Important information for healthcare professionals about the serious risks associated with CAPRELSA® ▽ (vandetanib) tablets

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

WARNING: QTc PROLONGATION, TORSADES DE POINTES, SUDDEN DEATH AND POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES; ALSO KNOWN AS REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME [RPLS])

- CAPRELSA can prolong the QTc interval. Torsades de pointes, sudden death and PRES (also known as RPLS) have been reported in patients receiving CAPRELSA
- CAPRELSA should not be used in patients with hypocalcaemia, hypokalaemia or hypomagnesaemia. CAPRELSA treatment must not be started in those patients whose QTc interval is >480 ms, who have congenital long QTc syndrome or who have a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected. Hypocalcaemia, hypokalaemia and/or hypomagnesaemia must be corrected prior to CAPRELSA administration and should be periodically monitored
- Drugs known to prolong the QTc interval are contraindicated or are not recommended. If a drug known to prolong the QTc interval must be administered, more frequent ECG monitoring is recommended
- Given the half-life of 19 days, ECGs should be obtained to monitor the QTc at baseline, and 1, 3, 6 and 12 weeks after starting treatment with CAPRELSA and every 3 months for at least a year thereafter. Following any dose reduction for QTc prolongation, or any dose interruptions greater than 2 weeks, QTc assessment should be conducted as described above
- Because of the 19-day half-life, adverse reactions including a prolonged QTc interval may not resolve quickly. Monitor appropriately

Suspected adverse reactions and medication errors should be reported. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and sent by post or email to:
P: ADR Reporting/203, Level 3, Rue D'Argens, Gzira GZR 1368
E: postlicensing.medicinesauthority@gov.mt
or to:
P: Associated Drug Co. Ltd., Triq l-Esportaturi, Mriehel, Birkirkara BKR 3000
E: alexia.farrugia@astrazeneca.com

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CAPRELSA can prolong the QTc interval, and cases of Torsades de pointes, sudden death and posterior reversible encephalopathy syndrome (PRES; also known as reversible posterior leukoencephalopathy syndrome [RPLS]) have been reported in clinical trials

Physicians prescribing CAPRELSA™ (vandetanib) **should**:

- Review the HCP education materials and the full Product Information for CAPRELSA, including:
  - Risk information including QTc prolongation, Torsades de pointes, sudden death and PRES (also known as RPLS) with CAPRELSA
  - Considerations for patient selection
  - ECG and electrolyte monitoring requirements
  - Drug interaction information
- Review the Patient Alert Card and explain its role and use to patients who will receive CAPRELSA. The patient should be provided with the Patient Alert Card with each prescription
  - It is important to counsel patients about the risk of prolonged QTc and PRES and inform them of what symptoms and signs to be aware of and actions to take

These education materials focus on the risks of QTc prolongation, Torsades de pointes, sudden death and PRES associated with CAPRELSA. These are not the only risks associated with CAPRELSA. Please see the accompanying full Product Information for CAPRELSA.

Report cases of QTc prolongation, Torsades de pointes, sudden death and PRES to AstraZeneca; case reporting should respect national pharmacovigilance legislation

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QT prolongation, Torsades de pointes and sudden death

- Torsades de pointes, ventricular tachycardia and sudden deaths have been reported in patients administered CAPRELSA
- CAPRELSA can prolong the QTc interval in a concentration-dependent manner
- Diarrhoea can cause electrolyte imbalances, which can increase the risk of prolongation of the electrocardiogram (ECG) QTc interval
- Diarrhoea can lead to dehydration and worsening renal function
- Please see the accompanying full Product Information for CAPRELSA for more information

Drug interactions

- Concomitant use of CAPRELSA with medicinal products known to also prolong the QTc interval and/or induce Torsades de pointes is either contraindicated or not recommended depending on existing alternative therapies:
  - Combinations contraindicated: cisapride, erythromycin intravenous (IV), toremifene, mizolastine, moxifloxacin, arsenic and Class IA and III antiarrhythmics
  - Combinations not recommended: methadone, amisulpride, chlorpromazine, haloperidol, sulpiride, zuclopenthixol, halofantrine, pentamidine and lumefantrine
- If there is no appropriate alternative therapy, not recommended combinations with CAPRELSA may be made with additional ECG monitoring of the QTc interval, evaluation of electrolytes and further control at onset or worsening of diarrhoea

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Posterior reversible encephalopathy syndrome (reversible posterior leukoencephalopathy syndrome)

- Posterior reversible encephalopathy syndrome (PRES; also known as reversible posterior leukoencephalopathy syndrome [RPLS]) is a syndrome of subcortical vasogenic oedema diagnosed by an MRI of the brain
- PRES has been reported infrequently in patients administered CAPRELSA. There have been no confirmed cases of PRES in patients with medullary thyroid cancer receiving CAPRELSA; however, cases of PRES have occurred in the CAPRELSA clinical programme
- This syndrome should be considered in any patient presenting with seizures, headaches, visual disturbances, confusion or altered mental function
- Patients should be informed of the symptoms of PRES and should be instructed to contact a physician immediately if they experience any of the symptoms
- If a patient presents with symptoms suggestive of PRES, it is recommended that physicians immediately perform an MRI of the brain

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Patient selection

When thinking about the risks of QTc prolongation, Torsades de pointes, sudden death and PRES (also known as RPLS) associated with CAPRELSA, consider the following when deciding whether a patient is appropriate for CAPRELSA treatment:

Considerations for patient selection

- Do not use CAPRELSA in patients with congenital long QTc syndrome
- CAPRELSA treatment must not be started in patients whose QTc interval is >480 ms
- CAPRELSA should not be given to patients who have a history of:
  - Torsades de pointes
  - Bradyarrhythmias
  - Uncompensated heart failure
- CAPRELSA has not been studied in patients with ventricular arrhythmias or recent myocardial infarction

Other facts about CAPRELSA

- In patients with pre-existing hypertension, blood pressure needs to be controlled before starting CAPRELSA treatment
- Fatigue, asthenia and weight loss have been identified as side effects of CAPRELSA; the occurrence of any of these conditions, especially in the elderly, may increase the risk of pneumonia
- All cases of adverse events should be reported to AstraZeneca; case reporting should respect national pharmacovigilance legislation

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ECG monitoring

Recommendations for ECG monitoring

- ECGs should be obtained:
  - At baseline
  - 1, 3, 6 and 12 weeks after starting treatment with CAPRELSA and every 3 months for at least a year thereafter – ECGs and blood tests should also be obtained as clinically indicated during this period and afterwards
  - Following any dose reduction for QTc prolongation or any dose interruptions >2 weeks (monitor as described above)
- Patients who develop a single value of QTc interval ≥500 ms should stop taking CAPRELSA. Dosing can be resumed at a reduced dose after return of the QTc interval to pretreatment status has been confirmed and correction of possible electrolyte imbalance has been made
- If QTc increases markedly but stays below 500 ms, cardiologist advice should be sought
- ECGs may require more frequent monitoring in cases of diarrhoea/dehydration, electrolyte imbalance and/or impaired renal function

Electrolyte monitoring

Recommendations for electrolyte monitoring

- To help reduce the risk of QTc prolongation:
  - Serum potassium, magnesium and calcium levels should be kept within normal range
- Levels of serum potassium, calcium, magnesium and thyroid-stimulating hormone (TSH) should be obtained:
  - At baseline
  - 1, 3, 6 and 12 weeks after starting treatment with CAPRELSA and every 3 months for at least a year thereafter – ECGs and blood tests should also be obtained as clinically indicated during this period and afterwards
  - Following any dose reduction for QTc prolongation or any dose interruptions >2 weeks (monitor as described above)
- Electrolytes may require more frequent monitoring in cases of diarrhoea/dehydration, electrolyte imbalance and/or impaired renal function

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