HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CAPRELSA safely and effectively. See full prescribing information for CAPRELSA.
CAPRELSA® (vandetanib) Tablets
For Oral use
Initial U.S. Approval: 2011

WARNING: QT PROLONGATION, TORSADES DE POINTES, AND SUDDEN DEATH
See full prescribing information for complete boxed warning.
CAPRELSA can prolong the QT interval. Torsades de pointes and sudden death have been reported in patients receiving CAPRELSA. CAPRELSA should not be used in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Hypocalcemia, hypokalemia and/or hypomagnesemia must be corrected prior to CAPRELSA administration and should be periodically monitored. Drugs known to prolong the QT interval should be avoided. If a drug known to prolong the QT interval must be administered, more frequent ECG monitoring is recommended. Given the half-life of 19 days, ECGs should be obtained to monitor the QT interval at baseline, at 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA and every 3 months thereafter. Following any dose reduction for QT prolongation, or any dose interruptions greater than 2 weeks, QT assessment should be conducted as described above. Because of the 19-day half-life, adverse reactions including a prolonged QT interval may not resolve quickly. Monitor appropriately. Only prescribers and pharmacies certified through the restricted distribution program are able to prescribe and dispense CAPRELSA (5.15).

INDICATIONS AND USAGE

CAPRELSA is a kinase inhibitor indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.
Use of CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of CAPRELSA.

DOSAGE AND ADMINISTRATION

- 300 mg once daily (2)
- CAPRELSA may be taken with or without food.
- Dosage reduction may be necessary in the event of severe toxicities or QTc interval prolongation. (2.1)
- The starting dose should be reduced to 200 mg in patients with moderate to severe renal impairment.

DOSAGE FORMS AND STRENGTHS

100 mg and 300 mg tablets (3)

CONTRAINDICATIONS

- Do not use in patients with congenital long QT syndrome.

WARNINGS AND PRECAUTIONS

- Prolonged QT Interval, Torsades de pointes, and sudden death have been reported. Monitor electrocardiograms and levels of serum potassium, calcium, magnesium and TSH at baseline, 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA, and every 3 months thereafter and following dose adjustments. Dose reduce as appropriate (2.1, 5.1).
- Stevens-Johnson syndrome resulting in death has been observed. Severe skin reactions may prompt permanent discontinuation of CAPRELSA (2.1, 5.2).
- Interstitial lung disease, resulting in death has been reported. Interrupt CAPRELSA and investigate unexplained dyspnea, cough, and fever. Appropriate measures should be taken for ILD (2.1, 5.3).
- Ischemic cerebrovascular events, hemorrhage, heart failure, diarrhea, hypothyroidism, hypertension, and reversible posterior leukoencephalopathy syndrome, have been observed (2.1, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 5.10).
- CAPRELSA can cause fetal harm when administered to a pregnant woman. Women should be advised to avoid pregnancy while receiving CAPRELSA and for four months following treatment (5.14, 8.1).
- Because of the risks of QT prolongation, Torsades de pointes and sudden death, CAPRELSA is available only through a restricted distribution program called the CAPRELSA REMS Program. Only prescribers and pharmacies certified with the program are able to prescribe and dispense CAPRELSA. To learn about the specific REMS requirements and to enroll in the CAPRELSA REMS Program call 1-800-236–9933 or visit www.caprelsarems.com (5.15).

ADVERSE REACTIONS

The most common adverse drug reactions (>20%) seen with CAPRELSA have been diarrhea, rash, acne, nausea, hypertension, headache, fatigue, upper respiratory tract infections, decreased appetite and abdominal pain. The most common laboratory abnormalities (>20%) were decreased calcium, increased ALT, and decreased glucose (2.1. 5.2, 5.7, 5.9, 6.1).
To report SUSPECTED ADVERSE REACTIONS, Contact AstraZeneca 1–800–236–9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

The concomitant use of known strong CYP 3A4 inducers may reduce drug levels of CAPRELSA and should be avoided (7.1). No clinically significant drug interaction was shown with CAPRELSA and the potent CYP 3A4 inhibitor, itraconazole (7.2). The administration of CAPRELSA with agents that may prolong the QT interval should be avoided (5.11)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS *

WARNING: QT PROLONGATION, TORSADES DE POINTES, AND SUDDEN DEATH
1. INDICATIONS AND USAGE
1.1. Medullary Thyroid Cancer (MTC)
2. DOSAGE AND ADMINISTRATION
2.1 Dosage Adjustment
2.2 Elderly
2.3 Concomitant Strong CYP3A4 Inducers
2.4 Patients With Renal Impairment
2.5 Patients with Hepatic Impairment
3. DOSAGE FORMS & STRENGTHS
4. CONTRAINDICATIONS
5. WARNINGS AND PRECAUTIONS
5.1 QT Prolongation and Torsades de Pointes
5.2 Skin Reactions and Stevens-Johnson Syndrome
5.3 Interstitial Lung Disease
5.4 Ischemic Cerebrovascular Events
5.5 Hemorrhage
5.6 Heart Failure
5.7 Diarrhea
5.8 Hypothyroidism
5.9 Hypertension
5.10 Reversible posterior leukoencephalopathy syndrome
5.11 Drug Interactions
5.12 Renal Impairment
5.13 Hepatic Impairment
5.14 Use in Pregnancy
5.15 CAPRELSA REMS (Risk Evaluation and Mitigation Strategy) Program
6. ADVERSE REACTIONS
6.1. Clinical Studies Experience
7. DRUG INTERACTIONS
7.1 CYP3A4 Inducers
7.2 CYP3A4 Inhibitors
7.3 Drugs that Prolong the QT Interval
8. USE IN SPECIFIC POPULATIONS
8.1. Pregnancy
8.3. Nursing Mothers
8.4. Pediatric Use
8.5. Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10. OVERDOSAGE
11. DESCRIPTION
12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3. Pharmacokinetics
12.4 QT Prolongation
13. NONCLINICAL TOXICOLOGY
13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2. Animal Pharmacology and/or Toxicology
14. CLINICAL STUDIES
15 REFERENCES
16. HOW SUPPLIED/STORAGE AND HANDLING
16.1. Storage and Handling
17. PATIENT COUNSELING INFORMATION
17.1 QT INTERVAL
17.2 Rash
17.3 Interstitial lung disease
17.4 Diarrhea
17.5 Reversible Posterior Leukoencephalopathy Syndrome
17.6 Pregnancy and Nursing
17.7 Drug Handling
17.8 MEDICATION GUIDE
PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 100 MG
PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 300 MG

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

WARNING: QT PROLONGATION, TORSADES DE POINTES, AND SUDDEN DEATH

CAPRELSA can prolong the QT interval. Torsades de pointes and sudden death have been reported in patients receiving CAPRELSA. CAPRELSA should not be used in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Hypocalcemia, hypokalemia and/or hypomagnesemia must be corrected prior to CAPRELSA administration and should be periodically monitored. Drugs known to prolong the QT interval should be avoided. If a drug known to prolong the QT interval must be administered, more frequent ECG monitoring is recommended. Given the half-life of 19 days, ECGs should be obtained to monitor the QT at baseline, at 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA and every 3 months thereafter. Following any dose reduction for QT prolongation, or any dose interruptions greater than 2 weeks, QT assessment should be conducted as described above. Because of the 19-day half-life, adverse reactions including a prolonged QT interval may not resolve quickly. Monitor appropriately. Only prescribers and pharmacies certified through the restricted distribution program are able to prescribe and dispense CAPRELSA *[see Warnings and Precautions (5.15)]*.

1. INDICATIONS AND USAGE

1.1. Medullary Thyroid Cancer (MTC)

CAPRELSA is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

Use of CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of CAPRELSA.

2. DOSAGE AND ADMINISTRATION

The recommended daily dose is 300 mg of CAPRELSA taken orally. CAPRELSA treatment should be continued until patients are no longer benefiting from treatment or an unacceptable toxicity occurs.

CAPRELSA may be taken with or without food.

If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose.

For Patients who have Difficulty Swallowing Solids
CAPRELSA tablets should not be crushed. If CAPRELSA tablets cannot be taken whole, the tablets can be dispersed in a glass containing 2 ounces of non-carbonated water and stirred for approximately 10 minutes until the tablet is dispersed (will not completely dissolve). No other liquids should be used. The dispersion should be swallowed immediately. To ensure the full dose is received, any residues in the glass should be mixed again with an additional 4 ounces of non-carbonated water and swallowed.
The dispersion can also be administered through nasogastric or gastrostomy tubes.
Direct contact of crushed tablets with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly. Avoid exposure to crushed tablets.

2.1 Dosage Adjustment
In the event of corrected QT interval, Fridericia (QTcF) greater than 500 ms, interrupt dosing until QTcF returns to less than 450 ms, then resume at a reduced dose.
For CTCAE (Common Terminology Criteria for Adverse Events) grade 3 or greater toxicity, interrupt dosing until toxicity resolves or improves to CTCAE grade 1, and then resume at a reduced dose.
Because of the 19-day half-life, adverse reactions including a prolonged QT interval may not resolve quickly. Monitor appropriately *[see Warnings and Precautions (5.1-5.7, 5.9)]*.
The 300-mg daily dose can be reduced to 200 mg (two 100-mg tablets) and then to 100 mg for CTCAE grade 3 or greater toxicities.

2.2 Elderly
No adjustment in starting dose is required for patients over 65 years of age. There are limited data for patients over the age of 75. *[see Dosage and Administration (2.4)]*

2.3 Concomitant Strong CYP3A4 Inducers
Avoid the concomitant use of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). Patients should also avoid taking St. John's Wort. *[see Warnings and Precautions (5.11)and Drug Interactions (7.1)]*

2.4 Patients With Renal Impairment
The starting dose should be reduced to 200 mg in patients with moderate (creatinine clearance ≥30 to <50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment. *[see Warnings and Precautions (5.12)and Use in Specific Populations (8.6)]*

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

3. DOSAGE FORMS & STRENGTHS
CAPRELSA 100-mg tablets are white, round, biconvex, film-coated, and intagliated with 'Z 100' on one side and plain on the reverse side.
CAPRELSA 300-mg tablets are white, oval, biconvex, film-coated, and intagliated with 'Z 300' on one side and plain on the reverse side.

4. CONTRAINDICATIONS
Do not use in patients with congenital long QT syndrome *[see Boxed Warning]*.

5. WARNINGS AND PRECAUTIONS

5.1 QT Prolongation and Torsades de Pointes
CAPRELSA can prolong the QT interval in a concentration-dependent manner *[see Clinical Pharmacology (12.4)]*. Torsades de pointes, ventricular tachycardia and sudden deaths have been reported in patients administered CAPRELSA.
CAPRELSA treatment should not be started in patients whose QTcF interval is greater than 450 ms. CAPRELSA should not be given to patients who have a history of Torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure. CAPRELSA has not been studied in patients with ventricular arrhythmias or recent myocardial infarction. CAPRELSA exposure is increased in patients with impaired renal function. The starting dose should be reduced to 200 mg in patients with moderate to severe renal impairment and QT interval should be monitored closely.
An ECG and levels of serum potassium, calcium, magnesium and TSH should be obtained at baseline, at 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA and every 3 months thereafter. Electrolytes and ECGs may require more frequent monitoring in case of diarrhea. Following any dose reduction for QT prolongation, or any dose interruptions greater than 2 weeks, QT assessments should be conducted as described above. Serum potassium levels should be maintained at 4 mEq/L or higher (within

normal range) and serum magnesium and serum calcium should be kept within normal range to reduce the risk of electrocardiogram QT prolongation.
Avoid using CAPRELSA with drugs known to prolong the electrocardiogram QT interval *[see Warnings and Precautions (5.11) and Drug Interactions (7.3)]*. 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.
Patients who develop a QTcF greater than 500 ms should stop taking CAPRELSA until QTcF returns to less than 450 ms. Dosing of CAPRELSA can be resumed at a reduced dose *[see Dosage and Administration (2.1)]*.

5.2 Skin Reactions and Stevens-Johnson Syndrome
Severe skin reactions (including Stevens-Johnson syndrome), some leading to death, have been reported with CAPRELSA. Treatment of severe skin reactions has included systemic corticosteroids and permanent discontinuation of CAPRELSA. Mild to moderate skin reactions may manifest as rash, acne, dry skin, dermatitis, pruritus and other skin reactions (including photosensitivity reactions and palmar-plantar erythrodysesthesia syndrome). Mild to moderate skin reactions have been treated with topical and systemic corticosteroids, oral antihistamines, and topical and systemic antibiotics. If CTCAE grade 3 or greater skin reactions occur, CAPRELSA treatment should be stopped until improved. Upon improvement, consideration should be given to continuing treatment at a reduced dose or permanent discontinuation of CAPRELSA. *[see Dosage and Administration (2.1)]*
Photosensitivity reactions are increased with CAPRELSA. Patients should be advised to wear sunscreen and protective clothing when exposed to the sun. Due to the long half-life of CAPRELSA, protective clothing and sunscreen should continue for 4 months after discontinuation of treatment.

5.3 Interstitial Lung Disease
Interstitial Lung Disease (ILD) 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 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.
For cases where symptoms of ILD are severe, discontinue CAPRELSA therapy and the use of corticosteroids and antibiotics may be indicated until clinical symptoms resolve. Even upon resolution of severe ILD, permanent discontinuation of CAPRELSA should be considered.

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

5.5 Hemorrhage
Serious hemorrhagic events, which in some cases were fatal, have been observed with CAPRELSA. There were no fatal bleeding events in the randomized MTC study. Three patients died of fatal bleeding events while on CAPRELSA therapy in clinical studies. Do not administer CAPRELSA to patients with recent history of hemoptysis of ≥ 1/2 teaspoon of red blood. Discontinue CAPRELSA in patients with severe hemorrhage.

5.6 Heart Failure
Heart failure has been observed with CAPRELSA and some cases have been fatal. Discontinuation of CAPRELSA may be necessary in patients with heart failure. Heart failure may not be reversible upon stopping CAPRELSA. Monitor for signs and symptoms of heart failure.

5.7 Diarrhea
Diarrhea was observed in patients who received CAPRELSA. Routine anti-diarrheal agents are recommended. Diarrhea may cause electrolyte imbalances. Since QT prolongation is seen with CAPRELSA, serum electrolytes and ECGs should be carefully monitored in patients with diarrhea. *[see Warnings and Precautions (5.1)]* If severe diarrhea develops, CAPRELSA treatment should be stopped until diarrhea improves. Upon improvement, treatment with CAPRELSA should be resumed at a reduced dose *[see Dosage and Administration (2.1)]*.

5.8 Hypothyroidism
In the randomized MTC study where 90% of the 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 the patients randomized to

placebo. Thyroid-stimulating hormone (TSH) should be obtained at baseline, at 2 to 4 weeks and 8 to 12 weeks after starting treatment with CAPRELSA and every 3 months thereafter. If signs or symptoms of hypothyroidism occur, thyroid hormone levels should be examined and thyroid replacement therapy should be adjusted accordingly.

5.9 Hypertension

Hypertension, including hypertensive crisis, has been observed with CAPRELSA. All patients should be monitored for hypertension and it should be controlled as appropriate. Dose reduction or interruption may be necessary. If high blood pressure cannot be controlled, CAPRELSA should not be restarted *[see Dosage and Administration, (2.1)]*.

5.10 Reversible posterior leukoencephalopathy syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by an MRI of the brain, has been observed with CAPRELSA. This syndrome should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. In clinical studies, three of four patients who developed RPLS while taking CAPRELSA, including one pediatric patient, also had hypertension. Discontinuation of CAPRELSA treatment in patients with RPLS should be considered.

5.11 Drug Interactions

The administration of CAPRELSA with agents that are strong CYP3A4 inducers should be avoided *[see Dosage and Administration (2.3)and Drug Interactions (7.1)]*.

The administration of CAPRELSA with anti-arrhythmic drugs (including, but not limited to amiodarone, disopyramide, procainamide, sotalol, dofetilide) and other drugs that may prolong the QT interval (including but not limited to cloroquine, clarithromycin, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, and pimozide) should be avoided *[see Drug Interactions (7.3)]*.

5.12 Renal Impairment

CAPRELSA exposure is increased in patients with impaired renal function. The starting dose should be reduced to 200 mg in patients with moderate to severe renal impairment and QT interval should be monitored closely. There is no information available for patients with end-stage renal disease requiring dialysis. *[see Boxed Warning, Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*

5.13 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 Dosage and Administration (2.5)]*

5.14 Use in Pregnancy

CAPRELSA can cause fetal harm when administered to a pregnant woman. 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.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, 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. Women should be advised that they must use effective contraception to prevent pregnancy during treatment and for at least four months following the last dose of CAPRELSA *[see Use in Specific Populations (8.1)]*.

5.15 CAPRELSA REMS (Risk Evaluation and Mitigation Strategy) Program

Because of the risk of QT prolongation, Torsades de pointes, and sudden death, CAPRELSA is available only through the restricted distribution program called CAPRELSA REMS Program. Only prescribers and pharmacies certified with the program are able to prescribe and dispense CAPRELSA.

An overview of the requirements for prescribers and pharmacies is included below.

1. To be certified, prescribers must review the educational materials, agree to comply with the REMS requirements, and enroll in the program.

2. To be certified, pharmacies that dispense CAPRELSA must enroll in the program, train their pharmacy staff to verify that each prescription is written by a certified prescriber before dispensing to a patient, and agree to comply with the REMS requirements.

To learn about the specific REMS requirements and to enroll in the CAPRELSA REMS Program, call 1-800-236-9933 or visit www.caprelsarems.com.

6. ADVERSE REACTIONS

The most commonly reported adverse drug reactions (>20%) have been diarrhea, rash, acne, nausea, hypertension, headache, fatigue, upper respiratory tract infections, decreased appetite, and abdominal pain. The most common laboratory abnormalities (>20%) were

decreased calcium, increased ALT, and decreased glucose *[see Dosage and Administration (2.1)and Warnings and Precautions (5.2, 5.3and 5.9)]*.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1. Clinical Studies Experience

Patients with unresectable locally advanced or metastatic medullary thyroid cancer were treated with CAPRELSA 300 mg (n=231) or Placebo (n= 99). Patients with investigator-determined progression or patients who continued treatment after the data cut-off could receive open label CAPRELSA. The following adverse reactions have been reported. *[see Clinical Studies (14)]*

Table 1- Adverse Reactions With a ≥ 5% Increased Incidence in Patients on CAPRELSA Compared to Placebo During Randomized Treatment

System Organ Class **Preferred Term**	**CAPRELSA 300 mg** **N=231**		**Placebo** **N=99**	
	All Grades	**Grade 3-4**	**All Grades**	**Grade 3**
Gastrointestinal Disorders				
Diarrhea/Colitis	132 (57%)	26 (11%)	27 (27%)	2 (2%)
Nausea	77 (33%)	2 (1%)	16 (16%)	0
Abdominal Pain*	48 (21%)	6 (3%)	11(11%)	0
Vomiting	34 (15%)	2 (1%)	7 (7%)	0
Dyspepsia	25 (11%)	0	4 (4%)	0
Dry Mouth	20 (9%)	0	3 (3%)	0
Skin and Cutaneous Disorders				
Rash†	123 (53%)	11 (5%)	12 (12%)	0
Dermatitis Acneiform/Acne	81 (35%)	2 (1%)	7 (7%)	0
Dry Skin	35 (15%)	0	5 (5%)	0
Photosensitivity Reaction	31 (13%)	4 (2%)	0	0
Pruritus	25 (11%)	3 (1%)	4 (4%)	0

Nail abnormalities[‡]	20 (9%)	0	0	0
Alopecia	18 (8%)	N/A	0	N/A
Vascular Disorders				
Hypertension/Hypertensive Crisis/Accelerated hypertension	76 (33%)	20 (9%)	5 (5%)	1 (1%)
Nervous System Disorders				
Headache	59 (26%)	2 (1%)	9 (9%)	0
Dysgeusia	19 (8%)	0	3 (3%)	0
General disorders				
Fatigue[§]	55 (24%)	13 (6%)	23(23%)	1 (1%)
Infections				
Upper Respiratory Tract Infections[¶]	54 (23%)	0	16(16%)	0
Metabolic and Nutritional Disorders				
Decreased Appetite	49 (21%)	10 (4%)	12 (12%)	0
Hypocalcemia	25 (11%)	4 (2%)	3 (3%)	0
Investigations				
ECG QT Prolonged[#]	33 (14%)	18 (8%)	1 (1%)	1 (1%)
Eye Disorders				
Corneal Abnormalities[Þ]	31 (13%)	0	1 (1%)	0
Blurred Vision	21 (9%)	0 (0%)	1 (1%)	0
Renal Disorders				

Proteinuria	23 (10%)	0	2 (2%)	0
Psychiatric Disorders				
Depression	22 (10%)	4 (2%)	3 (3%)	0
Endocrine Disorders				
Hypothyroidism	15 (6%)	0	0	0
Musculoskeletal Disorders				
Muscle Spasms	15 (6%)	0	1(1%)	0

*****Includes abdominal pain, abdominal pain upper, lower abdominal pain and abdominal discomfort.
†Includes rash, rash erythematous, generalized, macular, maculo-papular, papular, pruritic, exfoliative, dermatitis, dermatitis bullous, generalize erythema and eczema.
‡Includes nail disorder, nail bed inflammation, nail bed tenderness, paronychia, nail bed infection, and nail infection.
§Included in Table 1 due to the increased incidence of severe fatigue in the CAPRELSA group compared to the placebo group.
¶Includes laryngitis, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, acute sinusitis, rhinitis, and tracheitis.
#69% had QT prolongation >450ms and 7% had QT prolongation >500ms by ECG using Fridericia correction.
ÞIncludes corneal edema, corneal opacity, corneal dystrophy, corneal pigmentation, keratopathy, arcus lipoides, corneal deposits, acquired corn dystrophy.

Adverse reactions resulting in death in patients receiving CAPRELSA (N=5) were respiratory failure, respiratory arrest, aspiration pneumonia, cardiac failure with arrhythmia, and sepsis. Adverse reactions resulting in death in patients receiving placebo were gastrointestinal hemorrhage (1%) and gastroenteritis (1%). In addition there was one sudden death and one death from cardiopulmonary arrest, in patients receiving CAPRELSA after data cut-off. Causes of discontinuation in 2 or more CAPRELSA-treated patients included asthenia, fatigue rash, arthralgia, diarrhea, hypertension, prolonged QT interval, increase in creatinine and pyrexia. Serious adverse events reported in >2% of CAPRELSA-treated patients included diarrhea, pneumonia, and hypertension.
Clinically important uncommon adverse drug reactions in patients who received CAPRELSA versus patients who received placebo included pancreatitis (0.4% vs. 0%) and heart failure (0.9% vs. 0%). In the integrated summary of safety database, the most common cause of death in patients who received CAPRELSA was pneumonia.
The incidence of Grade 1-2 bleeding events was 14% in patients receiving CAPRELSA compared with 7% on placebo in the randomized portion of the medullary thyroid cancer (MTC) study. The incidence was similar in the 300 mg monotherapy safety program with a 13% incidence.
Blurred vision was more common in patients who received CAPRELSA versus patients who received placebo for medullary thyroid cancer (9% vs. 1%, respectively). 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. If a patient has blurred vision, do not drive or operate machinery.
Table 2 provides the frequency and severity of laboratory abnormalities reported for patients with medullary thyroid cancer receiving randomized treatment with CAPRELSA or placebo.
Table 2 - Laboratory Abnormalities in Patients with MTC

Laboratory Parameter	**CAPRELSA 300 mg N=231**		**Placebo N=99**	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Chemistries				
Calcium Decreased	132 (57%)	13 (6%)	25 (25%)	3 (3%)
ALT Increased	118 (51%)	4 (2%)	19 (19%)	0

Glucose Decreased	55 (24%)	0	7 (7%)	1 (1%)
Creatinine Increased	38 (16%)	0	1 (1%)	0
Bilirubin Increased	29 (13%)	0	17 (17%)	0
Magnesium Decreased	17 (17%)	1 (<1%)	2 (2%)	0
Calcium Increased	16 (7%)	2 (1%)	9 (9%)	1 (1%)
Potassium Decreased	15 (6%)	1 (<1%)	3 (3%)	0
Potassium Increased	13 (6%)	1 (<1%)	4 (4%)	2 (2%)
Glucose Increased	12 (5%)	4 (2%)	7 (7%)	0
Magnesium Increased	6 (3%)	0	4 (4%)	0
Hematologic				
WBC Decreased	45 (19%)	0	25 (25%)	0
Hemoglobin Decreased	31 (13%)	1 (<1%)	19 (19%)	2 (2%)
Neutrophils Decreased	21 (10%)	1 (<1%)	5 (5%)	2 (2%)
Platelets Decreased	18 (9%)	0	3 (3%)	0

Alanine aminotransferase elevations occurred in 51% of patients on CAPRELSA in the randomized medullary thyroid cancer (MTC) study. Grade 3-4 ALT elevations were seen in 2% of patients and no patients had a concomitant increase in bilirubin. Elevations in ALT have resulted in temporary discontinuation of CAPRELSA. However, 16 of 22 patients with a grade 2 elevation in ALT continued 300 mg CAPRELSA. Seven patients who continued CAPRELSA had a normal ALT within 6 months. In the protocol, ALT was monitored every 3 months and more frequently as indicated.

7. DRUG INTERACTIONS

7.1 CYP3A4 Inducers

Drugs that are CYP3A4 inducers can alter CAPRELSA plasma concentrations. The concomitant use of known strong CYP3A4 inducers should be avoided while receiving CAPRELSA therapy. St. John's Wort may decrease CAPRELSA exposure unpredictably and should be avoided *[see Dosage and Administration (2.3) and Warnings and Precautions (5.11)]*.

7.2 CYP3A4 Inhibitors

In healthy subjects, no clinically significant interaction was shown between CAPRELSA and the potent CYP3A4 inhibitor, itraconazole.

7.3 Drugs that Prolong the QT Interval

The administration of CAPRELSA with agents that may prolong the QT interval should be avoided *[see Warnings and Precautions (5.11)]*.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Pregnancy Category D*[see Warnings and Precautions (5.14)]*

CAPRELSA can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of CAPRELSA in pregnant women. Vandetanib is embryotoxic, fetotoxic, and teratogenic to rats, at exposures equivalent to or lower

than those expected at the recommended human dose of 300 mg/day. When vandetanib was administered to female rats prior to mating and through the first week of pregnancy, there were increases in pre-implantation loss and post-implantation loss resulting in a significant reduction in the number of live embryos. This dose administered to rats during organogenesis, caused an increase in post-implantation loss including embryofetal death. Vandetanib caused total litter loss when administered at a dose of 25 mg/kg/day during organogenesis until expected parturition. When administered during organogenesis, vandetanib doses of 1, 10 and 25 mg/kg/day (approximately 0.03, 0.4, and 1.0 times respectively, the C_{max} in patients with cancer at the recommended human dose) caused both malformations of the heart vessels and skeletal variations including delayed ossification of the skull, vertebrae and sternum, indicating delayed fetal development. A no effect level for the malformations was not identified in this study. In a rat pre- and post-natal development study, at doses producing maternal toxicity (1 and 10 mg/kg/day) during gestation and/or lactation, vandetanib decreased pup survival and/or reduced post-natal pup growth. Reduced post-natal pup growth was associated with a delay in physical development.
If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid pregnancy while taking CAPRELSA and for at least four months following the last dose of CAPRELSA.

8.3. Nursing Mothers
In nonclinical studies, vandetanib was excreted in rat milk and found in plasma of pups following dosing to lactating rats. Vandetanib transfer in breast milk resulted in relatively constant exposure in pups due to the long half-life of the drug. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CAPRELSA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4. Pediatric Use
Safety and efficacy of CAPRELSA in pediatric patients have not been established.

8.5. Geriatric Use
In total, 18% of medullary thyroid cancer patients treated with CAPRELSA were age 65 years or older, and 3% were 75 years and older. No overall differences in safety and efficacy were observed between elderly and younger patients. No adjustment in starting dose is required for patients over 65 years of age. There are limited data for patients over the age of 75 years.

8.6 Renal Impairment
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. Subjects with mild renal impairment had comparable mean AUC and clearance values to those with normal renal function. In subjects with moderate and severe renal impairment, the average AUC of CAPRELSA increased by 39% and 41%, respectively, compared to patients with normal renal function.
The starting dose should be reduced to 200 mg in patients with moderate and severe renal impairment *[see Dosage and Administration (2.4)and Warnings and Precautions (5.12)]*.

8.7 Hepatic Impairment
The pharmacokinetics of CAPRELSA were evaluated after a single dose of 800 mg in subjects with mild (n = 8), moderate (n = 7), and severe (n = 6) hepatic impairment and normal hepatic function (n = 5). Subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment had comparable mean AUC and clearance values to those with normal hepatic function.
There are limited data in patients with liver impairment (serum bilirubin greater than 1.5 times the upper limit of normal). CAPRELSA is not recommended for use in patients with moderate and severe hepatic impairment, as safety and efficacy have not been established. *[see Dosage and Administration (2.5) and Warnings and Precautions (5.13)]*.

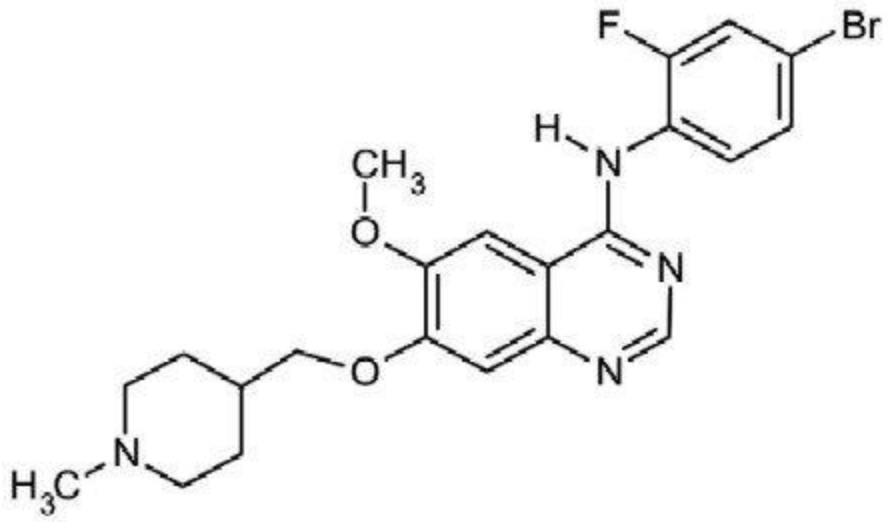
10. OVERDOSAGE
There is no specific treatment in the event of overdose with CAPRELSA and possible symptoms of overdose have not been established. Because of the 19-day half-life, adverse reactions may not resolve quickly. In phase 1 clinical trials, a limited number of patients were treated with daily doses of up to 600 mg and healthy volunteers with daily doses up to 1200 mg. 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 QTc prolongation and Torsades 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 QTc prolongation *[see Dosage and Administration (2.1)]*.

11. DESCRIPTION

CAPRELSA tablets for daily oral administration are available in two dosage strengths, 100 mg and 300 mg, containing 100 mg and 300 mg of vandetanib, respectively. The tablet cores contain the following inactive ingredients: Tablet core: calcium hydrogen phosphate dihydrate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate. The tablet film-coat contains the following inactive ingredients: hypromellose 2910, macrogol 300, and titanium dioxide E171.

Vandetanib is chemically described as N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl) methoxy]quinazolin-4-amine.

The structural and molecular formulas are:



$C_{22}H_{24}BrFN_4O_2$

Vandetanib has a molecular weight of 475.36. Vandetanib exhibits pH-dependent solubility, with increased solubility at lower pH. Vandetanib is practically insoluble in water with a value of 0.008 mg/mL at 25°C (77°F).

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vandetanib is a kinase inhibitor. *In vitro* studies have shown that vandetanib inhibits the activity of tyrosine kinases including members of the epidermal growth factor receptor (EGFR) family, vascular endothelial cell growth factor (VEGF) receptors, rearranged during transfection (RET), protein tyrosine kinase 6 (BRK), TIE2, members of the EPH receptors kinase family, and members of the Src family of tyrosine kinases. In addition, the N-desmethyl metabolite of the drug, representing 7 to 17.1% of vandetanib exposure, has similar inhibitory activity to the parent compound for VEGF receptors (KDR and Flt-1) and EGFR.

Vandetanib inhibits endothelial cell migration, proliferation, survival and new blood vessel formation in *in vitro* models of angiogenesis. Vandetanib inhibits EGFR-dependent cell survival *in vitro*. In addition, vandetanib inhibits epidermal growth factor (EGF)-stimulated receptor tyrosine kinase phosphorylation in tumor cells and endothelial cells and VEGF-stimulated tyrosine kinase phosphorylation in endothelial cells.

In vivo vandetanib administration reduced tumor cell-induced angiogenesis, tumor vessel permeability, and inhibited tumor growth and metastasis in mouse models of cancer.

There is no evidence of a relationship between RET mutations and efficacy with CAPRELSA.

12.3. Pharmacokinetics

A population pharmacokinetic analysis of CAPRELSA was conducted in 231 patients with MTC following oral administration of 300 mg daily doses. The pharmacokinetics of CAPRELSA at the 300 mg dose in MTC patients are characterized by a mean clearance of approximately 13.2 L/h, a mean volume of distribution of approximately 7450 L, and a median plasma half-life of 19 days.

Absorption

Following oral administration of CAPRELSA, absorption is slow with peak plasma concentrations typically achieved at a median of 6 hours, range 4-10 hours, after dosing. CAPRELSA accumulates approximately 8-fold on multiple dosing with steady state achieved from approximately 3 months.

Exposure to vandetanib is unaffected by food.

Distribution

Vandetanib binds to human serum albumin and α1-acid-glycoprotein with *in vitro* protein binding being approximately 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 ^{14}C-vandetanib, unchanged vandentanib and metabolites vandetanib N-oxide and N-desmethyl vandetanib were detected in plasma, urine and feces. A 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. N-desmethyl-vandetanib and vandetanib-N-oxide circulate at concentrations of approximately 7-17.1% and 1.4-2.2%, respectively, of those of vandetanib.

Excretion

Within a 21-day collection period after a single dose of ^{14}C-vandetanib, approximately 69% was recovered with 44% in feces 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. Vandetanib was not a substrate of hOCT2 expressed in HEK293 cells. Vandetanib inhibits the uptake of the selective OCT2 marker substrate ^{14}C-creatinine by HEK-OCT2 cells, with a mean IC_{50} of approximately 2.1 μg/mL. This is higher than vandetanib plasma concentrations (approximately 0.81 μg/mL) observed after multiple dosing at 300 mg. Inhibition of renal excretion of creatinine by vandetanib provides an explanation for increases in plasma creatinine seen in human subjects receiving vandetanib.

Special Populations

Effects of Age and Gender

In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between oral clearance and patient age or gender.

Ethnicity

Based on a cross-study comparison in a limited number of patients, Japanese (N=3) and Chinese (N=7) patients had on average exposures that were higher than Caucasian (N=7) patients receiving the same dose.

Pediatric

The pharmacokinetics of CAPRELSA have not been evaluated in pediatric patients.

12.4 QT Prolongation

In 231 medullary thyroid cancer patients randomized to receive CAPRELSA 300 mg once daily in the phase 3 clinical trial, CAPRELSA was associated with sustained plasma concentration-dependent QT prolongation. Based on the exposure-response relationship, the mean (90% CI) QTcF change from baseline (ΔQTcF) was 35 (33-36) ms for the 300-mg dose. The ΔQTcF 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 ΔQTcF and 4.3% of patients had QTcF greater than 500 ms. Cases of Torsades de pointes and sudden death have been reported *[see Boxed Warning and Warnings and Precautions (5.1, 5.11)]*.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with vandetanib.

Vandetanib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using human lymphocytes or in the *in vivo* rat micronucleus assay.

Based on nonclinical findings, male and female fertility may be impaired by treatment with vandetanib. In a fertility study in male rats, vandetanib had no effect on copulation or fertility rate 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 an increase in 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.

13.2. Animal Pharmacology and/or Toxicology

In an animal model of wound-healing, mice dosed with vandetanib had reduced skin-breaking strength compared with controls. This suggests that CAPRELSA slows but does not prevent wound healing. The appropriate interval between discontinuation of CAPRELSA and subsequent elective surgery required to avoid the risks of impaired wound healing has not been determined.

Nodular masses were observed in a 6-month toxicology study in rats during treatment with ≥5 mg/kg/day vandetanib (approximately 0.22 or 0.40 times, respectively, the AUC in patients with cancer at the recommended human dose of 300 mg/day). Masses were palpable during clinical assessments as early as week 13, were observed in multiple organs, and were associated with hemorrhagic or inflammatory findings.

14. CLINICAL STUDIES

A double-blind, placebo-controlled study randomized patients with unresectable locally advanced or metastatic medullary thyroid cancer to CAPRELSA 300 mg (n=231) versus Placebo (n=100).

The primary objective was demonstration of improvement in progression-free survival (PFS) with CAPRELSA compared to placebo. Other endpoints included evaluation of overall survival and overall objective response rate (ORR). Centralized, independent blinded review of the imaging data was used in the assessment of PFS and ORR. Upon objective disease progression based on the investigator's assessment, patients were discontinued from blinded study treatment and given the option to receive open-label CAPRELSA. Nineteen percent (44/231) of the patients initially randomized to CAPRELSA opted to receive open-label CAPRELSA after disease progression, and 58% (58/100) of the patients initially randomized to placebo opted to receive open-label CAPRELSA after disease progression.

The result of the PFS analysis, based on the central review RECIST assessment, showed a statistically significant improvement in PFS for patients randomized to CAPRELSA (Hazard Ratio (HR) = 0.35; 95% Confidence Interval (CI) = 0.24-0.53; p<0.0001). Analyses in the subgroups of patients who were symptomatic or had progressed within 6 months prior to their enrollment showed similar PFS results (HR = 0.31 95% CI: 0.19, 0.53 for symptomatic patients; HR = 0.41 95% CI: 0.25, 0.66 for patients who had progressed within 6 months prior to enrollment).

At the time of the primary analysis of PFS, 15% of the patients had died and there was no significant difference in overall survival between the two treatment groups. The overall objective response rate (ORR) for patients randomized to CAPRELSA was 44% compared to 1% for patients randomized to placebo. All objective responses were partial responses.

Figure 1- Progression Free Survival

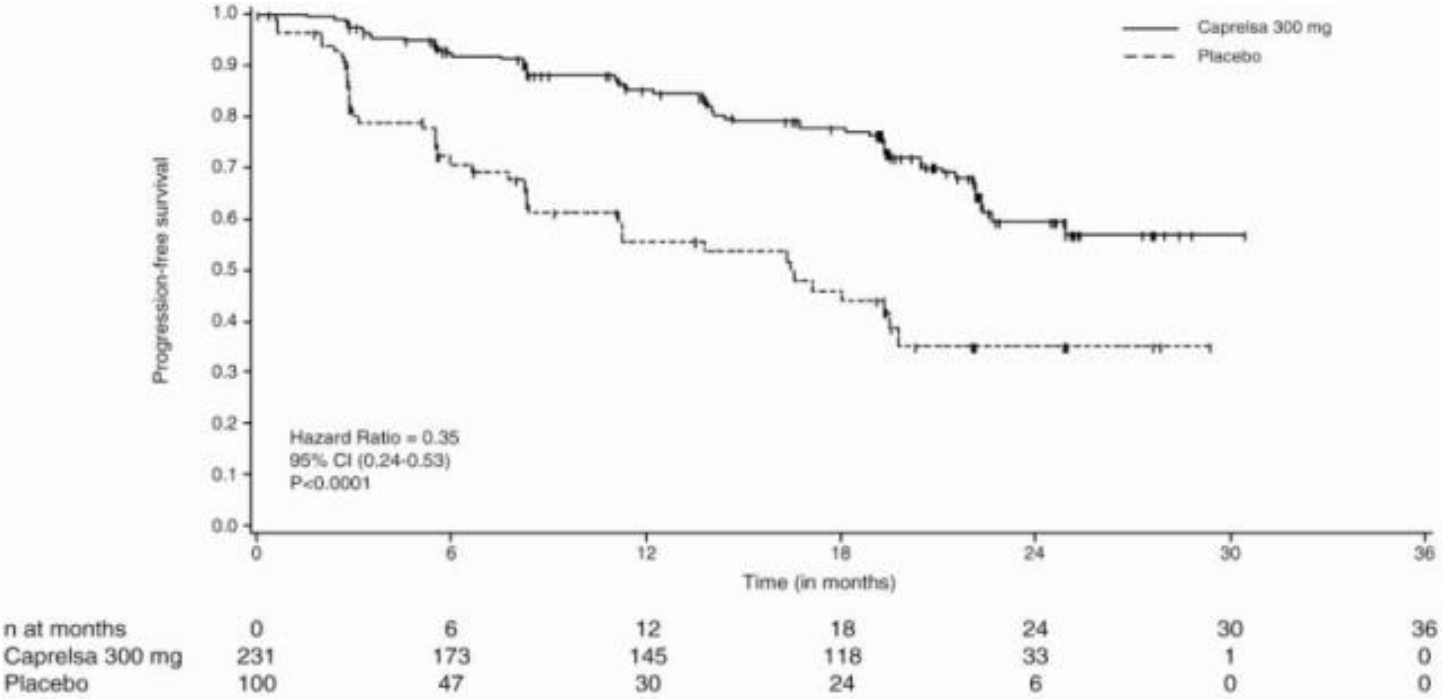


Table 3: Summary of key efficacy findings

Table 3: Summary of key efficacy findings

Progression-Free Survival (PFS)	N*	Median PFS (95% CI)	HR†	95% CI	p-value‡
CAPRELSA 300 mg	59/231 (26%)	Not reached (22.6 months, NE§)			
			0.35	0.24, 0.53	<0.0001
Placebo	41/100	16.4 Months (8.3, 19.7)			

*N = Number of events/number of randomized patients
†HR= Hazard Ratio, Cox Proportional Hazards Model
‡Logrank test
§NE = non-estimatable

15 REFERENCES

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2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs: Am J Health-Syst Pharm. (2006) 63:1172-1193.
4. Polovich, M., White, J. M., & Kelleher, L. O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16. HOW SUPPLIED/STORAGE AND HANDLING

100 mg Tablets Available in bottles containing 30 tablets (NDC 0310–7820–30).
300 mg Tablets Available in bottles containing 30 tablets (NDC 0310–7840–30).

16.1. Storage and Handling

CAPRELSA tablets should be stored at 25°C (77°F); excursions permitted to 15°C – 30°C (59°F – 86°F) [See USP controlled room temperature].
Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.1-4 CAPRELSA tablets should not be crushed. Direct contact of crushed tablets with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references. Personnel should avoid exposure to crushed tablets.

17. PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 QT INTERVAL

CAPRELSA can prolong the QT interval in a concentration-dependent manner. Torsades de pointes, ventricular tachycardia and sudden death have been reported in patients administered CAPRELSA. Patients should be advised that their electrolytes and the electrical activity of their heartbeat (via an ECG) should be monitored regularly during treatment with CAPRELSA.

17.2 Rash

Patients taking CAPRELSA should be told they may be more susceptible to sunburn and to use appropriate sun protection (e.g., sunscreen and/or clothing) while taking CAPRELSA and for at least 4 months after drug discontinuation. Patients should consult their physician promptly if they develop a skin rash.

17.3 Interstitial lung disease

Patients should be told to contact their physician promptly if they develop sudden onset or worsening of breathlessness, persistent cough or fever.

17.4 Diarrhea

Patients should be informed that they may experience diarrhea while taking CAPRELSA. Patients should also be advised to use standard anti-diarrheal medications and to seek medical attention if their diarrhea becomes persistent or severe. Patients with diarrhea should contact their physician to have their electrolytes monitored.

17.5 Reversible Posterior Leukoencephalopathy Syndrome

Patients should be told to contact their physician promptly if they experience seizures, headaches, visual disturbances, confusion or difficulty thinking.

17.6 Pregnancy and Nursing

Patients of childbearing potential must be told to use effective contraception during therapy and for at least four months following their last dose of CAPRELSA.
Breast-feeding mothers are advised to discontinue nursing while receiving CAPRELSA therapy.

17.7 Drug Handling

CAPRELSA tablets should not be crushed. Direct contact of crushed tablets with the skin or mucous membranes should be avoided.

17.8 MEDICATION GUIDE

MEDICATION GUIDE
CAPRELSA®(kap-rel-sah)
(vandetanib) Tablets

Read this Medication Guide before you start taking CAPRELSA and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about CAPRELSA?

CAPRELSA can cause a change in the electrical activity of your heart called QT prolongation, which can cause irregular heartbeats and that may lead to death. You should not take CAPRELSA if you have had a condition called long QT syndrome since birth.

Your healthcare provider should perform tests to check the levels of your blood potassium, calcium, magnesium, and thyroid-stimulating hormone (TSH) as well as the electrical activity of your heart with a test called an electrocardiogram (ECG). You should have these tests:

- Before starting CAPRELSA
- Regularly during CAPRELSA treatment:
  - 2 to 4 weeks after starting CAPRELSA
  - 8 to 12 weeks after starting CAPRELSA
  - Every 3 months thereafter
  - If your healthcare provider changes your dose of CAPRELSA
  - If you start taking medicine that causes QT prolongation
  - As instructed by your healthcare provider

Your healthcare provider may stop your CAPRELSA treatment for a while and restart you at a lower dose if you have QT prolongation.

Call your healthcare provider right away if you feel faint, light-headed, or feel your heart beating irregularly while taking CAPRELSA. These may be symptoms related to QT prolongation.

What is CAPRELSA?

CAPRELSA is a prescription medicine used to treat medullary thyroid cancer that cannot be removed by surgery or that has spread to other parts of the body. It takes a long time to get rid of CAPRELSA from your body and you may be at risk for side effects related to CAPRELSA after you have stopped your treatment.

It is not known if CAPRELSA is safe and effective in children.

Who should not take CAPRELSA?

Do not take CAPRELSA if you have had QT prolongation.

What should I tell my healthcare provider before taking CAPRELSA?

Before you take CAPRELSA, tell your healthcare provider if you:

- have any heart problems, including a condition called congenital long QT syndrome.
- have an irregular heartbeat
- take or have stopped taking a medicine that causes QT prolongation
- have low blood levels of potassium, calcium, or magnesium
- have high blood levels of thyroid-stimulating hormone
- have high blood pressure
- have skin problems
- have a history of breathing problems
- have a recent history of coughing up blood or bleeding
- have diarrhea
- have liver problems
- have kidney problems
- have seizures or are being treated for seizures
- are pregnant or plan to become pregnant. CAPRELSA can cause harm to your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
  - If you are able to become pregnant, you should use effective birth control during your treatment with CAPRELSA and for at least 4 months after your last dose of CAPRELSA.

- Talk to your healthcare provider about birth control methods to prevent pregnancy while you are taking CAPRELSA.

- are breastfeeding or plan to breastfeed. It is not known if CAPRELSA passes into your breast milk. You and your healthcare provider should decide if you will take CAPRELSA or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. CAPRELSA and other medicines may affect each other causing side effects.
Especially tell your healthcare provider if you take:

- St. John's Wort. You should not take St. John's Wort while taking CAPRELSA.

- certain medicines that can affect how your liver breaks down medicine

- a medicine for your heart

Ask your healthcare provider if you are not sure if your medicine is one listed above.
Do not take other medicines while taking CAPRELSA until you have talked with your healthcare provider or pharmacist.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.
How should I take CAPRELSA?

- Take CAPRELSA exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking CAPRELSA unless your healthcare provider tells you to.

- CAPRELSA may be taken with or without food.

- Swallow CAPRELSA tablets whole with water.

- Do not crush or chew CAPRELSA tablets. If CAPRELSA tablets are accidentally crushed, contact with skin should be avoided. If contact occurs, wash affected areas well with water.

- If you cannot swallow CAPRELSA tablets whole:
  - place your dose of CAPRELSA in a glass that contains 2 ounces of noncarbonated water (no other liquids should be used).
  - stir the CAPRELSA tablet(s) and water mixture for about 10 minutes or until the tablet(s) are in very small pieces (the tablets will not completely dissolve).
  - swallow CAPRELSA and water mixture right away.
  - if any CAPRELSA and water mixture remains in the glass, mix with an additional 4 ounces of noncarbonated water and swallow the mixture to make sure that you take your full dose of CAPRELSA.

- If you miss a dose and your next dose is in:
  - less than 12 hours, take your next dose at the normal time. Do not make up for the missed dose.
  - 12 hours or more, take the missed dose as soon as you remember. Take the next dose at the normal time.

Call your healthcare provider right away if you take too much CAPRELSA.

- During treatment with CAPRELSA, your healthcare provider should check your blood and heart for side effects. See "**What is the most important information I should know about CAPRELSA?**"

- Your healthcare provider should check your blood pressure regularly during your treatment with CAPRELSA.

What should I avoid while taking CAPRELSA?

- Limit exposure to the sun. CAPRELSA can make your skin sensitive to the sun. While taking CAPRELSA and for 4 months after stopping your CAPRELSA treatment, use sun block and wear clothes that cover your skin, including your head, arms and legs when you go outdoors.

- Use caution before driving or using machinery. Keep in mind CAPRELSA may make you feel tired, weak, or cause blurred vision.

What are the possible side effects of CAPRELSA?
CAPRELSA may cause serious side effects, including:

- See "**What is the most important information I should know about CAPRELSA?**"

- **Serious skin reactions.** CAPRELSA can cause a serious skin reaction, called Stevens-Johnson syndrome or other serious skin reactions that may affect any part of your body. These serious skin reactions may be life threatening and you may need to be treated in a hospital. Call your healthcare provider right away if you experience any of these symptoms.
  - Skin rash or acne

- Dry skin
- Itching
- Blisters on your skin
- Blisters or sores in your mouth
- Peeling of your skin
- Fever
- Muscle or joint aches
- Redness or swelling of your face, hands, or soles of your feet

- **Breathing problems (interstitial lung disease).** CAPRELSA may cause a breathing problem called interstitial lung disease that can lead to death. Tell your healthcare provider right away if you experience sudden or worsening shortness of breath or cough.

- **Stroke.** Strokes have been reported in some people who have taken CAPRELSA and in some cases have caused death. Stop taking CAPRELSA and call your healthcare provider right away if you have symptoms of a stroke which may include:
  - numbness or weakness of the face, arm or leg, especially on one side of the body
  - sudden confusion, trouble speaking or understanding
  - sudden trouble seeing in one or both eyes
  - sudden trouble walking, dizziness, loss of balance or coordination
  - sudden, severe headache

- **Bleeding.** Bleeding can happen during your treatment with CAPRELSA. Tell your healthcare provider right away if you have severe bleeding while you are taking CAPRELSA.

- **Heart failure.** CAPRELSA can cause heart failure that can lead to death. You may have to stop taking CAPRELSA if you have heart failure. Heart failure may not be reversible after stopping CAPRELSA. Your healthcare provider should monitor you for signs and symptoms of heart failure.

- **Diarrhea.** Diarrhea is often a symptom of medullary thyroid cancer. CAPRELSA can also cause diarrhea or make diarrhea worse. Your healthcare provider should check your blood levels to monitor your electrolytes more frequently if you have diarrhea.

- **Thyroid hormones.** You can have changes in your thyroid hormone when taking CAPRELSA. Your healthcare provider should monitor your thyroid hormone levels while taking CAPRELSA.

- **High blood pressure (hypertension).** If you develop high blood pressure or your high blood pressure gets worse, your healthcare provider may lower your dose of CAPRELSA or tell you to stop taking CAPRELSA until your blood pressure is under control. Your healthcare provider may prescribe another medicine to control your high blood pressure.

- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** A condition called reversible posterior leukoencephalopathy syndrome can happen while taking CAPRELSA. Call your healthcare provider right away if you have:
  - headaches
  - seizures
  - confusion
  - changes in vision
  - problems thinking

The most common side effects of CAPRELSA include:

- diarrhea
- rash
- acne
- nausea
- high blood pressure
- headache
- feeling tired

- loss of appetite
- stomach (abdominal) pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of CAPRELSA. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CAPRELSA?

- Store CAPRELSA tablets at 59°F to 86°F (15°C to 30°C).
- Safely throw away medicine that is out of date or that you no longer need. Ask your pharmacist how to safely throw away CAPRELSA tablets.

Keep CAPRELSA and all medicines out of the reach of children.

General information about CAPRELSA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CAPRELSA for a condition for which it was not prescribed. Do not give CAPRELSA to other people, even if they have the same symptoms you have. It may harm them.
This Medication Guide summarizes important information about CAPRELSA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about CAPRELSA that is written for health professionals.
For more information, go to www.caprelsa.com or call 1-800-236-9933.

What are the ingredients in CAPRELSA?

Active ingredient: vandetanib
Inactive ingredients:

- **Tablet core:** calcium hydrogen phosphate dihydrate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate
- **Tablet coating:** hypromellose 2910, macrogol 300, and titanium dioxide E171

This Medication Guide has been approved by the U.S. Food and Drug Administration.
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PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 100 MG

NDC 0310-7820-30
30 tablets
Caprelsa®
(vandetanib) tablets
100 mg
Rx only
Dispense the accompanying
Medication Guide to each patient.
AstraZeneca

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 300 MG
NDC0310-7840-30
30 tablets
Caprelsa®
(vandetanib) tablets
300 mg
Rx only
Dispense the accompanying
Medication Guide to each patient.
AstraZeneca

Revised: 10/2012

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