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NDA 22-405
Caprelsa® (vandetanib)
Kinase inhibitor
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355
1-800-236-9933

RISK EVALUATION AND MITIGATION STRATEGY

I. GOALS

The goals of the CAPRELSA REMS are:

1. to educate prescribers about the risk, appropriate monitoring, and management of QT prolongation to help minimize the occurrence of Torsades de pointes and sudden death associated with CAPRELSA.

2. to inform patients about the serious risks associated with CAPRELSA.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each CAPRELSA prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the CAPRELSA REMS Program and is appended.

B. Communication Plan

AstraZeneca will implement a communication plan to healthcare providers to support implementation of this REMS.

If AstraZeneca has a presence at the following conferences where commercial CAPRELSA product information is displayed, AstraZeneca will display the CAPRELSA *REMS Convention Panel* outlining details of the CAPRELSA REMS Program.

- American Society of Clinical Oncology (ASCO)
- American Thyroid Association (ATA)
- National Comprehensive Cancer Network (NCCN)
- Oncology Nursing Society (ONS)

The CAPRELSA *REMS Convention Panel* is part of the CAPRELSA REMS Program and is appended.

C. Elements to Assure Safe Use

1. Healthcare providers who prescribe CAPRELSA are specially certified.

a. AstraZeneca will ensure that healthcare providers who prescribe CAPRELSA are specially certified.

b. To become certified to prescribe CAPRELSA, prescribers will be required to enroll in the CAPRELSA REMS Program and must:

1) Review the CAPRELSA *REMS HCP Education Pamphlet* or *Slide Set* and the Full Prescribing Information which includes the Medication Guide.

2) Complete the *Prescriber Training*.

3) Complete and sign the *CAPRELSA Prescriber Enrollment Form* and submit it to the CAPRELSA REMS Program.

4) Agree to review the *Medication Guide* with the patient or caregiver.

c. Prescribers are required to be re-trained following substantive changes to the CAPRELSA REMS. Substantive changes are defined as 1) significant changes to the operation of the CAPRELSA REMS Program; 2) changes to the Prescribing Information and Medication Guide that affect the risk benefit profile of Caprelsa® (vandetanib).

d. AstraZeneca will:

1) Ensure that prescriber enrollment can successfully be completed via the CAPRELSA *REMS website,* or by phone via the call center.

The CAPRELSA *REMS Web Site* (www.caprelsarems.com) is part of the CAPRELSA REMS Program and is appended.

2) Ensure that, as part of the enrollment process, prescribers receive or have access to the following materials that are part of the CAPRELSA REMS

Program and are appended:

HCP Education Pamphlet
HCP Education slides set
Prescriber Training Program
Prescriber Enrollment form
Medication Guide

These materials will be sent promptly to any uncertified prescriber who attempts to prescribe CAPRELSA.

3) Ensure that prescribers have completed the training and ensure that the enrollment form is complete before activating a prescriber's enrollment in the CAPRELSA REMS Program.
4) Ensure that prescribers are notified when they are successfully enrolled in the CAPRELSA REMS Program, and therefore, are certified to prescribe CAPRELSA.

2. CAPRELSA will only be dispensed by pharmacies that are specially certified.

a. AstraZeneca will ensure that CAPRELSA will only be dispensed by certified pharmacies. To become certified to dispense CAPRELSA, each pharmacy must be enrolled in the CAPRELSA REMS Program.

b. To become certified, the authorized pharmacist on behalf of the pharmacy must agree to the following:

1) I understand that only prescribers enrolled in the CAPRELSA REMS Program can prescribe Caprelsa® (vandetanib).

2) The pharmacy must have a system in place to verify that the prescriber is enrolled in the CAPRELSA REMS Program each time CAPRELSA is dispensed. If the prescriber is not enrolled, CAPRELSA cannot be dispensed.

3) All pharmacy staff and critical employees involved in the dispensing of CAPRELSA will be educated on the risks and requirements of the CAPRELSA REMS Program.

4) The pharmacy will provide the Medication Guide each time CAPRELSA is dispensed.

5) The pharmacy will ensure that it has adequate processes and procedures in place and that those processes and procedures are being followed for the CAPRELSA REMS Program.

6) The pharmacy will maintain a system, records and documentation that can be audited to document compliance with the CAPRELSA REMS Program; including prescriber certification each time CAPRELSA is dispensed.

7) Complete and sign the *CAPRELSA Pharmacy Enrollment Form* and submit it to the CAPRELSA REMS Program.

   The *CAPRELSA Pharmacy Enrollment Form* is part of the REMS and is appended.

D Implementation System

1. AstraZeneca will ensure that pharmacies (including pharmacy distributors) dispensing CAPRELSA are specially certified using the criteria described above.

2. AstraZeneca will ensure that distributors who distribute CAPRELSA are specially certified. Specially certified distributors will agree to:

   a. Distribute CAPRELSA only to pharmacies certified in the CAPRELSA REMS.

   b. Put processes and procedures in place to ensure that the requirements of the CAPRELSA REMS are followed.

   c. Agree to be audited to ensure that CAPRELSA is distributed according to the REMS.

3. AstraZeneca will maintain a secure, validated, interactive, web-based database of all enrolled entities (prescribers, pharmacies, and distributors). Prescribers will be able to enroll in the program by completing the enrollment requirements online. Certified pharmacies can access the database to verify prescriber enrollment status as required by the REMS.

4. AstraZeneca will monitor distribution and prescription data to ensure that only enrolled distributors are distributing, enrolled pharmacies are dispensing, and enrolled prescribers are prescribing Caprelsa® (vandetanib). Corrective action will be initiated by AstraZeneca for prescribers, pharmacies, or distributors who are found not to be complying with the REMS.

   a. Inpatients in acute care settings will be shipped drug per patient if the prescriber is enrolled in the REMS

   b. Patients in long-term care facilities will be shipped drug per patient if the prescriber is enrolled in the REMS

   c. All shipments of CAPRELSA will be accompanied by a Medication Guide.

5. AstraZeneca will monitor and audit the online enrollment database, distribution, and dispensing systems to check that all processes and procedures are in place and functioning to support the requirements of the CAPRELSA REMS Program.

6. AstraZeneca will maintain a Program Coordinating Center with a Call Center to support patients, prescribers, pharmacies, and distributors in interfacing with the REMS. AstraZeneca will ensure that all materials listed in or appended to the CAPRELSA REMS Program will be available through the REMS website (www.caprelsarems.com) or by calling the Call Center at 1-800-236-9933.

7. If there are substantive changes to the CAPRELSA REMS Program, AstraZeneca will update all affected materials and notify pharmacies, prescribers, and distributors, as applicable. Substantive changes are defined as:

    a. Significant changes to the operation of the CAPRELSA REMS Program

    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of CAPRELSA.

8. Based on monitoring and evaluation of these elements to assure safe use, AstraZeneca will take reasonable steps to improve implementation of these elements and to maintain compliance with the CAPRELSA REMS Program requirements, as applicable.

9. AstraZeneca will develop, train appropriate personnel, and follow written procedures and scripts to implement the REMS program. AstraZeneca will modify them as required based on the results of assessments.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

AstraZeneca will submit assessments of the Caprelsa® (vandetanib) REMS Program to the FDA every 6 months for the first year following the approval of the CAPRELSA REMS, and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date of the assessment. AstraZeneca will submit each assessment so that it will be received by the FDA on or before the due date.

Prescriber Training Program

The goal of the Prescriber Training Program is to help ensure that healthcare providers treating patients with **CAPRELSA**® (vandetanib) Tablets; understand the risk for QT prolongation, Torsades de pointes and sudden death associated with CAPRELSA treatment. These are not the only risks associated with CAPRELSA. Please see the full Prescribing Information for additional Warnings and Precautions and safety information on CAPRELSA.

Review each of the six sections and answer the question following each section. Select the one answer that is the best choice for each question. This 6-question assessment should take approximately 15 minutes to complete.

QT Prolongation, Torsades de pointes, and Sudden Death

- Torsades de pointes, ventricular tachycardia, and sudden deaths have have occurred in patients treated with CAPRELSA® (vandetanib) Tablets
- CAPRELSA can prolong the QT interval in a concentration-dependent manner
    - In 231 medullary thyroid cancer patients randomized to receive CAPRELSA 300 mg once daily in the phase 3 clinical trial, CAPRELSA was associated with sustained plasma concentration-dependent QT prolongation.

	CAPRELSA 300 mg N=231		**Placebo N=99**	
	All Grades	**Grade 3-4**	**All Grades**	**Grade 3-4**
ECG QT Prolonged	14%	8%	1%	1%

    - Among all patients who received CAPRELSA, 69% had QT prolongation >450 ms and 7% had QT prolongation >500 ms by ECG using Fridericia correction (QTcF)
    - Based on the exposure-response relationship, among all patients who received CAPRELSA, the mean (90% CI) QTcF change from baseline (ΔQTcF) was 35 (33-36) ms for the 300-mg dose. The ΔQTcF remained above 30 ms for the duration of the trial (up to 2 years).
    - 36% of patients who received CAPRELSA experienced greater than 60 ms increase in ΔQTcF
    - Because of the 19-day half-life, adverse reactions including prolonged QT interval may not resolve quickly. Monitor appropriately

Q1. According to the Prescribing Information, QT prolongation, Torsades de pointes and sudden death have occurred in patients treated with CAPRELSA® (vandetanib) Tablets. CAPRELSA can prolong the QT interval in a concentration-dependent manner. Because of the 19-day half life, adverse reactions including prolonged QT interval may not resolve quickly

a. All the above statements are True

b. All the above statements are False

Patient Selection

CAPRELSA® (vandetanib) Tablets are approved 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.

In addition when thinking about the risks of QT prolongation, Torsades de pointes and sudden death associated with CAPRELSA, consider the following when deciding if a patient is appropriate for CAPRELSA treatment:

- Do not use CAPRELSA in patients with
    - Congenital long QT syndrome
    - Torsades de pointes
    - Bradyarrhythmias or
    - Uncompensated heart failure
- Do not start CAPRELSA treatment in patients whose QTcF interval is greater than 450 ms
- CAPRELSA has not been studied in patients with ventricular arrhythmias or recent myocardial infarction
- Vandetanib exposure is increased in patients with impaired renal function defined as a creatinine clearance <50 mL/min

Please note that there are other considerations when deciding if CAPRELSA is the appropriate treatment. This material focuses on the risks of QT prolongation, Torsades de pointes, and sudden death associated with CAPRELSA. These are not the only risks associated with CAPRELSA. Please see the full Prescribing Information for CAPRELSA, including the boxed WARNING.

Q2. According to the Prescribing Information for CAPRELSA® (vandetanib) Tablets, which of the following statements is true?

a. CAPRELSA is contraindicated in patients with congenital long QT syndrome
b. CAPRELSA should not be administered to patients with a history of Torsades de pointes, bradyarrhythmias, or uncompensated heart failure
c. CAPRELSA should not be started in patients with a QTcF interval greater than 450 ms
d. All the above

ECG Monitoring

- Obtain an ECG:
    - At baseline
    - 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA® (vandetanib) Tablets and every 3 months thereafter
    - Following any dose reduction for QT prolongation or any dose interruptions >2 weeks (monitor as described above)
- Stop CAPRELSA in patients who develop a QTcF greater than 500 ms until the QTcF returns to less than 450 ms. CAPRELSA can then be resumed at a reduced dose
- Monitor ECGs more frequently in patients who experience diarrhea

Q3. According to the Prescribing Information, patients who develop a QTcF greater than 500 ms while on CAPRELSA® (vandetanib) Tablets treatment should:

a. Continue CAPRELSA without interruption, at the current dose
b. Continue CAPRELSA without interruption, but at a reduced dose
c. Stop taking CAPRELSA until QTcF returns to less than 450 ms. Dosing of CAPRELSA can be resumed at a reduced dose.
d. None of the above

Electrolyte Monitoring

- To help reduce the risk of QT prolongation:
    - Maintain serum potassium levels at ≥4 mEq/L (within normal range)
    - Maintain serum magnesium and calcium levels within normal ranges
- Obtain serum potassium, calcium, magnesium, and thyroid-stimulating hormone (TSH):
    - At baseline
    - 2-4 weeks and 8-12 weeks after starting treatment with CAPRELSA® (vandetanib) Tablets and every 3 months thereafter
- Monitor electrolytes more frequently in patients who experience diarrhea. In the clinical trial, diarrhea occurred more frequently in patients treated with CAPRELSA compared to placebo

	CAPRELSA 300 mg N=231		**Placebo N=99**	
	All Grades	**Grade 3-4**	**All Grades**	**Grade 3-4**
Diarrhea/Colitis	57%	11%	27%	2%

Q4. According to the Prescribing Information, to help reduce the risk of electrocardiogram QT prolongation with CAPRELSA® (vandetanib) Tablets:

a. Serum potassium levels should be maintained at 4mEq/L or higher (within normal range)
b. Serum magnesium levels should be maintained within normal range
c. Serum calcium levels should be maintained within normal range
d. All the above

Drug Interactions

- Avoid the administration of CAPRELSA® (vandetanib) Tablets with agents that may prolong the QT interval or are associated with Torsades de pointes
    - These include antiarrhythmic drugs (including but not limited to amiodarone, disopyramide, procainamide, sotalol, dofetilide) and other drugs (including but not limited to chloroquine, clarithromycin, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, pimozide)
    - For lists of other possible or conditional risk drugs, please visit the CredibleMeds™ web site at www.azcert.org[1]
- If drugs known to prolong the QT interval are given to patients already receiving CAPRELSA and no alternative therapy exists, perform ECG monitoring of the QT interval more frequently

References: 1. CredibleMeds™. QT drug lists by risk groups. http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm. Accessed June 20, 2013.

Q5. According to the Prescribing Information, administration of CAPRELSA® (vandetanib) Tablets should be avoided in patients who are also receiving other drugs which include:

a. Drugs that may prolong QT interval
b. Anti-arrhythmic drugs
c. a and b
d. None of the above

Dosing and Administration

- The recommended dose of CAPRELSA® (vandetanib) Tablets is 300 mg taken orally once daily until disease progression or unacceptable toxicity occurs
- The 300 mg daily dose can be reduced to 200 mg (two 100 mg tablets) and then to 100 mg for CTCAE (Common Terminology Criteria for Adverse Events) grade 3 or greater toxicities
- 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
- CAPRELSA may be taken with or without food
- Do not take a missed dose within 12 hours of the next dose.
- CAPRELSA is available as 100 mg tablets and 300 mg tablets

Q6. According to the Prescribing Information, if a patient misses a dose of CAPRELSA® (vandetanib) Tablets:

a. The missed dose should be taken by the patient at any time
b. The missed dose should not be taken by the patient if it is less than 12 hours before the next dose
c. The missed dose should be taken along with the next dose
d. None of the above

CAPRELSA is a registered trademark of the AstraZeneca group of companies.

PRESCRIBER ENROLLMENT FORM

The CAPRELSA REMS Program Prescriber Enrollment Form

A prescriber must enroll in the CAPRELSA REMS Program to prescribe CAPRELSA® (vandetanib) Tablets. Please complete the information below and then continue with certification by clicking the NEXT button on your screen

Prescriber Information

First Name: _____Middle Initial: _____Last Name: _____

Credentials: □ MD □ DO □ NP □ PA □ Other

Physician Specialty: □ Medical Oncologist □ Endocrinologist □ Surgeon □ Other_____

Name of Facility: _____

Address 1: _____

Address 2: _____

City: _____ State: _____ Zip code: _____

Phone Number: _____Fax Number: _____

Email: _____

State License Number: _____ State of Issue: _____

National Provider Identification (NPI) Number: _____

Prescriber Agreement

I understand that CAPRELSA is only available through the CAPRELSA REMS Program and I must comply with the program requirements. In addition, I acknowledge that:

1. I have read the HCP Educational Pamphlet or the HCP REMS Education Slide Set, and the Full Prescribing Information for CAPRELSA, including the Medication Guide, and I have completed the prescriber training program.

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

3. **Risk of QT prolongation, Torsades de pointes, and Sudden Death**
    a. I understand that CAPRELSA can prolong the QT interval in a concentration-dependent manner, and that Torsades de pointes, ventricular tachycardia and sudden deaths have occurred in patients receiving CAPRELSA.
    b. I understand that a prolonged QT interval may NOT resolve quickly because of the 19-day half-life.

c. I understand that CAPRELSA® (vandetanib) Tablets must not be administered to patients with congenital long QT syndrome, a history of uncompensated heart failure, bradyarrhythmias, and Torsades de pointes.
d. I will report cases of Torsades de pointes and sudden death to AstraZeneca.

4. **QT Monitoring – I understand that**
   a. ECGs should be obtained to monitor the QT at **baseline**, **at 2-4 weeks** and **8-12 weeks after starting treatment** with CAPRELSA **and every 3 months** thereafter.
   b. Patients who develop a QTcF greater than 500 ms should stop taking CAPRELSA until QTcF returns to less than 450 ms. Dosing of CAPRELSA can then be resumed at a reduced dose.
   c. Following any dose reduction for QT prolongation, or any dose interruptions greater than 2 weeks, QT assessment should be conducted as described above.

5. **Electrolyte Monitoring – I understand that**
   a. CAPRELSA should not be used in patients with hypocalcemia, hypokalemia, and/or hypomagnesemia.
   b. Hypocalcemia, hypokalemia and/or hypomagnesemia must be corrected prior to CAPRELSA administration and should be periodically monitored.
   c. Electrolytes may require more frequent monitoring in patients who experience diarrhea.

6. **Drug Interactions – I understand that**
   a. Drugs known to prolong the QT interval should be avoided.
   b. If drugs known to prolong the QT interval are given to patients already receiving CAPRELSA and no alternative therapy exists, I need to perform ECG monitoring of the QT interval more frequently.

7. **Dosing – I understand**
   a. Vandetanib exposure is increased in patients with impaired renal function. The starting dose should be reduced to 200 mg in patients with moderate to severe renal impairment and QT interval should be monitored closely.
   b. How to properly dose and administer CAPRELSA.
8. I will review and counsel each patient or caregiver on the CAPRELSA Medication Guide and the risks and benefits of CAPRELSA.
9. I understand that CAPRELSA will only be available through pharmacies certified with the CAPRELSA REMS Program.
10. I understand that CAPRELSA is only available through the CAPRELSA REMS Program. I understand and agree to comply with the CAPRELSA REMS Program requirements for prescribers.

Prescriber Signature: _____ Date: _____

PHARMACY ENROLLMENT FORM

The CAPRELSA REMS Program Pharmacy Enrollment Form

A designated representative from the pharmacy must enroll and be certified by the CAPRELSA REMS Program before the pharmacy can dispense CAPRELSA® (vandetanib) Tablets. Please complete the information below and then continue with certification by clicking the NEXT button on your screen.

Pharmacy Information

Pharmacy Name: _____

Address: _____

City: _____ State: _____ Zip: _____

Phone: _____ Fax: _____

National Provider Identifier (NPI): _____ State License Number: _____

NCPDP Number: _____

1. I understand that CAPRELSA is only available through the CAPRELSA REMS Program and I and pharmacy staff must comply with the program requirements. In addition, as the designated authorized pharmacist, I acknowledge that:
    a. I understand that only prescribers enrolled in the CAPRELSA REMS Program can prescribe CAPRELSA.
    b. The pharmacy must have a system in place to verify that the prescriber is enrolled in the CAPRELSA REMS Program each time CAPRELSA is dispensed. If the prescriber is not enrolled, CAPRELSA cannot be dispensed.
    c. All pharmacy staff and critical employees involved in the dispensing of CAPRELSA will be educated on the risks and requirements of the CAPRELSA REMS Program.
    d. The pharmacy will provide Medication Guide each time CAPRELSA is dispensed.
    e. The pharmacy will ensure that it has adequate processes and procedures in place and that those processes and procedures are being followed for the CAPRELSA REMS Program.
    f. The pharmacy will maintain a system, records and documentation that can be audited to document compliance with the CAPRELSA REMS Program; including prescriber certification each time CAPRELSA is dispensed.

Authorized Pharmacist Signature: _____ Date_____

Title: _____ First Name: _____ Last Name: _____

Phone Number: _____ E-mail: _____

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® (vandetanib)?

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® (vandetanib) 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® (vandetanib) 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® (vandetanib)?

CAPRELSA may cause serious side effects, including:

- See **"What is the most important information I should know about CAPRELSA?"**
- **Serious skin reactions.** CAPRELSA can cause a serious skin reaction, called Stevens-Johnson syndrome or other serious skin reactions that may affect any part of your body. These serious skin reactions may be life threatening and you may need to be treated in a hospital. Call your healthcare provider right away if you experience any of these symptoms:
  - Skin rash or acne
  - Dry skin
  - Itching
  - Blisters on your skin
  - Blisters or sores in your mouth
  - Peeling of your skin
  - Fever
  - Muscle or joint aches
  - Redness or swelling of your face, hands, or soles of your feet
- **Breathing problems (interstitial lung disease).** CAPRELSA may cause a breathing problem called interstitial lung disease that can lead to death. Tell your healthcare provider right away if you experience sudden or worsening shortness of breath or cough
- **Stroke.** Strokes have been reported in some people who have taken CAPRELSA and in some cases have caused death. Stop taking CAPRELSA and call your healthcare provider right away if you have symptoms of a stroke which may include:
  - Numbness or weakness of the face, arm or leg, especially on one side of the body
  - Sudden confusion, trouble speaking or understanding
  - Sudden trouble seeing in one or both eyes
  - Sudden trouble walking, dizziness, loss of balance or coordination
  - Sudden, severe headache

- **Bleeding.** Bleeding can happen during your treatment with CAPRELSA® (vandetanib). 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
- Upper respiratory tract infections
- Loss of appetite
- Stomach (abdominal) pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of CAPRELSA® (vandetanib). For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CAPRELSA?

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

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

General information about CAPRELSA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CAPRELSA for a condition for which it was not prescribed. Do not give CAPRELSA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes important information about CAPRELSA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about CAPRELSA that is written for health professionals.

For more information, go to www.caprelsa.com or call 1-800-236-9933.

What are the ingredients in CAPRELSA® (vandetanib)?

Active ingredient: vandetanib

Inactive ingredients:

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

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

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/s/

JEFFERY L SUMMERS
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