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 POINTE, 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).

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

Recent Major Changes

Warnings and Precautions (5.14) 6/2020

INDICATIONS AND USAGE

CAPRELSA is a kinase inhibitor indicated for the treatment of symptomatic or metastatic disease.

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 to severe renal impairment. (2.1)

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: 06/2020

CONTRAINDICATIONS

Do not use in patients with congenital long QT syndrome. (4)

WARNINGS AND PRECAUTIONS

• Prolonged QT interval, torsades de pointes, and sudden death: Monitor electrocardiograms and levels of serum potassium, calcium, magnesium and TSH. Reduce CAPRELSA dose as appropriate. (2.1, 5.1)
• Severe skin reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, some fatal. Discontinue CAPRELSA for severe skin reactions. (2.1, 5.2)
• Intestinal lung disease (ILD), including fatalities: investigate unexplained non-specific respiratory signs and symptoms. Discontinue CAPRELSA for confirmed ILD. (2.1, 5.3)
• Ischemic cerebrovascular events, hemorrhage, heart failure, diarrrhea, hypertension, and reversible posterior leukoencephalopathy syndrome: Discontinue or interrupt CAPRELSA. (2.1, 5.4, 5.5, 5.6, 5.7, 5.9, 5.10)
• Risk of impaired wound healing: Withhold 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. (5.14)
• Embryo-fetal toxicity: Can cause fetal harm. Advise women of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with CAPRELSA and for 4 months following the last dose. (5.15, 8.1)
• REMS: CAPRELSA is available only through a restricted distribution program called the CAPRELSA REMS Program. (5.16)

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PATIENT COUNSELING INFORMATION

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

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. CAPRELSA may cause QT prolongation when used in patients with known QT prolongation. Do not use CAPRELSA in patients with congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure. CAPRELSA may also cause QT prolongation in patients with hypocalcemia, hypokalemia, hypomagnesemia or long QT syndrome. CAPRELSA administration may result in QT prolongation. 

1 INDICATIONS AND USAGE

CAPRELSA is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use CAPRELSA in patients with indolent, asymptomatic or slowly progressing disease only after careful consideration of the treatment related risks of CAPRELSA.

2 DOSAGE AND ADMINISTRATION

The recommended dose of CAPRELSA is 300 mg taken orally once daily until disease progression or unacceptable toxicity occurs. CAPRELSA may be taken with or without food. Do not take a missed dose within 12 hours of the next dose. 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.

The dispersion can also be administered through nasogastric or gastrostomy tubes.

2.1 Dosage Adjustment

For Adverse Reactions

The 300 mg daily dose can be reduced to 200 mg (two 100 mg tablets) and then to 100 mg for patients with moderate hepatic impairment (CTCAE Grade 2 or greater toxicities). Interact CAPRELSA for the following:

- Corrected QT interval, Fridericia (QTcF) greater than 500 ms: Resume at a reduced dose when the QTcF returns to less than 450 ms.
- CTCAE Grade 3 or greater toxicity: Resume at a reduced dose when the toxicity resolves or improves to CTCAE Grade 1.
- For renal impairment: Reduce the starting dose to 200 mg in patients with moderate (creatinine clearance ≥ 30 to < 50 mL/min) and severe (creatinine clearance < 30 mL/min) renal impairment [see Use in Specific Populations (8.6)].
- For patients with hepatic impairment: Reduce the starting dose to 200 mg in patients with moderate (creatinine clearance ≥ 30 to < 50 mL/min) and severe (creatinine clearance < 30 mL/min) renal impairment [see Use in Specific Populations (8.6)].

3 DOSAGE FORMS AND STRENGTHS

CAPRELSA 300 mg tablets are white, oval, 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 (12.2)]. Torsades de pointes, ventricular tachycardia and sudden deaths have occurred in patients treated with CAPRELSA. 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 or to a pregnant woman. In rats, vandetanib was embryotoxic, fetotoxic, and induced fetal malformations at exposures equivalent to or lower than those expected at the 300 mg dosing level in the randomized MTC study. If such drugs are given to patients already receiving CAPRELSA and no alternative therapy exists, perform ECG monitoring of the QT interval closely. There is no information available for patients with end-stage renal disease requiring dialysis [see Boxed Warning, Dosage and Administration (2.1), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

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 (2.1)].

5.14 Risk of Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF signaling pathway. Therefore, CAPRELSA has the potential to adversely affect wound healing.

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.

5.15 Embryo-Fetal Toxicity

Based on its mechanism of action, CAPRELSA can cause fetal harm when administered to a pregnant woman. In rats, vandetanib was embryotoxic, teratogenic, and induced fetal malformations at exposures equivalent to or lower than doses expected at the 300 mg clinical dose and had adverse effects on female fertility, embryofetal development, and postnatal development of pups. Advise women of the potential hazard to a fetus. Advise women of reproductive potential to use effective contraception during treatment with CAPRELSA and for at least 4 months following the last dose [see Use in Specific Populations (8.1), (8.3)].

5.16 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 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 1-800-817-2722 or visit www.caprelsa.com.

### 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the label:

- QT Prolongation and Torsades de Pointes [see Boxed Warning, Warnings and Precautions (5.1)]
- Severe Skin Reactions [see Warnings and Precautions (5.2)]
- Intestinal Lymph Disease [see Warnings and Precautions (5.3)]
- Ischemic Cerebrovascular Events [see Warnings and Precautions (5.4)]
- Hemorrhage [see Warnings and Precautions (5.5)]
- Heart Failure [see Warnings and Precautions (5.6)]
- Diarrhea [see Warnings and Precautions (5.7)]
- Hypothyroidism [see Warnings and Precautions (5.8)]
- Hypertension [see Warnings and Precautions (5.9)]
- Reversible Posterior Leukoencephalopathy Syndrome [see Warnings and Precautions (5.10)]
- 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.

Patients with unresectable locally advanced or metastatic medullary thyroid cancer were treated with CAPRELSA 300 mg (n=231) or Placebo (n=99). The population exposed to CAPRELSA was 58% male, 94% white, and had a median age of 50 years. The data described below reflect a median exposure to CAPRELSA for 607 days.

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/colitis, rash, acneiform 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 86 (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 (≥3%) 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</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=231</td>
<td>Grade 3–4</td>
<td>N=99</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea/Colitis</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><strong>Skin and Cutaneous Disorders</strong></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><strong>Vascular Disorders</strong></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><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>8</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td><strong>General Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue§</td>
<td>24</td>
<td>6</td>
<td>23</td>
</tr>
</tbody>
</table>

### 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</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=231</td>
<td>Grade 3–4</td>
<td>N=99</td>
</tr>
<tr>
<td><strong>Chemistries</strong></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>
</tbody>
</table>

CTCAE version 3 was used to grade adverse events. 
†Includes abdominal pain, abdominal pain upper, lower abdominal pain and abdominal discomfort. 
‡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 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. 
≥65% had QT prolongation ≥450 ms and 7% had QT prolongation ≥500 ms by ECG using Fridericia correction. 
¶Includes corneal edema, corneal opacity, corneal dystrophy, corneal pigmentation, keratopathy, arcus lipoides, corneal deposits, acquired corneal dystrophy.

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%). Blurred vision was more common in patients who received CAPRELSA versus patients who received placebo included pancreatitis (0.4% vs. 0%) and heart failure (0.9% vs. 0%). Blurred vision was more common in patients who received CAPRELSA versus patients who received placebo included pancreatitis (0.4% vs. 0%) and heart failure (0.9% vs. 0%). Blurred vision was more common in patients who received CAPRELSA versus patients who received placebo included pancreatitis (0.4% vs. 0%) and heart failure (0.9% vs. 0%).
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 ≥2% [All Grades]) (continued)

<table>
<thead>
<tr>
<th>Laboratory Abnormalities</th>
<th>CAPRELSA 300 mg</th>
<th>Placebo N=99</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</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>Hypomagnesaemia</td>
<td>7</td>
<td>&lt;1</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 3–4 ALT elevation had a concomitant increase in bilirubin in the MTC study.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval 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.

Vascular disorders: Arterial (including aortic) aneurysms, dissections, and rupture

7 DRUG INTERACTIONS

7.1 Effect of CYP3A4 Inducers on CAPRELSA

Rifampicin, a strong CYP3A4 inducer, decreased vandetanib plasma concentrations. Avoid concomitant use of known strong CYP3A4 inducers during CAPRELSA therapy. Avoid concomitant use of St. John’s wort because it can decrease vandetanib exposure unpredictably.

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.

7.3 Effect of CAPRELSA on Digoxin

CAPRELSA increased plasma concentrations of digoxin. Use caution and closely monitor for toxicities when administering CAPRELSA with digoxin.

7.4 Drugs that Prolong the QT Interval

Avoid concomitant use of CAPRELSA with agents that may prolong the QT interval.

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.

Animal data

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 C_{max}) resulted in increases in pre-implantation loss and post-implantation loss resulting in a reduction in the number of live embryos.

During organogenesis, vandetanib caused an increase 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 C_{max} at the 300 mg clinical dose) treatment with vandetanib resulted in increases in late embryofetal death and decreases in fetal weight. A no-effect level for malformations was not identified in this study.

In vitro studies have shown that vandetanib inhibits the tyrosine kinase activity of the EGFR and VEGFR families, RET, BRK, TIE2, and members of the EPH receptor and Src kinase families. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, and maintenance of the tumor microenvironment. 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.

In vitro, vandetanib inhibited 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.

12.2 Pharmacokinetics

Cardiac Electrophysiology

In 231 patients with medullary thyroid cancer 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 (33–38) 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 occurred [see Boxed Warning and Warnings and Precautions (5.1), (5.11)].

### 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. Vandetanib accumulates approximately 8-fold on multiple dosing with steady state achieved in 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 94%.

### Metabolism

Following oral dosing of 14C-vandetanib, unchanged vandetanib and metabolites vandetanib N-oxide and des-methyl vandetanib were detected in plasma, urine and feces. A glucuronide conjugate was seen as a minor metabolite in excreta only. N-desmethyl-vandetanib was 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% and 1.4-2.2%, respectively, of those of vandetanib.

### Excretion

Within a 21-day collection period after a single dose of 14C-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 HCT2 expressed in HEK293 cells. Vandetanib inhibits the uptake of the selective OCT2 marker substrate 14C-carnitine by HEK-OCT2 cells, with a mean IC50 of 2.1 μg/mL. This is higher than vandetanib plasma concentrations (0.81 μg/mL) observed after multiple dosing at 300 mg. Inhibition of renal excretion of carnitine by vandetanib provides an explanation for increases in plasma carnitine seen in human subjects receiving vandetanib.

### Specific Populations

#### Effects of age and gender

In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between oral clearance of vandetanib 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 average exposures of vandetanib that were higher than Caucasian (N=7) patients receiving the same dose of CAPRELSA.

#### Pediatric

The pharmacokinetics of vandetanib has not been evaluated in pediatric patients.

#### Effect of renal impairment

The pharmacokinetics of vandetanib were evaluated after a single CAPRELSA dose of 800 mg in six subjects with mild (creatinine clearance = 50 to <80 mL/min), eight subjects with moderate (creatinine clearance <30 to <50 mL/min), six subjects with severe (creatinine clearance <30 mL/min) renal impairment and ten subjects with normal (creatinine clearance >80 mL/min) renal function. Subjects with mild renal impairment had a comparable mean AUC of vandetanib to that with normal renal function. In subjects with moderate renal impairment, the average AUC of vandetanib increased by 39% and 41%, respectively, compared to patients with normal renal function [see Dosage and Administration (2.1), Warnings and Precautions (5.12) and Use in Specific Populations (8.6)].

### Drug Interactions

**Effect of other drugs on CAPRELSA**

**Strong CYP3A4 inducers:** In a cross-over study in 12 healthy volunteers, a single oral 300 mg dose of CAPRELSA was administered alone on day 1 and on day 10 in combination with daily doses of 800 mg of rifampicin (a strong CYP3A4 inducer) given on days 1–31. The coadministration of CAPRELSA decreased the geometric mean AUC0–504h of vandetanib by 39% (90% confidence interval [CI]: 56%, 63%) compared to vandetanib alone. No clinically meaningful change in the mean Cmax of vandetanib was observed. The geometric mean AUC0–504h and Cmax 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 and on day 4 in combination with daily doses of 200 mg of iraconazole (a strong CYP3A4 inhibitor) given on days 1–24. No change was observed in the geometric mean AUC0–504h or Cmax of vandetanib when iraconazole was coadministered with 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 a single 600 mg dose of CAPRELSA. The coadministration of CAPRELSA with metformin increased the geometric mean Cmax of metformin by 74% (90% CI: 58%, 92%) and geometric mean C0–504h of metformin by 50% (90% CI: 34%, 67%) compared to vandetanib alone [see Drug Interactions (7.2)].

### 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 AUC0–24h at the 300 mg clinical dose), or in the Tg-RasH2 mouse when administered by daily oral gavage at doses of up to 30 mg/kg (-5 times the human AUC0–24h at the clinical dose of 300 mg) for 26 weeks. Vandetanib did not affect reproductive function in vitro in the bacterial reverse mutation ( Ames) assay and was not clastogenic in either 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 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 area under the curve [AUC] in patients with an AUC0–24h 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 males treated at the 20 mg/kg/day dose level and an increase in preimplantation loss in females mated with males administered vandetanib at doses of ≥5 mg/kg/day. In a fertility study in female rats, 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 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 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.

### 14 CLINICAL STUDIES

#### A double-blind, placebo-controlled study (Study D4200C00058, 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 non-progression-free survival (NPS) with CAPRELSA compared to placebo. Other efficacy outcome measures included evaluation of overall survival (OS) and overall 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. Forty-seven percent (109/231) of the patients initially randomized to CAPRELSA opted to receive open-label CAPRELSA after disease progression, and 79% (179/231) 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 after disease progression (HR = 0.37, 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 months prior to enrollment). Median final OS were similar across both treatment arms.

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: Kaplan-Meier Curves for Progression Free Survival in Study D4200C00058**
Procedures for proper handling and disposal of anticancer drugs should be considered.

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 permitted 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.¹ Do not crush CAPRELSA tablets.

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 58468-7640-3).

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 permitted 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.¹ Do not crush CAPRELSA tablets.

17 PATIENT COUNSELING INFORMATION

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

17.2 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 (5.2)].

Interstitial Lung Disease (ILD)

Advise patients to contact their healthcare provider in the event of sudden onset or worsening of breathlessness, persistent cough or fever [see Warnings and Precautions (5.3)].

Diarrhea

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)].

Risk of 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 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)].

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Table 3: Efficacy Results in Study D4200C00058

<table>
<thead>
<tr>
<th>Progression Free Survival</th>
<th>Vandetanib 300 mg (N=231)</th>
<th>Placebo (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (%)</td>
<td>59 (26.0)</td>
<td>41 (41.0)</td>
</tr>
<tr>
<td>Median, months</td>
<td>NR</td>
<td>16.4</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>(22.6, NE¹)</td>
<td>(8.3, 19.7)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Overall Survival

| Deaths (%)                | 116 (50.2)               | 52 (52.0)      |
| Median, months            | 81.6                     | 80.4           |
| Hazard Ratio (95% CI)     | (64.6, 98.5)             | (52.5, NE)     |
| p-value                   | 0.99 (0.72, 1.38)        |                |

¹Not reached
²Not estimable

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:
  o 2 to 4 weeks after starting CAPRELSA
  o 8 to 12 weeks after starting CAPRELSA
  o every 3 months thereafter
  o if your healthcare provider changes your dose of CAPRELSA
  o if you start taking medicine that causes QT prolongation
  o 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.
• Tell 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.
• 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:

• certain medicines that can affect how your liver breaks down medicine
• a medicine for your heart
• certain medicines that can affect how your liver breaks down medicine

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 than12 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 serious skin reactions such as toxic epidermal necrolysis and 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
  - 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
- Possible 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:
- diarrhea
- rash
- acne
- nausea
- upper respiratory tract infections
- high blood pressure
- 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 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: vantedanib
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

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This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: June 2020

VAN-FPLR-SL-JUN20 Rx Only