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 occurred in patients receiving CAPRELSA. Do not use CAPRELSA in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Correct hypocalcemia, hypokalemia and/or hypomagnesemia prior to CAPRELSA administration. Monitor electrolytes periodically. Avoid drugs known to prolong the QT interval. Only prescribers and pharmacies certified with the restricted distribution program are able to prescribe and dispense CAPRELSA (5.1, 5.16).

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. (1)

Use CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease only after careful consideration of the treatment related risks of CAPRELSA. (1)

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

DOSAGE FORMS AND STRENGTHS
100 mg and 300 mg tablets (3)

ADVERSE REACTIONS
The most common adverse drug reactions (>20%) seen with CAPRELSA and with a between-arm difference of ≥5 % have been diarrhea/colitis, rash, acneiform dermatitis, hypertension, nausea, headache, upper respiratory tract infections, decreased appetite and abdominal pain. (6)

To report SUSPECTED ADVERSE REACTIONS, Contact Sanofi Genzyme at 1-800-817-2722 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• Avoid the use of strong CYP3A4 inducers because they may decrease CAPRELSA exposure. (7.1)
• Avoid the use of agents that prolong the QT interval. (5.11)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide
Revised: 12/2022
CAPRELSA can prolong the QT interval. Torsades de pointes, ventricular tachycardia and sudden deaths have occurred in patients treated with CAPRELSA. Discontinue CAPRELSA treatment in patients with a QT interval greater than 500 ms.

3.1 Dosage Forms and Strengths

300 mg tablets are white, oval, biconvex, film-coated, and intagliated with ‘Z 300’ on one side and plain on the reverse side.

3.2 Administration

Do not crush CAPRELSA tablets. The tablets can be dispersed in 2 ounces of water by stirring for approximately 10 minutes (will not completely dissolve). Do not use other liquids for dispersion. Swallow immediately after dispersion. Mix any remaining residue with 4 additional ounces of water and swallow.

3.3 Contraindications

Do not start CAPRELSA treatment in patients whose QTcF interval is greater than 450 ms. Do not administer CAPRELSA 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. Vandetanib exposure is increased in patients with impaired renal function. Reduce the starting dose to 200 mg in patients with moderate renal impairment and monitor the QT interval closely.

Obtain an ECG and serum potassium, calcium, magnesium and TSH at baseline, 2 to 4 weeks and 8 to 12 weeks after starting treatment with CAPRELSA, and every 3 months thereafter. Monitor electrolytes and ECGs more frequently in patients who experience diarrhea. Following any dose reduction, monitor QTcF interval more frequently. Conduct QT assessments as described above. Maintain serum potassium levels of 4 mEq/L or higher (within normal range) and maintain serum magnesium and calcium levels within normal ranges to reduce the risk of QT prolongation.

Avoid using CAPRELSA with drugs known to prolong the QT interval (see Warnings and Precautions (5.11) and Drug Interactions (7.4)). If such drugs are given to patients already receiving CAPRELSA and no alternative therapy exists, perform ECG monitoring of the QT interval more frequently.

Stop CAPRELSA in patients who develop a QTcF greater than 500 ms until the QTcF returns to less than 450 ms.

3.4 Drug Interactions

Avoid 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 chloroquine, clarithromycin, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, and pimozide) [see Drug Interactions (7.4) and Clinical Pharmacology (12.2)].

3.5QT Prolongation and Torsades de Pointes

3.6 Co-administration of CAPRELSA with anti-arrhythmic drugs (including but not limited to amiodarone, disopyramide, procainamide, sotalol, dovetilide) and other drugs that may prolong the QT interval (including but not limited to chloroquine, clarithromycin, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, and pimozide) [see Drug Interactions (7.4) and Clinical Pharmacology (12.2)].

3.7 Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF signaling pathway. Impaired wound healing has occurred in patients treated with CAPRELSA. Withhold CAPRELSA for at least 1 month prior to elective surgery. Do not administer CAPRELSA for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of treatment with CAPRELSA after resolution of wound healing complications has not been established.

3.8 Embryo-Fetal Toxicity

Based on its mechanism of action, CAPRELSA can cause fetal harm when administered to a pregnant woman. Pregnancy Category X. Avoid CAPRELSA use during pregnancy. If CAPRELSA use becomes unavoidable during pregnancy, counsels the potential risks and benefits of CAPRELSA use. Advise female patients of the need to use contraception during treatment with CAPRELSA and for at least 4 months following the last dose [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

3.9 Hemorrhage

Hemorrhage has occurred in patients treated with CAPRELSA. Do not administer CAPRELSA to patients who have a history of hemoptysis of ≥10 mL of red blood.

3.10 Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by an MRI of the brain, has occurred in patients treated with CAPRELSA. Consider this syndrome 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 also had hypotension. Discontinue CAPRELSA treatment in patients with RPLS.

3.11 Drug Interactions

At the time of treatment with CAPRELSA and for at least 4 months following the last dose [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

3.12 Renal Failure

Renal failure occurred in patients treated with CAPRELSA [see Adverse Reactions (6.1)]. Withhold, reduce the dose or permanently discontinue based on severity [see Dosage and Administration (2.1)]. Vandetanib exposure is increased in patients with impaired renal function. Reduce the starting dose to 200 mg in patients with moderate renal impairment and monitor the QT interval closely.

3.13 Hepatic Impairment

CAPRELSA is not recommended for use in patients with moderate and severe hepatic impairment [see Use in Specific Populations (8.7)].

3.14 Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF signaling pathway. Impaired wound healing has occurred in patients treated with CAPRELSA. Withhold CAPRELSA for at least 1 month prior to elective surgery. Do not administer CAPRELSA for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of treatment with CAPRELSA after resolution of wound healing complications has not been established.

6.1 Embryo-Fetal Toxicity

Based on its mechanism of action, CAPRELSA can cause fetal harm when administered to a pregnant woman. Pregnancy Category X. Avoid CAPRELSA use during pregnancy. If CAPRELSA use becomes unavoidable during pregnancy, counsels the potential risks and benefits of CAPRELSA use. Advise female patients of the need to use contraception during treatment with CAPRELSA and for at least 4 months following the last dose [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

6.2 Drug Interactions

At the time of treatment with CAPRELSA and for at least 4 months following the last dose [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

6.3 Hemorrhage

Hemorrhage [see Warnings and Precautions (5.5)].

6.4 Hypertension

Hypertension, including hypertensive crisis, has occurred in patients treated with CAPRELSA. Monitor all patients for hypertension. Dose reduction or interruption for hypertension may be necessary. If hypertension cannot be controlled, do not resume CAPRELSA [see Dosage and Administration (2.1)].

6.5 Diarrhea

Diarrhea of Grade 3 or greater severity occurred in 11% of patients receiving CAPRELSA in the randomized MTC study. If diarrhea occurs, carefully monitor serum electrolytes and ECGs to reduce the risk and enable early detection of QT prolongation resulting from dehydration [see Warnings and Precautions (5.1)]. Interrupt CAPRELSA for severe diarrhea. Upon improvement, resume CAPRELSA at a reduced dose [see Dosage and Administration (2.1)].

6.6 Heart Failure

Heart failure, including fatalities, occurred in patients treated with CAPRELSA. Do not administer CAPRELSA to patients with a recent history of hemoptysis of ≥10 mL of red blood. Discontinue CAPRELSA in patients with severe heart failure.

6.7 Hypothyroidism

Hypothyroidism has been reported in patients treated with CAPRELSA. Monitor thyroid function periodically. Avoid drugs known to prolong the QT interval. Only prescribers and pharmacies certified with the program are able to prescribe and dispense CAPRELSA [see Warnings and Precautions (5.1, 5.6)].
• Hypothyroidism [see Warnings and Precautions (5.6)]
• Hypertension [see Warnings and Precautions (5.9)]
• Reversible Posterior Leukoencephalopathy Syndrome [see Warnings and Precautions (5.10)]
• Renal Failure [see Warnings and Precautions (5.12)]
• Embryo-Fetal Toxicity [see Warnings and Precautions (5.15)]

6.1 Clinical Trials Experience
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.

The most commonly reported adverse drug reactions which occurred in >20% of CAPRELSA-treated patients and with a between-arm difference of ≥5% included, in order of decreasing frequency: diarrhea/collitis, rash, acniform dermatitis, hypertension, nausea, headache, upper respiratory tract infection, decreased appetite, and abdominal pain.

Among CAPRELSA-treated patients, dose interruption occurred in 109 (47%) and dose reduction occurred in 83 (36%). Adverse reactions led to study treatment discontinuation in 28 of 231 patients (12%) receiving CAPRELSA and in 3 of 99 patients (3.0%) receiving placebo. Adverse reactions leading to permanent discontinuation in 2 or more (≥0.9%) patients treated with CAPRELSA were: asthenia (1.7%), rash (1.7%), diarrhea (0.9%), fatigue (0.9%), pyrexia (0.9%), elevated creatinine (0.9%), QT prolongation (0.9%), and hypertension (0.9%).

Table 1: Per-Patient Incidence of Selected Adverse Reactions Occurring at a Higher Incidence in CAPRELSA-Treated Patients During Randomized Treatment (Between-Arm Difference of ≥5% [All Grades])

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>CAPRELSA 300 mg N=231</th>
<th>Placebo N=99</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea/Collitis</td>
<td>57</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Nausea</td>
<td>33</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal Pain‡</td>
<td>21</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>9</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Skin and Cutaneous Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash‡</td>
<td>53</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Dermatitis Acneiform/Acne</td>
<td>35</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>15</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Photosensitivity Reaction</td>
<td>13</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Nail abnormalities§</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>8</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension/Hypertensive Crisis/Accelerated Hypertension</td>
<td>33</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>28</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Dygeusia</td>
<td>8</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue§</td>
<td>24</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infections</td>
<td>23</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>21</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>11</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG QT Prolonged§</td>
<td>14</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal Abnormalities§</td>
<td>13</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

CTCAE version 3 was used to grade adverse events.
†Includes rash, rash (erythematous, generalized, macular, maculopapular, papular, pruritic, and exfoliative), dermatitis, dermatitis bullous, generalized erythema, and eczema.
‡Includes nail disorder, nail bed inflammation, nail bed tenderness, paronychia, nail bed infection, and nail infection.
§Includes corneal edema, corneal opacity, corneal dystrophy, corneal pigmentation, keratopathy, arcus lipoides, corneal deposits, and acquired corneal dystrophy.

Other Clinically Relevant Adverse Effects
In patients with medullary thyroid cancer treated with CAPRELSA or placebo (NCT00410761), clinically important uncommon adverse drug reactions included pancreatitis (0.4% vs 0.9%), intestinal perforation (0.4% vs 0.5%), and heart failure (0.9% vs 0.5%).

Blurred vision was commonly reported (9% vs 1%) in this trial. Scheduled slit lamp examinations revealed corneal opacities (vortex keratopathies) in treated patients, which can lead to halos and decreased visual acuity. Perform ophthalmologic examination, including slit lamp examination, in patients who report visual changes.

Grade 1 to 2 bleeding events were also more common in patients receiving CAPRELSA compared to placebo (14% vs 7%).

Table 2: Per-Patient Incidence of Selected Laboratory Abnormalities in Patients with MTC Occurring at a Higher Incidence in CAPRELSA-Treated Patients (Between-Arm Difference of ≥5% [All Grades])

<table>
<thead>
<tr>
<th>Laboratory Abnormalities</th>
<th>CAPRELSA 300 mg N=231</th>
<th>Placebo N=99</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>57</td>
<td>6</td>
</tr>
<tr>
<td>ALT increased</td>
<td>51</td>
<td>2</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine Increased</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

CTCAE version 3 was used to grade laboratory abnormalities.

No patient with a Grade 3 to 4 ALT elevation had a concomitant increase in bilirubin in the MTC study.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of CAPRELSA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
7.2 Effect of CAPRELSA on OCT2 Transporter
CAPRELSA increased plasma concentrations of metformin that is transported by the organic cation transporter type 2 (OCT2). Use caution and closely monitor for toxicities when administering CAPRELSA with drugs that are transported by OCT2 [see Clinical Pharmacology (12.3)].

7.3 Effect of CAPRELSA on Dioxin
CAPRELSA increased plasma concentrations of dioxin. Use caution and closely monitor for toxicities when administering CAPRELSA with dioxin [see Clinical Pharmacology (12.3)].

7.4 Drugs that Prolong the QT Interval
Avoid concomitant use of CAPRELSA with agents that may prolong the QT interval [see Warnings and Precautions (5.11)].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on its mechanism of action, CAPRELSA can cause fetal harm when administered to a pregnant woman. Vandetanib is embryotoxic, fetotoxic, and induced fetal malformations in rats at exposures less than or equal to those expected at the recommended human dose of 300 mg/day. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In reproductive toxicity studies, administration of vandetanib to female rats prior to mating and through the first week of pregnancy at a dose of 25 mg/kg/day (approximately equal to the human exposure at the 300 mg clinical dose based on Cmax), there were increases in pre-implantation loss and post-implantation loss resulting in a reduction in the number of live embryos. During organogenesis, vandetanib caused an increased in post-implantation loss, including occasional total litter loss at a dose of 25 mg/kg/day. At doses greater than 10 mg/kg/day (approximately 0.4 times the human Cmax, at the 300 mg clinical dose) treatment with vandetanib resulted in increases in late embryofetal death and decreases in fetal birth weight. A no-effect level for malformations was not identified in this study. Administration of vandetanib at doses greater than or equal to 1 mg/kg/day (approximately 0.033 times the human Cmax, at the 300 mg clinical dose) resulted in dose-dependent increases in both malformations of the heart vessels and skeletal variations including delayed ossification of the skull, vertebrae, and sternum, indicating delayed fetal development.

In a rat prenatal and postnatal development study, at doses (1 and 10 mg/kg/day) producing mild maternal toxicity during gestation and/or lactation, vandetanib decreased pup survival and reduced postnatal pup growth. Reduced postnatal pup growth was associated with a delay in physical development.

8.2 Lactation
There are no data on the presence of vandetanib or its metabolites in human milk or the effects of vandetanib on the breastfed child or on milk production. Vandetanib was present in the milk of lactating rats [see Data]. Because of the potential for serious adverse reactions from CAPRELSA in breastfed children, advise women not to breastfeed during treatment with CAPRELSA and for 4 months after the final dose.

Data
Animal data
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.

8.3 Females and Males of Reproductive Potential

8.3.1 Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating treatment with CAPRELSA [see Use in Specific Populations (8.1)].

Contraception
CAPRELSA can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Females
Advise females of reproductive potential to use effective contraception during treatment with CAPRELSA and for 4 months after the final dose.

Infertility
There are no data on the effect of CAPRELSA on human fertility. Results from animal studies indicate that vandetanib can impair male and female fertility [see Nonclinical Toxicology (12.1)].

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

8.5 Geriatric Use
The MTC study of CAPRELSA did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently compared to younger patients.

8.6 Renal Impairment
Vandetanib exposure is increased in patients with impaired renal function. Reduce the starting dose to 200 mg in patients with moderate (creatinine clearance 30 to < 50 mL/min) renal impairment [see Dosage and Administration (2.1), Warnings and Precautions (5.12), and Clinical Pharmacology (12.3)]. Vandetanib is not recommended for use in patients with severe renal impairment (creatinine clearance 30 mL/min) [see Warnings and Precautions (5.12)]. Patients with end-stage renal disease requiring dialysis were not studied [see Adverse Reactions (6.1)].

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 (2.1) and Warnings and Precautions (5.15)].

10 OVERDOSAGE
In the event of an overdose, monitor patients closely for QTc prolongation. Adverse events including QT interval prolongation should be monitored closely as they may not resolve fully until approximately three plasma half-lives of the drug.

Vandetanib has the chemical name N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylperidin-4-yl) methoxy]quinazolin-4-amine.

The structural and molecular formulas are:
strong CYP3A4 inducers: In a cross-over study of 12 healthy volunteers, a single oral 30 mg dose of CAPRELSA was administered alone on day 1 and on day 10 in combination with daily doses of 600 mg of rifampicin (a strong CYP3A4 inducer) given on days 1 to 3. The coadministration of rifampicin with CAPRELSA decreased the geometric mean AUC0-50h of vandetanib by 40% (90% confidence interval: 36%, 45%) compared to vandetanib alone. No clinically meaningful change in the geometric mean Cmax and Cmin of vandetanib was observed. The geometric mean of AUC0-24h and geometric mean of N-desmethyl-vandetanib increased by 266% and 414%, respectively, in the presence of rifampicin compared with vandetanib alone [see Drug Interactions (7.1)].

Strong CYP3A4 inhibitors: In a cross-over study in 14 healthy volunteers, a single oral 300 mg dose of CAPRELSA was administered alone on day 1 and on day 4 in combination with daily doses of 200 mg of ranitidine (a histamine H2 receptor antagonist) administered for 12 hours apart. No change was observed in the geometric mean AUC0-50h, Cmax, and Cmin of vandetanib when ranitidine was coadministered with CAPRELSA.

Effect of other drugs on CAPRELSA

Gastric pH elevating agents: In a cross-over study of 14 healthy volunteers, a single oral 300 mg dose of CAPRELSA was administered alone and in combination with daily doses of 40 mg of omeprazole (a proton pump inhibitor). No clinically meaningful change was observed in the geometric mean AUC0-50h, Cmax, and Cmin of vandetanib when omeprazole was coadministered with CAPRELSA.

In a cross-over study of 16 healthy volunteers, a single 300 mg oral dose of CAPRELSA was administered alone and after two oral doses of 150 mg of ranitidine (a histamine H2 receptor antagonist) administered 12 hours apart. No change was observed in the geometric mean AUC0-50h, Cmax, and Cmin of vandetanib when ranitidine was coadministered with CAPRELSA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Vandetanib was not carcinogenic in a 2-year study in rats when administered by daily oral gavage at doses of up to 10 mg/kg (0.7 times the human Cmax at the 300 mg clinical dose), or in the ThyRatH2 mouse when administered by daily oral gavage at doses of up to 30 mg/kg (-5 times the human Cmax at the clinical dose of 300 mg) for 26 weeks. Vandetanib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay and was not clastogenic in either the in vivo 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 CAPRELSA. In a fertility study of male rats, vandetanib had no effect on copulation or fertility rate when untreated 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 human exposure based on area under the curve (AUC) in patients with cancer at the 300 mg clinical dose); however, in the same study there was a slight decrease in the number of live embryos in females mated with treated at the 20 mg/kg/day dose level and an increase in implantations per ovulation in females mated with males administered vandetanib at doses of ≥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 one-month 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 of vandetanib (approximately 1.8 times the human exposure based on AUC at the 300 mg clinical dose).

13.2 Animal Toxicology and/or Pharmacology

In an animal model of wound-healing, mice dosed with vandetanib had reduced skin-breaking strength compared with control mice. This could lead to the 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.

14 CLINICAL STUDIES

A double-blind, placebo-controlled study (Study D4200C00098, NCT00410761) randomized patients with unresectable locally advanced or metastatic medullary thyroid cancer to CAPRELSA 300 mg (n=231) versus placebo (n=100). The major efficacy outcome measure was progression-free survival (PFS) with CAPRELSA compared to placebo. Other efficacy outcome measures included evaluation of overall survival (OS) and overall response rate realized, independent blind reviewed 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. Forty-seven percent (109/231) of the patients initially randomized to CAPRELSA opted to receive open-label CAPRELSA after disease progression, and 79% (79/100) of the patients initially randomized to placebo opted to receive open-label CAPRELSA after disease progression.

The results 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<0.001). 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). Median final OS were similar across both 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.

15 REFERENCES

1. OSHA Hazardous Drugs (OSHA Technical Manual). OSHA.

16 HOW SUPPLIED/STORAGE AND HANDLING

100 mg Tablets available in bottles containing 30 tablets (NDC 58468-7820-3).

300 mg Tablets available in bottles containing 30 tablets (NDC 58468-7840-3).

16.1 Storage and Handling

CAPRELSA tablets should be stored at room temperature between 68°F and 77°F (20°C and 25°C); excursions to 59°F–86°F (15°C–30°C) [see USP controlled room temperature].

Procedures for proper handling and disposal of anticancer drugs should be considered. A guideline on this subject has been published.

Do not crush CAPRELSA tablets.

17 PATIENT COUNSELING INFORMATION

Advising the patient to read the FDA-approved patient labeling (Medication Guide).

QT Prolongation and Torsades de Pointes

Advise patients to contact their healthcare provider in the event of syncope, pre-syncope symptoms, and cardiac palpitations. Advise patients that their healthcare provider will monitor their electrolytes and ECGs during treatment [see Warnings and Precautions (5.1)].

Severe Skin Reactions

Advise patients to contact their healthcare provider in the event of skin reactions or rash [see Warnings and Precautions (5.3)].

Intestinal Lymphoid Disease (ILD)

Advise patients to contact their healthcare provider in the event of diarrhea [see Warnings and Precautions (5.7)].

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Advise patients to contact their healthcare provider in the event of seizures, headaches, visual disturbances, confusion or difficulty thinking [see Warnings and Precautions (5.10)].
Impaired Wound Healing
Advise patients that CAPRELSA may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure [see Warnings and Precautions (5.14)].

Embryo-Fetal Toxicity
Advise females of reproductive potential to use effective contraception during treatment with CAPRELSA and for 4 months following the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with CAPRELSA [see Use in Specific Populations (8.1), (8.3)].

Lactation
Advise women not to breastfeed during treatment with CAPRELSA and for at least 4 months after the last dose [see Use in Specific Populations (8.2)].

Photosensitivity
Advise patients to use appropriate sun protection due to the increased susceptibility to sunburn while taking CAPRELSA and for at least 4 months after drug discontinuation [see Warnings and Precautions (5.2)].

Administration
Advise patients that CAPRELSA can be taken with or without food and not to crush CAPRELSA tablets [see Clinical Pharmacology (12.3)].

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 congenital 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, lightheaded, 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.

Females who are able to become pregnant:
- Your healthcare provider should do a pregnancy test before you begin treatment with CAPRELSA.
- 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. Do not breastfeed during treatment and for 4 months after your last dose of CAPRELSA.
- plan to have surgery or have had a recent surgery. You should stop taking CAPRELSA at least 1 month before planned surgery. See “What are the possible side effects of CAPRELSA?”

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 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. During treatment with CAPRELSA and for at least 4 months after stopping treatment with CAPRELSA, 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, 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?”
- Severe skin reactions. CAPRELSA can cause severe skin reactions that can lead to death, such as toxic epidermal necrolysis and Stevens-Johnson syndrome, or other serious skin reactions that may affect any part of your body. These severe 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
  - redness or swelling of your face, hands, or soles of your feet
  - blisters or sores in your mouth
  - peeling of your skin
  - fever
  - muscle or joint aches
- 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, cough that does not go away (persistent) or fever.
- 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. CAPRELSA can cause serious bleeding that can lead to death. 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 common with CAPRELSA and can be severe. Your healthcare provider should check your blood levels to monitor your electrolytes more frequently if you have diarrhea. Tell your healthcare provider if you develop diarrhea during treatment with CAPRELSA.
- 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:
  - seizures
  - headaches
  - changes in vision
  - confusion
  - problems thinking
- Kidney problems. CAPRELSA may cause problems with your kidneys, including kidney failure.
- Wound healing problems. Wounds may not heal properly during CAPRELSA treatment. Tell your healthcare provider if you plan to have any surgery before starting or during treatment with CAPRELSA.
  - You should stop taking CAPRELSA at least 1 month before planned surgery.
  - Your healthcare provider should tell you when you may start taking CAPRELSA again after surgery.

The most common side effects of CAPRELSA include:

- rash
- acne
- high blood pressure
- nausea
- headache
- upper respiratory tract infections
- decreased appetite
- stomach-area (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 room temperature between 68°F and 77°F (20°C and 25°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 1-800-817-2722.

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 film-coat: hypromellose 2910, macrogol 300, and titanium dioxide E171

Manufactured for: Genzyme Corporation, Cambridge, MA 02141
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