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, 5.15).

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)

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2. DOSAGE AND ADMINISTRATION
2.1 Dosage Adjustment
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5.1 QT Prolongation and Torsades de Pointes
5.2 Severe Skin Reactions
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DOSEAGE FORMS AND STRENGTHS
100 mg and 300 mg tablets (3)

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)
• Interstitial 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, diarrhea, hypertension, and reversible posterior leukoencephalopathy syndrome: Discontinue or interrupt CAPRELSA. (2.1, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 5.10)
• Embryofetal toxicity: Can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy during and for four months following treatment with CAPRELSA. (5.14, 8.1)
• REMS: CAPRELSA is available only through a restricted distribution program called the CAPRELSA REMS Program. (5.15)

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)
Pharmacology (12.2) returns to less than 450 ms. Dosing of CAPRELSA can then be resumed at a reduced dose when the QTcF returns to less than 450 ms. Do not use in patients with congenital long QT syndrome [see Warnings and Precautions (5.1, 5.15)]. See Dosage and Administration (2.1). Use in pregnant women [see Use in Specific Populations (8.1), (8.8)].

### Dosage and Administration

**2.1 Dosage Adjustment**

For adverse reactions:
- Corrected QT interval (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 patients with hepatic impairment:

**5.12 Renal Impairment**

Interstitial Lung Disease (ILD) or pneumonitis, including fatalities, has occurred in patients treated with CAPRELSA. Consider a diagnosis of ILD in patients presenting with dyspnea of ≥1/2 teaspoon of red blood. Discontinue CAPRELSA in patients with severe hemor-

**3. DOSAGE FORMS AND STRENGTHS**

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.caprelsarems.com.

**5.5 Hemorrhage**

Serious hemorrhagic events, including fatalities, occurred in patients treated with CAPRELSA. Do not administer CAPRELSA to patients with a recent history of hemopoeisis of ≥1/2 teaspoon of red blood. Discontinue CAPRELSA in patients with severe hemor-

**5.6 Heart Failure**

Heart failure, including fatalities, occurred in patients treated with CAPRELSA. Monitor for signs and symptoms of heart failure. Consider discontinuation of CAPRELSA in patients with heart failure. Heart failure may not be reversible upon stopping CAPRELSA.

**5.7 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)].

**5.8 Hypothyroidism**

In the randomized MTC study in which 90% of the patients enrolled had prior thyroidectomy, increased dosing of thyroid replacement therapy was required in 49% of patients compared to 17% of placebo-treated patients. Obtain thyroid-stimulating hormone (TSH) at baseline, at 2–4 weeks and 8–12 weeks after starting treatment with CAPRELSA, and every 3 months thereafter. If signs or symptoms of hypothyroidism occur, examine thyroid hormone levels and adjust thyroid replacement therapy accordingly.

**5.9 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)].

**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 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 hypertension. Discontinue CAPRELSA in patients with RPLS.

**5.11 Drug Interactions**

Avoid administration of CAPRELSA with anti-arrhythmic drugs (including but not limited to amiodarone, disopyramide, procaminamide, Saulot, dolasetron) and other drugs that may prolong the QT interval (including but not limited to chloroquine, clindamycin, dolasetron, granisetron, haloperidol, methadone, metoclopramide, and pimozide) [see Drug Interactions (7.4) and Clinical Pharmacology (12.2)].

**5.12 Renal Impairment**

Vandetanib exposure is increased in patients with impaired renal function. Reduce the starting dose to 200 mg in patients with moderate to severe renal impairment and monitor 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 [see Use in Specific Populations (8.6)].

**5.14 Embryofetal Toxicity**

Based on its mechanism of action, CAPRELSA can cause fetal harm when administered to a pregnant woman. 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 and had adverse effects on female fertility, development of pups, and postnatal development, and postnatal development of pups. Therefore, it should not be taken during pregnancy. 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 a fetus. Women of childbearing potential should avoid pregnancy. Advise women of childbearing potential that they should use effective contraception during CAPRELSA treatment and for at least four months following the last dose of CAPRELSA [see Use in Specific Populations (8.1), (8.8)].

**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 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.caprelsarems.com.
6. ADVERSE REACTIONS

The following serious adverse reactions were 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)]
- Interstitial Lung 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)]
- Embryofetal Toxicity [see Warnings and Precautions (5.14)]

6.1 Clinical Studies 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/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 83 (36%). Adverse reactions leading to permanent discontinuation in 2 or more (≥2%) patients treated with CAPRELSA were: asthma (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>CAPRELSA 300 mg N=231</th>
<th>Placebo N=99</th>
<th>All Grades (%)</th>
<th>Grade 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea/Colitis</td>
<td>57 11 27 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>33 1 16 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>21 3 11 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 1 7 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11 0 4 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>9 0 3 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and Cutaneous Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>53 5 12 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis Acneiform/Acne</td>
<td>35 1 7 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Skin</td>
<td>15 0 5 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photosensitivity Reaction</td>
<td>13 2 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>11 1 4 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail abnormalities</td>
<td>9 0 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>8 N/A 0 N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension/Hypertensive Crisis/Accelerated Hypertension</td>
<td>33 9 5 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26 1 9 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyseusia</td>
<td>8 0 3 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 6 23 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infections</td>
<td>23 0 16 0</td>
<td></td>
<td></td>
<td></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 N=231</th>
<th>Placebo N=99</th>
<th>All Grades (%)</th>
<th>Grade 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>57 6 25 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT Increased</td>
<td>51 2 19 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>24 0 7 1</td>
<td></td>
<td></td>
<td></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 ≥25% (All Grades)] (Continued)

<table>
<thead>
<tr>
<th>Laboratory Abnormalities</th>
<th>CAPRELSA 300 mg</th>
<th>Placebo</th>
<th>Placebo</th>
<th>N=231</th>
<th>N=99</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
<td></td>
</tr>
<tr>
<td>Creatinine Increased</td>
<td>16</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>7</td>
<td>&lt;1</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10</td>
<td>&lt;1</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td></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.

7. DRUG INTERACTIONS

7.1 Effect of CYP3A4 Inducers on CAPRELSA

Rifaxipin, 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 [see Clinical Pharmacology (12.3)].

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 Digoxin

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

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

Risk Summary

Based on its mechanism of action, CAPRELSA can cause fetal harm when administered to a pregnant woman. Vandetanib is embryotoxic, fetotoxic, and teratogenic in rats, at exposures less than or equal to those expected at the recommended human dose of 300 mg/day. If CAPRELSA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Animal data

When vandetanib was administered 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 recommended 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, a vandetanib dose of 25 mg/kg administered to rats caused an increase in post-implantation loss, including occasional total litter loss. At doses greater than 10 mg/kg (approximately 0.4 times the human exposure at the recommended dose by Cmax), 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 0.03 times the Cmax in patients with cancer at the recommended 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 pre- and postnatal development study, at doses producing mild maternal toxicity (1 and 10 mg/kg/day) during gestation and/or lactation, vandetanib decreased pup survival and/or reduced postnatal pup growth. Reduced postnatal pup growth was associated with a delay in physical development.

8.2 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

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 <50 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment [see Dosage and Administration (2.1), Warnings and Precautions (5.12) and Clinical Pharmacology (12.3)].

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 (5.13)].

8.8 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential should avoid pregnancy.

Use effective contraception during treatment and up to 4 months after the last dose of CAPRELSA.

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 (13.1)].

10. OVERDOSAGE

In the event of an overdose, monitor patients closely for QTc prolongation. Because of the 19-day half-life, adverse reactions may not resolve quickly.

11. DESCRIPTION

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

The structural and molecular formulas are:
Metabolism

Following oral dosing of 14C-vandetanib, unchanged vandetanib and metabolites vandetanib N-oxide and N-desmethyl vandetanib were detected in plasma, urine and feces. 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 monooxygenases 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 OCT2 expressed in HEK293 cells. Vandetanib inhibits the uptake of the selective OCT2 marker substrate 13C-creatinine 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 creatinine by vandetanib provides an explanation for increases in plasma creatinine 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=17) 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 < 30 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 ≥ 50 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 or severe renal impairment, the average AUC of vandetanib increased by 39% and 41%, respectively, compared to patients with normal renal function [see Doseage and Administration (2.1), Warnings and Precautions (5.1) and Use in Specific Populations (8.4)].

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 600 mg of rifampicin (a strong CYP3A4 inducer) given on days 1–31. The coadministration of rifampicin with CAPRELSA decreased the geometric mean AUC(0–504h) of vandetanib by 40% (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 AUC(0–504h) and Cmax of N-desmethylvandetanib 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 itraconazole (a strong CYP3A4 inhibitor) given on days 1–24. No change was observed in the geometric mean AUC(0–504h) or Cmax of vandetanib when itraconazole 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 on day 4 in combination with daily doses of 150 mg of ranitidine (a H2 receptor antagonist) given on days 1–24. No change was observed in the geometric mean AUC(0–504h) or Cmax of vandetanib when ranitidine was coadministered with CAPRELSA.

Effect of CAPRELSA on Other Drugs

Sensitive CYP3A4 substrates: In a cross-over study of 16 healthy volunteers, a single oral 7.5 mg dose of midazolam (as 2 mg/mL oral syrup), a sensitive CYP3A4 substrate, was administered alone and after receiving a single 800 mg oral dose of CAPRELSA. No change was observed in the geometric mean Cmax and AUCinf of midazolam when CAPRELSA was coadministered with midazolam.

Substrates of OCT2 transporter: In a cross-over study of 13 healthy volunteers, a single oral 1000 mg dose of methimarin, a substrate of OCT2, was administered alone and 3 hours after receiving a single 800 mg oral dose of CAPRELSA. The coadministration of CAPRELSA with metformin increased the geometric mean AUCmax of metformin by 74% (90% CI: 58%, 92%) and geometric mean Cmax of metformin by 50% (90% CI: 34%, 67%) compared to metformin alone [see Drug Interactions (7.2)].

Substrates of P-glycoprotein transporter: In a cross-over study of 14 healthy volunteers, a single oral 0.25 mg dose of digoxin, a substrate of P-glycoprotein, was administered alone and in combination with a single 300 mg oral dose of CAPRELSA. The coadministration of CAPRELSA increased the geometric mean Cmax digoxin by 29% (90% CI: 10%, 52%) and the geometric mean of AUC(0–504h) digoxin by 23% (90% CI: 12%, 34%) compared to digoxin alone [see Drug Interactions (7.3)].

13. NONCLINICAL TOXICOLOGY


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 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 AUC in patients with cancer at the recommended human dose of 300 mg/day); however, in the same study there was a slight decrease in the number of live embryos in females mated with males administered 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 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 vandetanib (approximately 1.8 times the exposure measured by AUC in patients with cancer at the recommended human dose).
17. PATIENT COUNSELING INFORMATION

17.1 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. A guideline on this subject has been published. Do not crush CAPRELSA tablets.

17.2 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 diabetes
- 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 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
  - Blister on your skin
  - Blister 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
- Upper respiratory tract infections
- 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.

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.