AYVAKYT Safety Information[1]

HAEMORRHAGES

Avapritinib has been associated with an increased incidence of haemorrhagic adverse reactions, including serious and severe adverse reactions, like gastrointestinal haemorrhage and intracranial haemorrhage in patients with AdvSM.

Routine surveillance of haemorrhagic adverse reactions in patients with AdvSM must include physical examination. Complete blood counts, including platelets, and coagulation parameters must be monitored in patients with AdvSM, particularly in patients with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding.

INTRACRANIAL HAEMORRHAGES

Adverse reactions of intracranial haemorrhage occurred in AdvSM patients who received avapritinib.

Before initiating avapritinib at any dose the risk for intracranial haemorrhage should be carefully considered in patients with potential increased risk including those with a history of vascular aneurysm, intracranial haemorrhage, cerebrovascular accident within the prior year, concomitant use of anticoagulants or thrombocytopenia.

Patients who experience clinically relevant neurological signs and symptoms (e.g. severe headache, vision problems, somnolence, and/or focal weakness) during treatment with avapritinib must interrupt dosing of avapritinib and inform their healthcare professional immediately.

Brain imaging by magnetic resonance imaging (MRI) or computed tomography (CT) may be performed at the discretion of the physician based on severity and the clinical presentation. For patients with observed intracranial haemorrhage during treatment with avapritinib in any indication, regardless of severity grade, avapritinib must be permanently discontinued.

Serious adverse reactions of intracranial haemorrhage occurred in patients with AdvSM receiving avapritinib. The exact mechanism is unknown. The incidence of intracranial haemorrhage was higher in patients with platelet counts <50 x 10_9/L and in patients with a starting dose of ≥300 mg.

Considering the above, a platelet count must be performed prior to initiating therapy. Avapritinib is not recommended in patients with platelet counts <50 x 10_9/L. Following treatment initiation, platelet counts must be performed every 2 weeks for the first 8 weeks regardless of baseline platelet count. After 8 weeks of treatment, monitor platelet counts every 2 weeks (or more frequently as clinically indicated) if values are less than 75 x 10_9/L, every 4 weeks if values are between 75 and 100 x 10_9/L, and as clinically indicated if values are greater than 100 x 10_9/L.

Manage platelet counts of <50 x 10_9/L by temporarily interrupting avapritinib. Platelet support may be necessary, and the recommended dose modification must be followed. Thrombocytopenia was generally reversible by reducing or interrupting avapritinib in clinical studies.

The maximum dose for patients with AdvSM should not exceed 200 mg once daily.

COGNITIVE EFFECTS

Cognitive effects, such as memory impairment, cognitive disorder, confusional state, and encephalopathy, can occur in patients receiving avapritinib. The mechanism of the cognitive effects is not known.

It is recommended that patients with AdvSM are clinically monitored for signs and symptoms of cognitive events such as new or increased forgetfulness, confusion, and/or difficulty with cognitive functioning. Patients with AdvSM must notify their healthcare professional immediately if they experience new or worsening cognitive symptoms.

For AdvSM patients with observed cognitive effects related to treatment with avapritinib, the recommended dose modification must be followed. In clinical studies conducted in patients with AdvSM, dose reductions or interruptions improved Grade ≥2 cognitive effects compared to no action.

In patients with ISM, cognitive effects can be one of the disease symptoms. Patients with ISM must notify their healthcare professional if they experience new or worsening cognitive symptoms.

FLUID RETENTION

In patients with AdvSM, localised (facial, periorbital, peripheral, pulmonary oedema, pericardial and/or pleural effusion) or generalised oedema, and ascites have been observed with a frequency category of at least common. Other localised oedemas (laryngeal oedema) have been reported uncommonly.

Therefore, it is recommended that patients with AdvSM be evaluated for these adverse reactions including regular assessment of weight and respiratory symptoms. An unexpected rapid weight gain or respiratory symptoms indicating fluid retention must be carefully investigated and appropriate supportive care and therapeutic measures, such as diuretics, should be undertaken. For AdvSM patients presenting with ascites, it is recommended to evaluate the aetiology of ascites.

In patients with ISM, localised (peripheral, facial) oedemas have been reported with a frequency category of at least common.

QT INTERVAL PROLONGATION

Prolongation of QT interval has been observed in patients with AdvSM treated with avapritinib in clinical studies. QT interval prolongation may induce an increased risk of ventricular arrhythmias, including Torsade de pointes.

Avapritinib should be used with caution in AdvSM patients with known QT interval prolongation or at risk of QT interval prolongation (e.g. due to concomitant medicinal products, pre-existing cardiac disease and/or electrolyte disturbances). Concomitant administration with strong or moderate CYP3A4 inhibitors should be avoided due to the increased risk of adverse reactions, including QT prolongation and related arrhythmias.

If concomitant use of moderate CYP3A4 inhibitors cannot be avoided, the recommended dose modification must be followed.

In patients with AdvSM interval assessments of QT by electrocardiogram (ECG) should be considered if avapritinib is taken concurrently with medicinal products that can prolong QT interval.

In patients with ISM, QT interval assessments by ECG should be considered, in particular in patients with concurrent factors that could prolong QT (e.g. age, pre-existing heart rhythm disorders, etc.).

GASTROINTESTINAL DISORDERS

Diarrhoea, nausea and vomiting were the most commonly reported gastrointestinal adverse reactions in patients with AdvSM. AdvSM patients who present with diarrhoea, nausea and vomiting should be evaluated to exclude disease-related aetiologies. Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with antiemetic, antidiarrhoeal, or antacid properties.

The hydration status of AdvSM patients experiencing gastrointestinal adverse reactions must be closely monitored and treated as per standard clinical practice.

LABORATORY TESTS

Treatment with avapritinib in patients with AdvSM is associated with anaemia, neutropenia and/or thrombocytopenia. Complete blood counts must be performed on a regular basis during the treatment with avapritinib in patients with AdvSM.

Treatment with avapritinib is associated in patients with AdvSM with elevations in bilirubin and liver transaminases. Liver function (transaminases and bilirubin) should be monitored regularly in patients with AdvSM receiving avapritinib.

CYP3A4 INHIBITORS AND INDUCERS

Co-administration with strong or moderate CYP3A inhibitors should be avoided because it may increase the plasma concentration of avapritinib.

Co-administration with strong or moderate CYP3A inducers should be avoided because it may decrease the plasma concentrations of avapritinib.

PHOTOSENSITIVITY REACTION

Exposure to direct sunlight must be avoided or minimised due to the risk of phototoxicity associated with avapritinib. Patients must be instructed to use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

SODIUM

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

For additional information on dosing and administration, please see the EMA- Summary of Product Characteristics (AYVAKYT). Accessed March 2024.

1. AYVAKYT Summary of Product Characteristics; July 2023.