0.4%), cerebral ischemia (0.4%), depressed level of consciousness (0.4%), peripheral sensorimotor neuropathy (0.4%).

Psychiatric Disorders: Bipolar disorder (0.4%).

Renal and Urinary Disorders: Nephrolithiasis (0.9%), anuria (0.4%), calculus ureteric (0.4%), renal colic (0.4%), renal failure (0.4%), tubulointerstitial nephritis (0.4%).

Respiratory, Thoracic and Mediastinal Disorders: Pneumonitis (0.9%), hemoptysis (0.4%), bronchospasm (0.4%), chylothorax (0.4%), dyspnea (0.4%), pneumonia aspiration (0.4%), respiratory arrest (0.4%), respiratory failure (0.4%).

Skin and Subcutaneous Tissue Disorders: Photosensitivity reaction (0.9%), pruritis (0.4%), rash (0.4%), skin ulcer (0.4%).

Vascular Disorders: Accelerated hypertension (0.4%), pelvic venous thrombosis (0.4%), vena cava thrombosis (0.4%).

Additional uncommon ($\geq 0.1\%$ to $< 1\%$) adverse drug reactions include Stevens-Johnson syndrome, Erythema multiforme and Toxic epidermal necrolysis. The frequency of these adverse drug reactions is based on the cumulative number of patients exposed to CAPRELSA across all clinical trials in a range of tumour types.

Abnormal Hematologic and Clinical Chemistry Findings

Table 3 provides the frequency and severity of laboratory abnormalities reported for patients receiving CAPRELSA for unresectable locally advanced and metastatic medullary thyroid cancer.

Table 3 Frequency and severity of laboratory abnormalities from the ZETA pivotal phase III study (Study 58) for medullary thyroid cancer

Laboratory parameter	CAPRELSA 300 mg daily N=231			Placebo N=99		
	All grades N (%)	CTCAE grade 3 N (%)	CTCAE grade 4 N (%)	All grades N (%)	CTCAE grade 3 N (%)	CTCAE grade 4 N (%)
Decreased hemoglobin	23 (10)	1 (0.4)	0	19 (19)	2 (2)	0
Decreased leucocytes	45 (20)	0	0	25 (25)	0	0
Decreased absolute neutrophils	21 (9)	1 (0.4)	0	5 (5)	2 (2)	0
Decreased platelets	18 (8)	1 (0.4)	0	3 (3)	0	0
Increased alanine aminotransferase	118 (51)	4 (2)	0	19 (19)	0	0
Increased aspartate aminotransferase	69 (30)	0	0	12 (12)	0	0
Increased total bilirubin	29 (13)	0	0	16 (16)	0	0
Increased creatinine	38 (17)	0	0	1 (1)	0	0
Decreased serum calcium	132 (57)	10 (4)	3 (1)	25 (25)	3 (3)	0
Decreased serum magnesium	17 (8)	1 (0.4)	0	2 (2)	0	0

Decreased serum potassium	16 (7)	1 (0.4)	0	3 (3)	0	0
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Twenty two (9.5%) and 4 (4.0%) patients in the CAPRELSA and placebo arms, respectively, had laboratory International Normalized Ratio (INR) increases of CTCAE grade 3 or 4.

Abnormal Electrocardiographic (ECG) Findings

A total of 17 patients in the CAPRELSA arm (7%) had a QTcF prolongation greater than 500 ms while on randomised treatment or during the 60-day follow-up period after the last dose of randomised treatment.

Serious Adverse Drug Events in non-pivotal Clinical Trial

The following serious adverse events were reported during the open-label phase of the non-pivotal clinical trial (D4200C00097) with patients receiving CAPRELSA monotherapy for unresectable locally advanced or metastatic medullary thyroid cancer (N=39).

- **Renal and Urinary Disorders:** Renal failure (1 of 39; 2.6%)
- **Neoplasms benign, malignant and unspecified (including cysts and polyps):** Adenocarcinoma pancreas (1 of 39; 2.6%)
- **Musculoskeletal and connective tissue disorders:** Soft tissue necrosis (1 of 39; 2.6%)

DRUG INTERACTIONS

Serious Drug Interactions

- Concomitant use of drugs that prolong QT interval should be avoided.
- Potent CYP3A4 inhibitors should be avoided as they can increase vandetanib serum concentrations.

Drug-Drug Interactions

Drugs That May Decrease Vandetanib Serum Concentrations

CYP3A4 Inducers: The concomitant administration of medications that induce CYP3A4 (these may include phenytoin, rifampin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to CAPRELSA and should be avoided. In patients for whom CYP3A4 inducers are indicated, concomitant use of alternative therapeutic agents with less potential for CYP3A4 enzyme induction potential should be considered.

The metabolism of CAPRELSA is mediated by CYP3A4 to produce the N-desmethyl metabolite and drugs that are CYP3A4 inducers can therefore alter CAPRELSA plasma concentrations. In a phase I study where a single 300 mg dose of CAPRELSA was given in combination with rifampicin (a CYP3A4 inducer) to healthy subjects, the AUC was reduced by 40% while the C_{max} was unchanged. The reduction in exposure would appear to be due to a 91.1% increase in metabolic clearance of CAPRELSA, with the systemic clearance being 2-fold faster when given with rifampicin (20.14 L/h vs 10.54 L/h when given alone). The apparent clearance of CAPRELSA was increased by 91.1% from 10.54 L/h to 20 L/h and the terminal half-life was decreased from 217.6 hours to 116.3 hours.

Drugs That May Increase Vandetanib Serum Concentrations

CYP3A4 Inhibitors: In healthy subjects, no clinically significant interaction was shown between CAPRELSA (vandetanib) and the potent CYP3A4 inhibitor itraconazole. During a phase I study, a 9% increase in AUC was observed when a single 300 mg CAPRELSA dose was given in combination with itraconazole to healthy volunteers. The terminal half-life was increased by 12.6% when CAPRELSA was co-administered with itraconazole from 209.2 hours to 235.5 hours, whereas the clearance was reduced by 12.0% from 10.77 L/h to 9.467 L/h. Alternative concomitant medications with no or minimal CYP3A4 inhibition should be considered.

Anti-arrhythmic Medicines and Other Drugs That May Prolong QTcF Intervals

Concomitant use of CAPRELSA with **anti-arrhythmic medicines** and other drugs that may prolong the QTcF interval should be avoided (see WARNINGS AND PRECAUTIONS).

The concomitant use of CAPRELSA with another QT/QTcF-prolonging drug is discouraged. If such drugs are given to patients already receiving CAPRELSA and no alternative therapy exists, ECG monitoring of the QT interval should be performed more frequently. Drugs that have been associated with QT/QTcF interval prolongation and/or Torsade de Pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTcF prolongation and/or Torsade de Pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide);
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide);
- Class IC antiarrhythmics (e.g., flecainide, propafenone);
- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone);
- antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants [e.g., amitriptyline, imipramine, maprotiline]);
- opioids (e.g., methadone);

- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus);
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin);
- pentamidine;
- antimalarials (e.g., quinine, chloroquine);
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole);
- domperidone;
- 5-hydroxytryptamine (5-HT)₃ receptor antagonists (e.g., dolasetron, ondansetron, metoclopramide);
- prochlorperazine;
- tyrosine kinase inhibitors (e.g., sunitinib, lapatinib);
- histone deacetylase inhibitors (e.g., vorinostat);
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

The above list of potentially interacting drugs is not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QT/QTcF interval, inhibit P-gP, or cause electrolyte disturbances, as well as for older drugs for which these effects have recently been established (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS; Cardiovascular).

Effect of CAPRELSA on Other Drugs

Midazolam (CYP3A4 substrate): In healthy subjects, CAPRELSA 800 mg single dose did not affect the exposure of midazolam (see ACTION AND CLINICAL PHARMACOLOGY). Steady state concentrations of CAPRELSA were not achieved during this study.

Metformin (OCT2 substrate): *In vitro*, CAPRELSA is an inhibitor of the organic cation transporter 2 (OCT2). In healthy subjects (wild type for OCT2), a statistically significant interaction was shown between CAPRELSA and the OCT2 substrate metformin. AUC(0-t) and C_{max} for a single 1000 mg metformin dose were increased by 74% and 50%, respectively and CLR of metformin was decreased by 52% when given together with a single 800 mg CAPRELSA dose. Therefore CAPRELSA may have the potential to decrease the elimination of drugs that are excreted by OCT2 and increase a patient's exposure to these drugs. It is expected that the magnitude of this drug-drug interaction (DDI) will be greater when co-administration occurs once vandetanib achieves steady state plasma concentration given that it accumulates approximately 8 fold following 2 months of daily dosing at 300 mg od. Appropriate clinical and/or laboratory monitoring is recommended for patients receiving

concomitant metformin and CAPRELSA, and such patients may require a lower dose of metformin. (For CAPRELSA monitoring, see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Digoxin (P-gp substrate): *In vitro*, CAPRELSA inhibits the transporter P-glycoprotein (P-gp). In healthy subjects, a statistically significant interaction was shown between CAPRELSA and the P-gp substrate digoxin. AUC(0-t) and C_{max} for digoxin were increased by 23% and 29% respectively, when given together with a single 300 mg CAPRELSA dose. Therefore, the co-administration of CAPRELSA and drugs excreted by P-gp such as digoxin may result in increased plasma concentrations for these drugs. Appropriate clinical and/or laboratory monitoring is recommended for patients receiving concomitant digoxin (or other drugs excreted by P-gp) and CAPRELSA, and such patients may require a lower dose of digoxin. (For CAPRELSA monitoring, see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Effect of Other Drugs on CAPRELSA

Omeprazole and Ranitidine: In healthy subjects, the C_{max} for vandetanib was decreased by 15% while the AUC(0-t) for vandetanib was not affected when given together with omeprazole, a proton pump inhibitor. Neither the C_{max} nor the AUC(0-t) for vandetanib was affected when given together with ranitidine, an H₂-antagonist. No change in dose of CAPRELSA is required when CAPRELSA is given with either omeprazole or ranitidine.

Drug-Food Interactions

Exposure to CAPRELSA is not affected by a meal.

Products and juices containing grapefruit, star fruit, pomegranate, Seville oranges and other similar fruits that are known to inhibit CYP3A4 should be avoided at any time.

Drug-Herb Interactions

Interactions with herbal products have not been studied. St. John's Wort is a potent CYP3A4 inducer. Co-administration with CAPRELSA may lead to increased CAPRELSA metabolism, therefore decreased CAPRELSA serum concentrations.

Co-administration with CAPRELSA should be avoided.

Drug-Laboratory Tests Interactions

Interactions with laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Renal impairment

Clinical data, together with pharmacokinetic data from volunteers suggests that no change in starting dose of CAPRELSA (vandetanib) is required in patients with mild renal impairment. Patients with mild renal impairment have a safety profile similar to that of patients with normal renal function.

The starting dose should be reduced to 200 mg in patients with moderate (creatinine clearance ≥ 30 to <50 mL/min) and severe (< 30 mL/min) renal impairment.

A pharmacokinetic study suggests that in volunteers with severe renal impairment defined as a creatinine clearance of < 30 mL/min, exposure to vandetanib may be increased up to 2-fold. There is limited clinical experience in patients with severe renal impairment.

Hepatic impairment

CAPRELSA is not recommended for use in patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment, as safety and efficacy have not been established.

Single dose pharmacokinetic data from volunteers with hepatic impairment receiving 800 mg of vandetanib suggests that there were no differences in pharmacokinetics compared to patients with normal hepatic function. There is limited data in patients with liver impairment (serum bilirubin greater than 1.5 times the upper limit of normal).

Recommended Dose and Dosage Adjustment

The recommended dose of CAPRELSA is 300 mg taken once daily.

Therapy with CAPRELSA must only be initiated by a physician experienced in the treatment of patients with medullary thyroid cancer and who has completed the certification in the CAPRELSA Restricted Distribution Program.

CAPRELSA monotherapy may be administered until adult symptomatic or progressive medullary thyroid cancer patients with unresectable locally advanced or metastatic disease are no longer benefiting from treatment. CAPRELSA use should be carefully considered based on a risk:benefit assessment in patients with indolent, asymptomatic or slowly progressive disease because of the significant treatment-related risks.

Table 4 Summary of CAPRELSA-associated Toxicities and Recommendations for Dosage Adjustment

Toxicity	Recommendation for Dosage Adjustment
QTc value \geq 500 ms	In the event of a QTcF interval \geq 500 ms, interrupt dosing until QTcF returns to less than 450 ms, then resume at a reduced dose. The 300 mg daily dose can be reduced to 200 mg (two 100 mg tablets), and then to 100 mg if necessary.
Grade 3 or 4 cutaneous toxicity	In the event of CTCAE grade 3 or higher toxicity, dosing with CAPRELSA should be temporarily stopped and resumed at a reduced dose when toxicity has resolved or improved to CTCAE grade 1. The 300 mg daily dose can be reduced to 200 mg (two 100 mg tablets), and then to 100 mg if necessary.
Grade 3 or 4 hypertension	If high blood pressure cannot be controlled with medical management, CAPRELSA should not be restarted until the blood pressure is controlled medically. Reduction in dose may be necessary.
Grade 3 or 4 diarrhea	If severe diarrhea (CTCAE grade 3-4) develops, CAPRELSA should be stopped until diarrhea improves. Upon improvement, treatment with CAPRELSA should be resumed at a reduced dose.
Other grade 3 or 4 toxicity related to CAPRELSA	In the event of CTCAE grade 3 or higher toxicity, dosing with CAPRELSA should be temporarily stopped and resumed at a reduced dose when toxicity has resolved or improved to CTCAE grade 1. The 300 mg daily dose can be reduced to 200 mg (two 100 mg tablets), and then to 100 mg if necessary.

QTcF interval prolongation

In the event of a corrected QTcF interval of \geq 500 ms, dosing with CAPRELSA should be interrupted and/or resumed at a reduced dose when the QTcF has returned to less than 450 ms. The 300 mg daily dose should be reduced to 200 mg (two 100 mg tablets), and then to 100 mg if necessary (as in Table 4 above).

Machine-read QTcF interval measurements may not be accurate. Consultation with a cardiologist should be considered when assessing the QTcF intervals to ensure appropriate treatment decisions. Baseline ECG QTcF intervals should be measured prior to initiating therapy with CAPRELSA and ECGs should be repeated at 2-4 weeks and 8-12 weeks during treatment with CAPRELSA and every three months thereafter, and after dose adjustments.

Hypokalemia, hypomagnesemia and hypocalcemia must be corrected prior to CAPRELSA administration. Potassium and magnesium blood levels should be monitored at 2-4 weeks and 8-12 weeks and every three months thereafter, and after dose adjustments particularly in patients at risk for these electrolyte abnormalities (see WARNINGS AND PRECAUTIONS).

Missed Dose

If a patient misses a dose 12 hours or more before the next scheduled dose, the patient should take the missed tablet immediately and then take the next scheduled dose at the normal time.

If a patient misses a dose less than 12 hours before the next scheduled dose, the patient should skip the missed dose and then take the next scheduled dose at the normal time. Patients should be instructed not to take a double dose to make up for a forgotten tablet.

Administration

CAPRELSA tablets may be taken with or without food.

Do not crush CAPRELSA tablets. If direct contact of crushed tablets with the skin or mucous membranes occurs, wash the area thoroughly. Avoid contact with crushed tablets. In patients who are unable to take CAPRELSA tablets whole, the tablets may be dispersed (will not completely dissolve) in half a glass (50 mL) of non-carbonated drinking water. No other liquids should be used. The tablet is dropped in water (do not crush), stirred until dispersed (approximately 10 minutes) and the resultant dispersion swallowed immediately. Any residues in the glass are mixed with half a glass of water and swallowed. The liquid dispersion can also be administered through nasogastric or gastrostomy tubes.

Special Populations

Renal Impairment

CAPRELSA is partly eliminated by urinary excretion. The pharmacokinetics of CAPRELSA were evaluated after a single dose of 800 mg in subjects with mild (n = 6), moderate (n = 8), and severe (n = 6) renal impairment and normal (n = 10) renal function. Renal impairment has an effect on the pharmacokinetics of CAPRELSA. Single dose administration of CAPRELSA 800 mg resulted in increases in AUC of 46%, 62% and 79% in subjects with mild, moderate and severe renal impairment, respectively, compared to a control group of subjects with normal renal function. The increased exposure is considered to be a consequence of slower clearance of vandetanib in subjects with mild, moderate and severe renal impairment (10.310 L/hr, 8.440 L/hr and 8.315 L/hr respectively, compared to 11.740 L/hr in subjects with normal renal function). The slower clearance resulted in an increased terminal half-life of 290.6 hr, 298.9 hr and 409.8 hr, respectively, in subjects with mild, moderate and severe renal impairment compared to 261.1 hr for subjects with normal renal impairment. It is expected that for once-daily dosing, the steady-state exposure to CAPRELSA will be increased in patients with renal impairment. There is no information available for patients with end-stage renal disease requiring dialysis.

Hepatic Impairment

Single dose administration of CAPRELSA 800 mg did not affect the AUC of CAPRELSA in patients with hepatic impairment while a 29% decrease in the C_{max} for patients with severe hepatic impairment was observed. Hepatic impairment did not affect the clearance of CAPRELSA but there was an increase in the volume of distribution with geometric means of 4498 L, 5059 L and 6025 L in subjects with mild, moderate and severe hepatic impairment, respectively, compared to 3810 L in healthy subjects. The increase in volume of distribution resulted in an increased terminal half-life of CAPRELSA with geometric means of 262.6, 276.6 and 325.7 hours for subjects with mild, moderate or severe hepatic impairment, respectively, compared to 215.7 hours for subjects with normal liver function.

OVERDOSAGE

There is no specific treatment in the event of overdose with CAPRELSA (vandetanib) and possible symptoms of overdose have not been established. An increase in the frequency and severity of some adverse reactions, like rash, diarrhea and hypertension, was observed at multiple doses at and above 300 mg in healthy volunteer studies and in patients. In addition, the possibility of QTcF prolongation and Torsade de Pointes should be considered.

Adverse reactions associated with overdose are to be treated symptomatically; in particular, severe diarrhea must be managed appropriately. In the event of an overdose, further doses of CAPRELSA must be interrupted, and appropriate measures taken to assure that an adverse event has not occurred, i.e., ECG within 24 hours to determine QTcF prolongation.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Vandetanib is a potent and selective inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2, KDR), epidermal growth factor receptor (EGFR), and Rearranged during Transfection (RET) receptor tyrosine kinases. At sub-micromolar concentrations vandetanib also inhibits VEGFR-3 (Flt-4) and VEGFR-1 (Flt-1) with approximately 3 – 7 fold selectivity, respectively.

Vandetanib inhibits vascular endothelial growth factor (VEGF)-stimulated endothelial cell migration, proliferation, survival and new blood vessel formation in *in vitro* models of angiogenesis. *In vivo* vandetanib administration reduced tumour cell-induced angiogenesis, tumour vessel permeability and tumour microvessel density, and inhibited tumour growth and metastasis in human xenograft models of lung cancer in athymic mice.

In addition, vandetanib inhibits epidermal growth factor (EGF)-stimulated EGF receptor tyrosine kinase in tumour cells and endothelial cells. Vandetanib inhibits EGFR-dependent cell proliferation and cell survival *in vitro*.

In cellular assays, vandetanib has been shown to inhibit wild-type RET kinase activity and the kinase activity of the majority of RET kinase mutants that occur in both sporadic and hereditary forms of medullary thyroid cancer.

Pharmacodynamics

Animal data suggests that hemoglobin levels may increase due to increased hepatic erythropoietin production in patients receiving VEGF inhibitors. At various exposure durations, median hemoglobin levels in patients treated with vandetanib were increased by 5–15 g/L compared to baseline.

Pharmacokinetics

The pharmacokinetics of vandetanib at the 300 mg dose in medullary thyroid cancer patients is characterized in Table 5 below. The half-life of vandetanib is 19 days.

Table 5 Summary of CAPRELSA’s Pharmacokinetic Parameters in medullary thyroid cancer patients

	C_{max} (ng/mL)	t_{1/2} (d)	Clearance (L/hr)	Volume of distribution (L)	AUC (ng·h/mL)
Single dose mean (300mg)	810	19	13.2	7450	18782

Absorption: Following a single oral administration of vandetanib absorption is slow with peak plasma concentrations typically achieved at a median of 6 hours, range 4 - 10 hours, after dosing. Vandetanib accumulates ~8-fold on multiple dosing with steady state achieved from ~2 months.

Distribution: Vandetanib binds to human serum albumin and α 1-acid-glycoprotein with *in vitro* protein binding being ~90%. In *ex vivo* plasma samples from colorectal cancer patients at steady state exposure after 300 mg once daily, the mean percentage protein binding was 93.7% (range 92.2 to 95.7 %).

Metabolism: Following oral dosing of ¹⁴C- vandetanib, unchanged vandetanib and metabolites vandetanib N-oxide and N-desmethyl vandetanib were detected in plasma, urine and feces. Glucuronide conjugate was seen as a minor metabolite in excreta only. N-desmethyl vandetanib is primarily produced by CYP3A4 and vandetanib-N-oxide by flavin – containing monooxygenase enzymes FMO1 and FMO3 -desmethyl-vandetanib and vandetanib-N-oxide circulate at concentrations of ~11% and 1.4% of those of vandetanib.

Excretion: Within a 21 day collection period after a single dose of ¹⁴C-vandetanib, ~69% was recovered with 44% in faeces and 25% in urine. Excretion of the dose was slow and further excretion beyond 21 days would be expected based on the plasma half-life.

Across the clinical program the pharmacokinetics of vandetanib have been shown to be linear in both healthy volunteers (up to 1200 mg single dose) and patients receiving once daily dosing (100 mg and 300 mg multiple doses).

Vandetanib was not a substrate of hOCT2 expressed in HEK293 cells. Vandetanib was an inhibitor of OCT2 inhibiting the uptake of the selective OCT2 marker substrate ¹⁴C-creatinine by HEK293-OCT2 cells, with a mean IC₅₀ of approximately 2.1 µg/mL. This is higher than vandetanib plasma concentrations (~ 0.81 and 0.32 µg/mL) observed after multiple dosing at 300 and 100 mg, respectively. Inhibition of renal excretion of creatinine by vandetanib offers an explanation for increases in plasma creatinine seen in human subjects receiving CAPRELSA.

Special Populations and Conditions

Pediatrics

The safety and efficacy of CAPRELSA in children have not been established.

Patient with Renal Impairment

CAPRELSA (vandetanib) is partly eliminated by urinary excretion. The pharmacokinetics of CAPRELSA were evaluated after a single dose of 800 mg in subjects with mild (n = 6), moderate (n = 8), and severe (n = 6) renal impairment and normal (n = 10) renal function. Renal impairment has an effect on the pharmacokinetics of CAPRELSA. Single dose administration of CAPRELSA 800 mg resulted in increases in AUC of 46%, 62% and 79% in subjects with mild, moderate and severe renal impairment, respectively, compared to a control group of subjects with normal renal function. The increased exposure is considered to be a consequence of slower clearance of vandetanib in subjects with mild, moderate and severe renal impairment (10.310 L/hr, 8.440 L/hr and 8.315 L/hr, respectively, compared to 11.740 L/hr in subjects with normal renal function). The slower clearance resulted in an increased terminal half-life of 290.6 hr, 298.9 hr and 409.8hr, respectively, in subjects with mild, moderate and severe renal impairment compared to 261.1 hr for subjects with normal renal impairment. It is expected that for once-daily dosing, the steady-state exposure to CAPRELSA will be increased in patients with renal impairment. There is no information available for patients with end-stage renal disease requiring dialysis.

Patients with Hepatic Impairment

Single dose administration of CAPRELSA 800 mg did not affect the AUC of CAPRELSA in patients with hepatic impairment while a 29% decrease in the C_{max} for patients with severe hepatic impairment was observed. Hepatic impairment did not affect the clearance of CAPRELSA but there was an increase in the volume of distribution with geometric means of 4498 L, 5059 L and 6025 L in subjects with mild, moderate and severe hepatic impairment, respectively, compared to 3810 L in healthy subjects. The increase in volume of distribution resulted in an increased terminal half-life of CAPRELSA with geometric means of 262.6, 276.6 and 325.7 hours for subjects with mild, moderate or severe hepatic impairment, respectively, compared to 215.7 hours for subjects with normal liver function.

STORAGE AND STABILITY

CAPRELSA (vandetanib) should be stored between 15-30°C.

SPECIAL HANDLING INSTRUCTIONS

No special requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CAPRELSA (vandetanib) 100 mg tablets

Each tablet is presented as a round, biconvex, white, film-coated tablet containing 100 mg of vandetanib. 'Z100' is impressed on one side; the other side is plain.

CAPRELSA (vandetanib) 300 mg tablets

Each tablet is presented as an oval-shaped, biconvex, white, film-coated tablet containing 300 mg of vandetanib. 'Z300' is impressed on one side; the other side is plain.

Composition

CAPRELSA tablets are available in two dosage strengths, 100 mg and 300 mg, containing 100 mg and 300 mg of vandetanib, respectively.

Non-Medicinal Ingredients: The tablets also contain the following inactive ingredients: calcium hydrogen phosphate dihydrate, crospovidone, hypromellose 2910, macrogol 300, magnesium stearate, microcrystalline cellulose, povidone, and titanium dioxide E171.

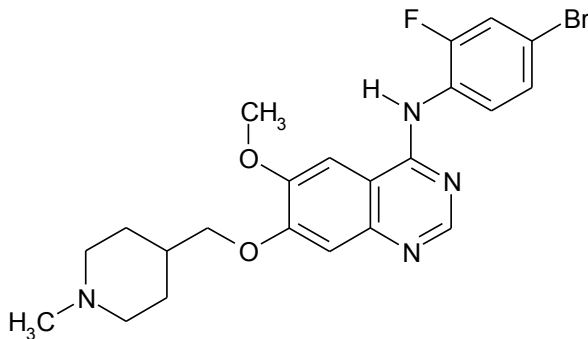
Packaging

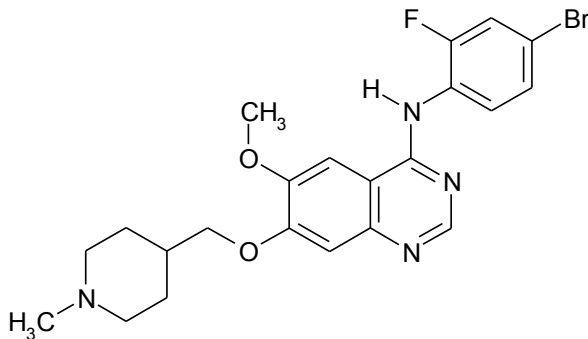
CAPRELSA is available in blister packages containing 30 tablets (3 x 10 tablets).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	Vandetanib
Chemical Name:	N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine
Code Name:	ZD6474
Molecular Formula and Molecular Mass:	C ₂₂ H ₂₄ BrFN ₄ O ₂ (475.36)
Structural Formula:	



Physicochemical Properties:

Appearance: Vandetanib is a white to yellow powder.

Solubility: Vandetanib exhibits pH dependent solubility. Vandetanib is practically insoluble in water with a value of 0.008 mg/mL at 77°F (25°C).

pKa: 5.2 (aminoquinazoline moiety) and 9.4 (piperidine moiety)

Partition coefficient: 4.7 at pH 11

Melting point: 235°C

CLINICAL TRIALS

Symptomatic or progressive unresectable locally advanced or metastatic medullary thyroid cancer

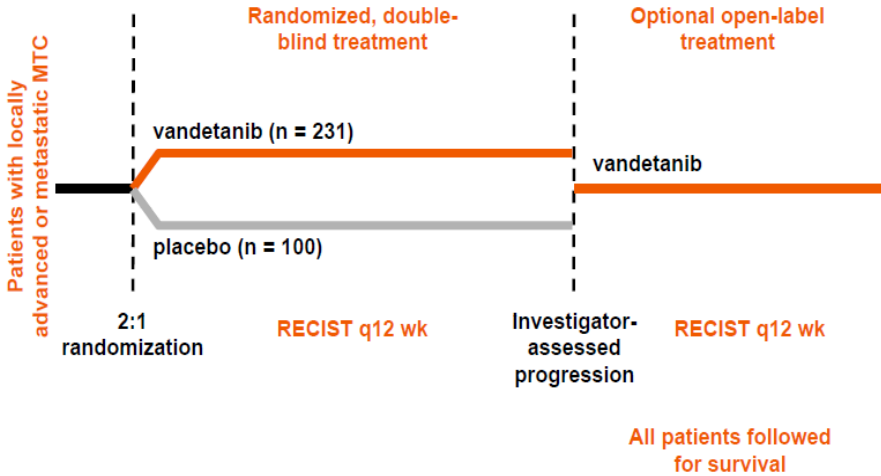
Study Demographics and Trial Design

The pivotal ZETA study (Study 58) was a multicentre, international, randomized, double-blind, parallel group, Phase III efficacy and safety study of a 300 mg daily oral dose of

CAPRELSA (vandetanib) compared with placebo in 331 patients with unresectable locally advanced or metastatic medullary thyroid cancer (MTC).

A schematic of the study design is shown in Figure 1 below:

Figure 1 ZETA (Study 58) Design



The primary endpoint was progression-free survival (PFS) based on RECIST criteria assessed by independent central blinded review.

Key secondary endpoints were evaluation of overall objective response rate (ORR) and overall survival (OS). ORR was based on centralized, independent blinded review of the imaging data using RECIST criteria.

Patient demographics from the ZETA study are summarized in Table 6. Patients enrolled in the ZETA trial were predominantly Caucasian.

Table 6 Summary of patient demographics for the pivotal ZETA trial in medullary thyroid cancer (intention to treat population)

Characteristics	CAPRELSA 300 mg daily, oral (N=231)	Placebo (N=100)	Total (N=331)
Mean Age	50.7	53.4	51.5
Sex			
Female (%)	97 (42%)	44 (44%)	141 (43%)
Male (%)	134 (58%)	56 (56%)	190 (57%)
Race			

Characteristics	CAPRELSA 300 mg daily, oral (N=231)	Placebo (N=100)	Total (N=331)
Caucasian (%)	218 (94%)	97 (97%)	315 (95%)
Other (%)	13 (6%)	3 (3%)	16 (5%)
Performance Status			
WHO PS ^a 0 (%)	154 (67%)	58 (58%)	212 (64%)
WHO PS ^a ≥ 1 (%)	77 (33%)	42 (42%)	119 (36%)
Disease Parameters			
Hereditary disease (%)	28 (12%)	5 (5%)	33 (10%)
Sporadic or unknown disease (%)	203 (88%)	95 (95%)	298 (90%)
Locally advanced disease (%)	14 (6%)	3 (3%)	17 (5%)
Metastatic disease (%)	217 (94%)	97 (97%)	314 (95%)
0 or 1 organ involved ^b (%)	29 (13%)	8 (8%)	37 (11%)
≥ 2 organs involved ^b (%)	202 (87%)	92 (92%)	294 (89%)
Prior Treatment			
No prior systemic therapy for MTC ^c (%)	141 (61%)	58 (58%)	199 (60%)
≥ 1 prior systemic therapy for MTC ^c (%)	90 (39%)	42 (42%)	132 (40%)
RET Mutation Status			
RET mutation positive	137 (59%)	50 (50%)	187 (56%)
RET mutation negative	6 (6%)	2 (1%)	8 (2%)
RET mutation unknown	92 (40%)	44 (44%)	136 (41%)

[a] WHO PS = World Health Organization Performance Status.

[b] Not including thyroid

[c] MTC= Medullary thyroid cancer

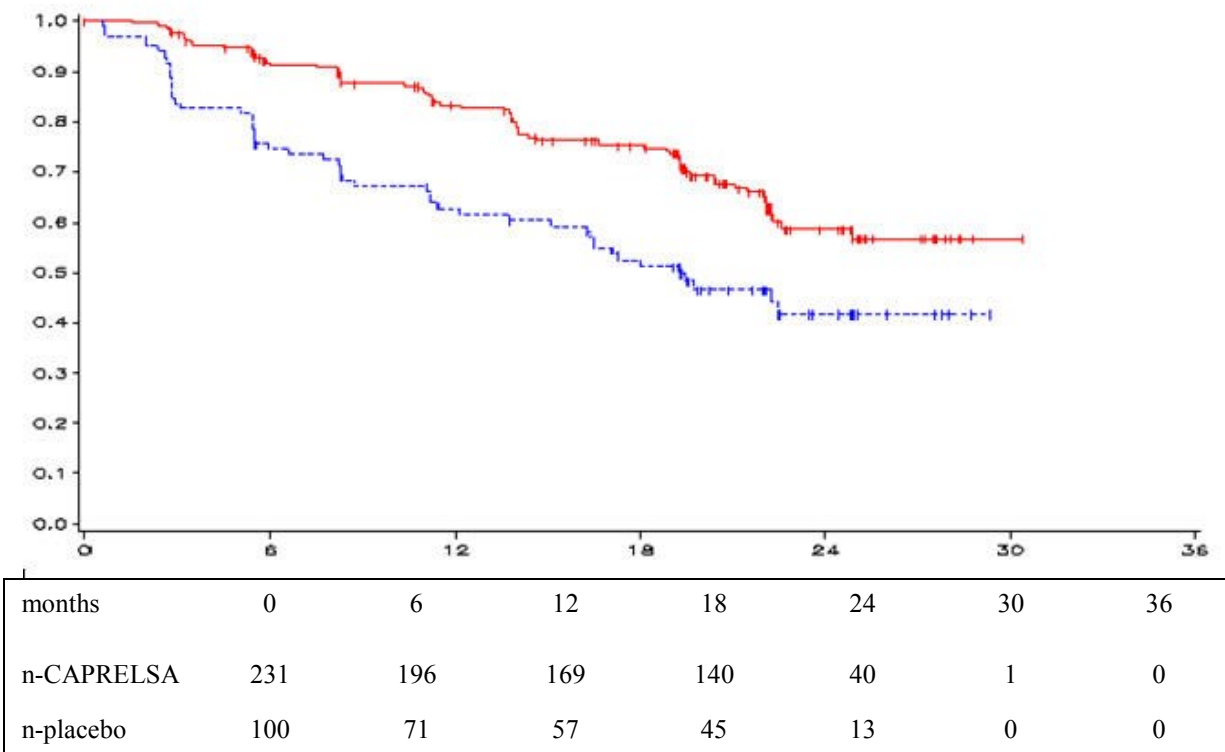
Study Results

Primary Efficacy Endpoint: Progression-Free Survival (PFS)

The result of the primary analysis of PFS showed a statistically significant improvement in PFS for patients randomized (2:1) to CAPRELSA compared to placebo (Hazard Ratio (HR) = 0.46; 95% Confidence Interval (CI) = 0.31-0.69; p=0.0001). The median duration of treatment on the CAPRELSA arm was 90 weeks, compared to 40 weeks on placebo.

The median PFS for patients randomized to placebo was 19.3 months. The median PFS for patients randomized to CAPRELSA has not been reached by data cut-off of 30 months (Figure 2).

Figure 2 Kaplan Meier plot of Progression-Free Survival in the ZETA Study



— CAPRELSA 300 mg, - - - - - placebo, y-axis=PFS, x-axis=time in months, n-CAPRELSA=number of patients at risk-CAPRELSA, n-placebo=number of patients at risk-placebo

Pre-defined subgroup analyses were supportive of the primary analysis.

Secondary Efficacy Endpoints: Objective Response Rate and Overall Survival

The overall objective response rate for patients randomized to CAPRELSA was 45% (N=104/231) compared to 13% (N=13/100) for patients randomized to placebo (Odds Ratio = 5.48; 95% CI = 2.99-10.79; p<0.0001). All objective responses were partial responses. Of the 13 responses for patients randomized to placebo, 12 occurred while patients were receiving open label CAPRELSA.

At the time of the primary analysis of PFS (data cut-off date 31 July 2009), 48 (15%) of the patients had died. There was no statistically significant difference in overall survival between treatment groups.

DETAILED PHARMACOLOGY

Vandetanib was identified as an inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase, that has additional activity against epidermal growth factor

receptor (EGFR) and RET (Rearranged during Transfection) receptor tyrosine kinases *in vitro* and *in vivo*. Pre-clinical *in vivo* studies demonstrated that vandetanib targets two separate aspects of cancer (i) indirectly inhibiting tumour growth through antiangiogenic effects on endothelial cell proliferation, migration and survival, primarily through inhibition of VEGFR-2, and (ii) directly inhibiting EGFR and/or RET dependent tumour growth (see ACTION AND CLINICAL PHARMACOLOGY).

In recombinant enzyme assays *in vitro*, and in cell culture, vandetanib was a potent inhibitor of VEGFR-2 ($IC_{50} = 0.04\mu M$), EGFR ($IC_{50} = 0.5\mu M$) and RET ($IC_{50} = 0.1\mu M$) receptor tyrosine kinases, and a potent inhibitor of both wild-type and many mutant variants of RET kinase.

In cellular assays, vandetanib treatment reduced intracellular levels of phosphorylated RET in cells expressing two prevalent gain-of-function activating mutations found in papillary thyroid cancer (PTC) and MTC. In addition, vandetanib inhibited the proliferation of two human PTC cell lines (TPC-1 and FB2) carrying RET/PTC1 genetic rearrangements.

The inhibitory activities of the two predominant metabolites of vandetanib, N-desmethyl vandetanib and vandetanib N-oxide, were found to retain potency broadly similar to vandetanib for inhibition of VEGFR-2, EGFR and FGFR-1 (fibroblast growth factor receptor-1) in recombinant enzyme assays. In contrast, while N-desmethyl vandetanib inhibited VEGF-, EGF- and bFGF (basic fibroblast growth factor)-stimulated HUVEC proliferation with similar potency to vandetanib, vandetanib N-oxide had only weak inhibitory activity in these cellular assays.

Vandetanib has broad spectrum antitumour activity in a range of tumour models *in vivo*. Treatment with vandetanib significantly inhibited established NIH-RET/PTC3 tumour growth, reducing both tumour blood vessel density and levels of phosphorylated RET protein.

TOXICOLOGY

Single oral dose toxicity

A single oral dose of vandetanib at 2000 mg/kg to mice was not tolerated and all animals died or were killed for humane reasons on Day 1. A single oral dose of 1000 mg/kg resulted in the death of 1 out of 10 mice. There were no salient histopathology findings except for ulceration in the stomach in 1 animal dosed at 2000 mg/kg. In the rat, a single oral dose at 2000 mg/kg was not tolerated and all animals died or were killed for humane reasons by Day 4. Histopathological findings in these rats included hepatocyte vacuolation, fat deposition and necrosis in the liver, ulceration in the stomach, mucosal single cell necrosis and erosion in the duodenum, and macrophage vacuolation in the spleen. There were no adverse effects in rats dosed at 1000 mg/kg. 1000 mg/kg in rats corresponds to a dose of 6000 mg/m^2 , which is approximately 30 times the recommended daily dose for a 70 kg patient.

Intravenous dose toxicity

For intravenous single dose toxicity studies in mice, vandetanib was formulated in 45% hydroxypropyl- β -cyclodextrin in pH 7 Sorenson's phosphate buffer. A single intravenous dose of 50 mg/kg resulted in early death in 1 of 10 mice. However, in the rat, the administration of the vehicle alone was not tolerated at dose volumes that would allow meaningful doses of vandetanib to be administered. Therefore a single intravenous dose was not administered in rats. After daily intravenous doses of 25 mg/kg to rats, foamy macrophages were observed in the spleen, consistent with the induction of phospholipidosis.

Repeat dose toxicity

Dose-limiting toxicities in 1, 6 and 9 month studies included (variously across the studies) gastrointestinal effects in dogs (including loose/abnormal feces, emesis and body weight loss), and skin and hepatotoxicity in rats. The morbidity and mortality associated with these key findings at the initial high doses resulted in either dose reduction (high dose reduced from 20 mg/kg/day to 10 mg/kg/day from Week 13 of the 6 month rat, and the 20 mg/kg/day top dose of the 9 month dog study was reduced to 15 mg/kg/day in Week 17) or the early cessation of dosing of the high dose groups of the 1 month rat study (Day 25) and the 1 month dog study (Day 15).

In the 6 month rat study, the unscheduled deaths of several animals in the 20 mg/kg/day group were attributed in part to acute cholangitis and/or pancreatitis. However, these findings were not present following subsequent dose reduction from 20 mg/kg/day to 10 mg/kg/day. Elevated ALT and AST activities were found in some rats receiving 5 or 25 mg/kg/day for 1 month or 20/10 mg/kg/day for 6 months without histopathological correlate. Hepatobiliary changes were not seen in the 1 or 9 month dog studies.

In the four week period after cessation of dosing in the one month rat study, dysplasia of incisor teeth was observed in animals previously given 75 mg/kg/day, and similar changes were seen in several decedents at 20/10 mg/kg/day in the 6 month rat study. Daily oral dosing of vandetanib for 1 month resulted in a dose-related, reversible dysplasia of the epiphyseal growth plates of the femorotibial joint in rats dosed at 25 or 75 mg/kg/day and in the femur of dogs dosed at 40 mg/kg/day.

Renal papillary necrosis was observed in rats dosed orally for 1 month at 25 or 75 mg/kg/day and was still present at the end of the 4 week recovery period. Renal papillary necrosis was not seen in the 6 month rat study or in any dog study.

Histopathological and/or ultrastructural changes consistent with the induction of phospholipidosis, were present in rats in the 1 month oral study (lungs, lymph nodes spleen, trachea, centrilobular hepatocytes, renal tubular epithelium), in the 6 month oral study (lungs) and in the intravenous studies (principally lungs and spleen, though phospholipidosis was also caused by the vehicle used). While no histological evidence of phospholipidosis was observed in dogs dosed orally, phospholipidosis was however present in alveoli and mesenteric lymph node of dogs administered vandetanib by the intravenous route in studies of up to 2 weeks duration.

Small, dose-related haematological changes (increased levels of haemoglobin, haematocrit, red blood cells, reticulocytes and some white blood cells) were seen in oral and intravenous rat studies, generally showing reversal after cessation of dosing.

In the 104-week carcinogenicity study, rats were exposed to oral daily doses of up to 10 mg/kg/day vandetanib. In the kidney, chronic progressive nephropathy was observed in rats dosed at 10 mg/kg/day. In the uterus, dilatation, hemorrhage in the mucosa or the lumen, pigmented macrophages, and necrotic or purulent luminal material was present in female rats dosed at 10 mg/kg/day correlating with the macroscopic abnormal consistency, dark discoloration, enlargement and fluid accumulation. In the heart of females dosed from 3 mg/kg/day, progressive cardiomyopathy was observed. Females rats dosed at 10 mg/kg/day presented some mastocytosis in the mesenteric lymph nodes. In the stomach of females dosed at 10 mg/kg/day, there was an increase in epithelial ulceration of the non-glandular region. Some findings were considered to be test item-related although observed only macroscopically in females at 10 mg/kg/day, consisting of a higher incidence of ovarian cysts and a higher incidence of dark focus in the adrenal gland.

Cardiovascular effects

In vitro data in hERG-expressing Chinese hamster ovary cells showed that vandetanib decreased the hERG current by 55.5% at 4×10^{-7} M. Vandetanib caused a concentration dependent increase in action potential duration in canine Purkinje fibres that was significant at 1×10^{-6} M (1 μ M) and greater, with an enhanced effect at low frequency stimulation and low potassium conditions.

Genotoxicity

Vandetanib has shown no genotoxic, mutagenic or clastogenic potential.

Reproductive toxicology

Vandetanib had no effect on copulation or fertility indices in male rats when undosed females were mated with males administered 1, 5 or 20 mg/kg/day of vandetanib (approximately 0.03, 0.22, or 0.40 times, respectively, the AUC in patients with cancer at the recommended human dose of 300 mg/day). There was a slight decrease in the number of live embryos at 20 mg/kg/day and an increase in preimplantation loss at ≥ 5 mg/kg/day.

In a female fertility study, there was a trend towards increased estrus cycle irregularity, a slight reduction in pregnancy incidence and increase in post-implantation loss. In a repeat-dose toxicity study in rats, there was a decrease in the number of corpora lutea in the ovaries of rats administered 75 mg/kg/day vandetanib (approximately 1.8 times the AUC in patients with cancer at the recommended human dose) for 1 month.

In rats, embryofetal toxicity was evident as embryo-fetal loss, delayed fetal development, heart vessel abnormalities and precocious ossification of some skull bones. In a rat pre- and post-natal development study, at doses producing maternal toxicity during gestation and/or lactation, vandetanib increased pre-birth loss and reduced post-natal pup growth. Vandetanib

was excreted into milk in rat and found in plasma of pups following dosing to lactating rats. With regard to embryo-fetal toxicity, vandetanib exposure during gestation caused a number of teratogenic effects including increased post-implantation loss, decreased fetal weight, increased heart vessel abnormalities and increased abnormal ossification effects. These effects were mainly seen at the 10 and 25 mg/kg dose but one fetus from the 1 mg/kg dose had a heart vessel defect, which is likely due to the pharmacological activity of vandetanib. Together the data indicate that vandetanib is teratogenic.

In nonclinical studies in rats, vandetanib was embryotoxic, fetotoxic, and teratogenic, at exposures equivalent to or lower than those expected at the recommended human dose of 300 mg/ day. As expected from its pharmacological actions, vandetanib has shown significant effects on all stages of female reproduction in rats.

In a pre- and post-natal development study by oral route (gavage) in the rat, the findings showed that vandetanib was transferred to the pups by milk secretion (levels ranging from ~12-18% of C_{max} levels observed in dams). It is not known whether CAPRELSA is excreted in human milk.

Wound Healing

In an animal model of wound-healing, mice dosed with vandetanib had reduced skin-breaking strength compared with controls. This suggests that vandetanib slows but does not prevent wound healing. The appropriate interval between discontinuation of CAPRELSA (vandetanib) and subsequent elective surgery required to avoid the risks of impaired wound healing has not been determined. In clinical studies of CAPRELSA, a small number of patients had surgery while receiving CAPRELSA and there were no reported wound healing complications.

Carcinogenicity

Vandetanib was not carcinogenic in a 6-month carcinogenicity study in rasH2 transgenic mice and in a 2-year bioassay in rats.

Phototoxicity

In an *in vitro* cytotoxic assay, vandetanib was reported to have a photo-irritation factor (PIF) of 19.9 suggesting a potential for phototoxicity upon sun exposure.

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**PART III:
CONSUMER INFORMATION**

Pr **CAPRELSA**[®]
Vandetanib tablets

This leaflet is part III of a three-part "Product Monograph" published when CAPRELSA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CAPRELSA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

CAPRELSA (vandetanib) is only available through a controlled program referred to as the CAPRELSA Restricted Distribution Program. Under this program, only patients who are enrolled and meet all of the requirements of the CAPRELSA Restricted Distribution Program can receive CAPRELSA. For further information about the program, please call 1 (800) 589-6215 or visit www.caprelsa.ca/rdp.

WHAT THE MEDICATION IS USED FOR:

CAPRELSA is used to treat medullary thyroid cancer in adult patients whose tumour cannot be removed by surgery or has spread from the thyroid to other parts of the body. Side effects you may experience related to CAPRELSA treatment may not go away as quickly after stopping treatment, given that it takes longer for the body to get rid of the drug.

WHAT IT DOES:

CAPRELSA is one of a group of drugs that specifically target the activity of a group of proteins known to be involved in the growth and spread of certain types of cancer. These proteins stimulate the development of new blood vessels that allow certain types of tumours to grow. CAPRELSA works by blocking the production of these proteins in tumour cells, which slows down the growth of new blood vessels in these tumours. This cuts off the supply of nutrients and oxygen to the tumour thereby slowing or preventing its growth. CAPRELSA also acts directly on cancer cells to kill them or slow down their rate of growth.

WHEN IT SHOULD NOT BE USED:

Do not use CAPRELSA if you:

- have congenital long QT syndrome - a heart disorder that exists before or at birth (this is seen on a test by your doctor that measures the electrical activity of your heart known as an ECG, or "electrocardiogram");
- have low calculated levels of potassium, magnesium, or calcium in your blood;

- have uncontrolled high blood pressure;
- are allergic to vandetanib or any of the other ingredients in CAPRELSA.

If you are not sure, talk to your doctor before taking CAPRELSA.

WHAT THE MEDICINAL INGREDIENT IS:

Vandetanib

WHAT THE NONMEDICINAL INGREDIENTS ARE:

Calcium hydrogen phosphate dihydrate, , crospovidone, hypromellose, macrogol, magnesium stearate, microcrystalline cellulose, povidone, and titanium dioxide.

WHAT DOSAGE FORMS IT COMES IN:

- Tablets: 100 mg and 300 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

CAPRELSA (vandetanib) should only be prescribed by a doctor who has completed the certification with the CAPRELSA Restricted Distribution Program and who is experienced in the use of anti-cancer drugs.

Possible serious side effects with CAPRELSA include:

- Heart rhythm changes (also known as "QT prolongation" - this is seen on a test by your doctor that measures the electrical activity of your heart known as an ECG, or "electrocardiogram")
- Heart failure (a condition where the heart cannot pump blood well and may lead to death)
- High blood pressure, which may be severe

BEFORE you use CAPRELSA talk to your doctor if any of the following conditions apply to you:

- Abnormal heart rhythm (also known as "QT prolongation") or a family history of abnormal heart rhythm;
- Heart disease or a family history of heart disease;
- A personal history of fainting spells;
- Low calculated levels of potassium, magnesium, or calcium in your blood – or a condition that could lead to lower levels such as diarrhea, vomiting, or dehydration;
- High blood pressure;
- Problems with blood clotting or excessive bleeding;
- Liver or kidney problems; or
- A condition in which the thyroid gland does not make enough thyroid hormone (also known as "hypothyroidism")

Talk to your doctor immediately if you experience seizures, headaches, visual disturbances, confusion or difficulty thinking.

CAPRELSA may harm an unborn child. Female patients who can get pregnant must use an effective birth control method while taking CAPRELSA and for at least three months after the last dose. If you are pregnant, think you may be pregnant, or plan to get pregnant while taking CAPRELSA, tell your doctor right away. Male patients must use an acceptable method of contraception, or be surgically sterile, while taking CAPRELSA and for two months after the last dose.

You should not breastfeed while taking CAPRELSA. If you are considering breastfeeding, you should talk to your doctor.

CAPRELSA is not likely to affect your ability to drive or use machines. However, if you feel weak or tired or your vision is blurred while taking this medicine, take care when you are driving or using tools or machines.

CAPRELSA may cause a breathing problem called interstitial lung disease that can lead to death. Tell your doctor right away if you experience sudden or worsening shortness of breath or cough.

CAPRELSA can make your skin sensitive to the sun. While taking CAPRELSA and for four months after the last dose of CAPRELSA you should use sun block and wear clothes that cover your skin, including your head, arms and legs when you go outdoors to prevent sunburn.

It is possible that CAPRELSA may delay the time it takes for your body to heal from skin wounds. Talk to your doctor if you are considering surgery, including dental surgery.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines that you obtain without a prescription or herbal medicines. This is because CAPRELSA can affect the way some medicines work and some medicines can have an effect on how CAPRELSA works.

Keep a list of the medicines you take and show it to your doctor and pharmacist when you get a new medicine.

Do not start, stop or change any medicine without talking to your doctor or pharmacist first.

The following list includes some, but not all, of the types of drugs that may increase the risk of heart rhythm problems while receiving CAPRELSA. You should check with your doctor before taking any other medication with CAPRELSA.

- Drugs known to cause heart rhythm changes;
- Antipsychotics or antidepressants;

- A specific class of pain relieving medications;
- Specific classes of antibiotics;
- Antimalarials or a specific class of antifungals;
- Specific classes of anti-nausea medications;
- Specific classes of anticancer medications; or
- A specific class of asthma and chronic obstructive pulmonary disease medications.

Avoid taking products and juices containing grapefruit, star fruit, pomegranate, Seville oranges and other similar citrus fruits.

PROPER USE OF THIS MEDICATION

Always take CAPRELSA exactly as your doctor has told you. You should check with your doctor if you are not sure.

Take CAPRELSA at about the same time each day.

CAPRELSA may be taken with or without food.

Do NOT crush the tablet.

Avoid contact with broken or crushed tablets. If they touch your skin, wash the area well.

If you have trouble swallowing the tablet, you can mix it with water as follows:

- Take half a glass (50 mL) of still (non-carbonated) water. Only use water – not any other liquids.
- Put the tablet into the water. Do NOT crush the tablet.
- Stir the water until the tablet has disintegrated into the water. This may take about 10 minutes.
- Drink it right away. This liquid can be given by nasogastric or gastrostomy tubes.
- To make sure there is no medicine left, rinse the empty glass very well with another half a glass of water and drink it.

While taking CAPRELSA your doctor will order certain tests to monitor your blood and heart.

Recommended Adult Dose: 300 mg once a day.

The doctor should temporarily stop or reduce the dose if you:

- have moderate to severe kidney disease
- get certain side effects

OVERDOSE:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

MISSED DOSE:

What you should do if you forget to take a tablet depends on the length of time until your next dose.

- **If it is 12 hours or more until your next dose:**
Take the missed tablet as soon as you remember. Then take the next dose as normal.
- **If it is less than 12 hours until your next dose:**
Skip the missed dose. Then take the next dose at the normal time.

Do not take a double dose (two doses at the same time) to make up for a forgotten tablet.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, CAPRELSA can cause side effects. Possible side effects of CAPRELSA reported in clinical trials include:

Very common (affects more than 1 in 10 patients)

- Diarrhea (your doctor may prescribe a medicine to treat this. If it gets severe, tell your doctor immediately.)
- Skin rash or acne
- Anorexia (loss of appetite)
- Feeling tired, lack of energy and/or muscle weakness
- High blood pressure, which may be severe
- Headache
- Trouble sleeping
- Sensitivity of the skin to sunlight
- Abdominal pain
- Indigestion
- Cough
- Weight loss
- Viral infection of the upper respiratory system

Common (affects less than 1 in 10 patients)

- Dehydration (your body does not have enough water and fluids as it should; this can be a result of diarrhea, vomiting or other causes)
- Weight loss
- Conditions where the brain may not get enough blood
- A type of rash that affects the hands and feet (hand-foot syndrome)
- Irritation of the lining of the mouth or lips or tongue
- Dry mouth
- Kidney stones or lower urinary tract stones
- Nose bleed
- Loss of hair
- Nail problems
- Vision blurred

- Corneal opacity (mild changes in the eye which can lead to blurred vision)
- Dry eye
- Conjunctivitis (an irritation of the inner eyelid or surface of the eye)
- Visual impairment
- Dysgeusia (abnormal taste or changes in taste of foods)
- Depression
- Back pain
- Joint pain/pain in the extremities
- Tremor

Uncommon (affects less than 1 in 100 patients):

- Heart failure (a condition where the heart cannot pump blood well); symptoms include shortness of breath and swelling of the ankles

The following side effects are only seen in tests your doctor may ask you to have done:

- Protein or blood in your urine (shown in a urine test).
- Heart rhythm changes (shown in an ECG, or “electrocardiogram”). Your doctor may tell you to take CAPRELSA at a lower dose if this happens.
- Abnormalities in your liver or pancreas (blood tests). These usually do not cause symptoms but your doctor may want to check you for them.
- Decreased levels of calcium in your blood (blood test). This may mean you need thyroid hormone treatment or a change in your current thyroid hormone treatment.

If any of the side effects get worse, or if you notice any side effects not listed in this leaflet, please contact your doctor immediately. You may need further examinations or treatment.

Your doctor will tell you if you have any of these side effects and may prescribe medication to control them.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist*
		Only if severe	In all cases	
Very Common	Nausea (a sensation of having an urge to vomit or queasy stomach)		√	
	Vomiting		√	
	Severe diarrhea		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist*
		Only if severe	In all cases	
Common	Visual disturbances		√	
	Headaches	√		
	Seizures		√	
	Confusion or difficulty thinking		√	
Common /Uncommon	Severe skin reactions (e.g. redness, pain, ulcers, blisters and shedding of the skin) - The frequency of these types of skin reactions may be common or uncommon depending on the type of skin reaction		√	
Uncommon	Fainting		√	
	Dizziness		√	
	Sudden or worsening shortness of breath or cough		√	

***If you think you have these side effects, it is important that you seek medical advice from your doctor or pharmacist immediately.**

This is not a complete list of side effects. For any unexpected effects while taking CAPRELSA, contact your doctor or pharmacist.

HOW TO STORE IT

Store CAPRELSA between 15° and 30°C.

Keep out of the reach and sight of children.

Do not use CAPRELSA after the expiry date that is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer require. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This INFORMATION FOR THE CONSUMER leaflet provides you with the most current information at the time of printing.

For the most current information, the Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at: www.sanofigenzyme.ca,

or by contacting the sponsor, Sanofi Genzyme at: Questions and concerns – 1 (800) 589-6215

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