CAPRELSA® (vandetanib) tablets, for oral use
Initial U.S. Approval: 2011

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

These highlights do not include all the information needed to use CAPRELSA

1 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)

2 DOSAGE AND ADMINISTRATION
Dosage reduction may be necessary in the event of severe toxicities or QT c prolongation. (2.1)

• The starting dose is 200 mg in patients with moderate renal impairment. (2.1)

• CAPRELSA may be taken with or without food. (2)

• Dosage reduction may be necessary in the event of severe toxicities or QT c interval prolongation. (2.1)

• The starting dose is 200 mg in patients with moderate renal impairment. (2.1)

3 DOSAGE FORMS AND STRENGTHS

100 mg and 300 mg tablets (3)

4 CONTRAINDICATIONS
Avoid the use of agents that prolong the QT interval. (5.11)

• 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)

5 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, diarrhea, hypertension, and reversible posterior leukoencephalopathy syndrome: Discontinue or interrupt CAPRELSA. (2.1, 5.4, 5.5, 5.6, 5.7, 5.9, 5.10)

• 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)

6 ADVERSE REACTIONS

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide Revised: 03/2022

7 DRUG INTERACTIONS

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7.2 Effect of CAPRELSA on OCT2 Transporter

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*Sections or subsections omitted from the full prescribing information are not listed
5.2 Severe Skin Reactions
Severe and sometimes fatal skin reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome, have occurred in patients treated with CAPRELSA. Permanently discontinue CAPRELSA for severe skin reactions and refer the patient for urgent medical evaluation. Systemic therapies such as corticosteroids may be required.

5.3 Interstitial Lung Disease
Interstitial Lung Disease (ILD) or pneumonitis, including fatalities, has occurred in patients treated with CAPRELSA. Consider a diagnosis of ILD in patients presenting with non-specific respiratory signs and symptoms. Interrupt CAPRELSA for acute or worsening pulmonary symptoms. Discontinue CAPRELSA if ILD is confirmed.

5.4 Ischemic Cerebrovascular Events
Ischemic cerebrovascular events, including fatalities, occurred in patients treated with CAPRELSA. Do not administer CAPRELSA to patients with a recent history of hemoptysis or recent myocardial infarction.

5.5 Hemorrhage
Serious hemorrhagic events, including fatalities, occurred in patients treated with CAPRELSA.

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, the estimated rate of abnormal thyroid function tests was 49% of patients enrolled treated with CAPRELSA compared to 17% of placebo-treated patients. Obtain Thyroid-stimulating hormone (TSH) at baseline, at 2 to 4 weeks and 8 to 12 weeks after starting treatment with CAPRELSA, and every 3 months thereafter. If TSH levels are normal or low, consider thyroxine replacement therapy.

5.9 Hypertension
Hypertension, including hypertensive crisis, has occurred in patients treated with CAPRELSA. Monitor all patients for hypertension. Dose reduction or interruption of 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.

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

5.12 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)].

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

5.14 Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF receptor pathway. Impaired wound healing has occurred in patients treated with CAPRELSA.

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, fetotoxic, and induced fetal
The following serious adverse reactions are discussed elsewhere in the label:

Program, call 1-800-817-2722 or visit www.caprelsarems.com.

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.caprelsarems.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)]
- Interstitial Lung Disease [see Warnings and Precautions (5.3)]
- Hemorrhage [see Warnings and Precautions (5.4)]
- 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)]
- 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.

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 included in clinical trials of another drug and may not reflect the rates observed in practice.

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></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea/Colitis</td>
<td></td>
<td>57</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal Pain†</td>
<td></td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td></td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Cutaneous Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash‡</td>
<td></td>
<td>53</td>
<td>5</td>
</tr>
<tr>
<td>Dermatitis Acneiform/Acne</td>
<td></td>
<td>35</td>
<td>1</td>
</tr>
<tr>
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<td></td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Photosensitivity Reaction</td>
<td></td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Nail abnormalities§</td>
<td></td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
<td>8</td>
<td>N/A</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.

6.2 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%), intestinal perforation (0.4% vs 0%), and heart failure (0.9% vs 0%). 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%).
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.

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

General disorders: Impaired wound healing

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 [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

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 miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. In nonclinical studies, vandetanib resulted in increases in late embryofetal death and decreases in fetal birth weight and pup survival and reduced postnatal pup growth. Reduced postnatal pup growth was associated with a delay in physical development.

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. The structural and molecular formulas are:

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

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

In vitro studies have shown that vandetanib inhibits the tyrosine kinase activity of the EGFR and VEGF family members, 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 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 Pharmacodynamics
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 concentrations of vandetanib and N-desmethyl vandetanib. 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 to 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 in vitro. Protein binding is approximately 90%. In ex vivo plasma samples from colorectal cancer patients, 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 N-desmethyl vandetanib were detected in plasma, urine, and feces. The 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 FM01 and FM03. 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 OCT22 expressed in HEK293 cells. Vandetanib inhibits the uptake of the selective OCT2 marker substrate 14C-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=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 >100 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 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 and in combination with five daily doses of 40 mg of ropivacaine (a protein pump inhibitor). No clinically meaningful change was observed in the geometric mean AUC of midazolam (as 2 mg/mL oral syrup), a sensitive CYP3A4 substrate, was administered alone and 8 days after receiving a single 800 mg oral dose of CAPRELSA. No change was observed in the geometric mean Cmax and AUC of midazolam when CAPRELSA was coadministered with midazolam.

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 on day 10 in combination with a single 300 mg oral dose of CAPRELSA. The coadministration of CAPRELSA with midazolam increased the geometric mean AUC of midazolam by 74% (90% CI: 58%, 92%) and geometric mean Cmax of midazolam when CAPRELSA was coadministered with midazolam.

Substrates of OCT2 transporter: In a cross-over study of 13 healthy volunteers, a single 1000 mg oral dose of metformin, 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 AUC 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 25 mg dose of digoxin, a substrate of P-glycoprotein and administered alone and in combination with a single 300 mg oral dose of CAPRELSA. The coadministration of CAPRELSA increased the geometric mean Cmax of digoxin by 29% (90% CI: 10%, 52%) and the geometric mean of AUC of digoxin by 23% (90% CI: 12%, 34%) compared to digoxin alone [see Drug Interactions (7.3)].

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 Tg-RasH2 mouse when administered by daily oral gavage at doses of up to 30 mg/kg (less than 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 vitro cytogenetic assay using human lymphocytes or in the in vitro micronucleus assay using mouse lymphocytes.

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 AUC (0–504 h) 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 female fertility study, there was a trend towards increased embryolethality, a slight decrease in the rate of pregnancy 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). 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). 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). 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). 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).
A guideline on this subject has been published.

Procedures for proper handling and disposal of anticancer drugs should be considered.

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].

16.1 Storage and Handling

300 mg Tablets

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

100 mg Tablets

Do not crush CAPRELSA tablets.

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)].

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)].

Manufactured for:
Genzyme Corporation
Cambridge, MA 02142

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Table 3: Efficacy Results in Study D4200C00588

<table>
<thead>
<tr>
<th>Progression Free Survival</th>
<th>Vandetanib 300 mg (N=231)</th>
<th>Placebo (N=100)</th>
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<tbody>
<tr>
<td>Events (%)</td>
<td>59 (26.0)</td>
<td>41 (41.0)</td>
</tr>
<tr>
<td>Median, months</td>
<td>NR¹</td>
<td>16.4</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(22.6, NE¹)</td>
<td>(8.3, 19.7)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.35 (0.24, 0.53)</td>
<td></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            |
| (95% CI)                   | (64.6, 98.5)              | (52.5, NE)      |
| Hazard Ratio (95% CI)      | 0.99 (0.72, 1.38)         |                 |
| p-value                    | 0.975                     |                 |

*Not reached
†Not estimable

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 permitted to 59°F–86°F (15°C-30°C) [See USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

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

17.1 QT Prolongation and Torsades de Pointes

Advise patients to take their antihypertensive medications as directed, to maintain their electrolyte levels during treatment, and to have their electrocardiogram (ECG) monitored 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)].

Intestinal 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)].

Diabetes

Advise patients to contact their healthcare provider in the event of diabetes [see Warnings and Precautions (5.6)].

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)].

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

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

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

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

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

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

What is CAPRELSA?

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

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

Who should not take CAPRELSA?

Do not take CAPRELSA if you have had QT prolongation.

What should I tell my healthcare provider before taking CAPRELSA?

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

- have any heart problems, including a condition called congenital long QT syndrome
• have an irregular heartbeat
• take or have stopped taking a medicine that causes QT prolongation
• have low blood levels of potassium, calcium, or magnesium
• have high blood levels of thyroid-stimulating hormone
• have high blood pressure
• have skin problems
• have a history of breathing problems
• have a recent history of coughing up blood or bleeding
• have diarrhea
• have liver problems
• have kidney problems
• have seizures or are being treated for seizures
• are pregnant or plan to become pregnant. CAPRELSA can cause harm to your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
  o **Females who are able to become pregnant:** Your healthcare provider should do a pregnancy test before you begin treatment with CAPRELSA.
  o You should use effective birth control during your treatment with CAPRELSA and for at least 4 months after your last dose of CAPRELSA.
  o Talk to your healthcare provider about birth control methods to prevent pregnancy while you are taking CAPRELSA.
  o 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:
  o place your dose of CAPRELSA in a glass that contains 2 ounces of noncarbonated water (no other liquids should be used).
  o 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).
  o swallow CAPRELSA and water mixture right away.
  o 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:
  o less than 12 hours, take your next dose at the normal time. Do not make up for the missed dose.
  o 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.
  o skin rash or acne
  o dry skin
  o itching
  o blisters on your skin
  o 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, 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:
  o numbness or weakness of the face, arm or leg, especially on one side of the body
  o sudden confusion, trouble speaking or understanding
  o sudden trouble seeing in one or both eyes
  o sudden trouble walking, dizziness, loss of balance or coordination
  o 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.