ZYTIGA® (abiraterone acetate)
ZYTIGA - Drug Interactions with Hydroxychloroquine

SUMMARY

- No clinical studies have been conducted to evaluate the potential for drug-drug interactions between abiraterone acetate and hydroxychloroquine.
- Evidence-based guidelines recommend against the use of hydroxychloroquine for the treatment of COVID-19 in hospitalized patients (AI: strong recommendation for the statement based on one or more randomized trials without major limitations) and in nonhospitalized patients (AIIa: strong recommendation for the statement based on other randomized trials or subgroup analyses of randomized trials).[1]
- If a patient has a confirmed COVID-19 infection, physicians should consider the risk vs benefit of continuing ZYTIGA plus prednisone based on the nature and status of the patient's underlying cancer, comorbidities, and the potential risks associated with the COVID-19 infection. Providers should refer to product labeling for additional information, including safety, dosage & administration, dose modifications, and drug-drug interactions (eg, for antivirals, antibiotics, or other medications used concomitantly in the management of an active COVID-19 infection).
- In the absence of formal drug-drug interaction studies, the pharmacodynamic and pharmacokinetic profiles of these medications were reviewed for potential concerns associated with concomitant use.
- ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition and is indicated for use in combination with prednisone/prednisolone.[2] Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia, or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly.[3]
- Cardiovascular adverse reactions have been reported from the pivotal studies of ZYTIGA plus prednisone/prednisolone, including cardiac arrhythmias, and case reports of torsades de pointes have been published.
    - QT prolongation and torsades de pointes have been observed in patients who develop hypokalemia while taking ZYTIGA.[4,5]
    - In a phase 1b, open-label, single-arm, multicenter study conducted to assess the effect of ZYTIGA and prednisone on QT interval, 33 patients with metastatic castration-resistant prostate cancer (mCRPC) received ZYTIGA 1,000 mg once daily in combination with prednisone 5 mg orally twice daily. No patient had a left ventricular ejection fraction (LVEF) <50%. Assessments up to cycle 2, day 2 showed the upper bound of the 2-sided 90% CI for the mean baseline-adjusted corrected QT interval by Fredericia (QTcF) change was <10 ms. No patient discontinued therapy due to QTc prolongation or adverse event (AE). No apparent relationship between change in QTcF and ZYTIGA plasma concentrations was observed.[6]
    - In the integrated safety population from 5 phase 3 randomized clinical studies of ZYTIGA plus prednisone/prednisolone, treatment-emergent AEs of special interest included arrhythmias in 212/2230 (9.5%) of patients in the treatment group compared to 123/1763 (7.0%) in the placebo group.[3]
    - Hydroxychloroquine is associated with QT prolongation.[7-11] When hydroxychloroquine is used, clinicians should monitor the patient for AEs, especially prolonged QTc interval. QTc prolongation due to agents such as hydroxychloroquine is a potential problem for patients with underlying heart disease and/or those who concurrently use drugs that prolong the QTc interval. The risk and benefit of using hydroxychloroquine must be carefully weighed, with close monitoring of QTc and

concomitant medication use.[1,11] Health care providers should carefully review product labeling before prescribing hydroxychloroquine sulfate.

- Abiraterone acetate is an inhibitor of CYP2D6 and CYP2C8.[3]
  - Caution is advised when ZYTIGA is administered with drugs activated by or metabolized by CYP2D6, particularly with drugs that have a narrow therapeutic index. Dose reduction of narrow therapeutic index drugs metabolized by CYP2D6 should be considered.[3]
  - Patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA.[3]
  - Hydroxychloroquine is metabolized to N-desethylhydroxychloroquine in the liver through the N-desethylation pathway. This reaction is mediated by CYP2D6, CYP2C8, CYP3A4 and CYP3A5 isoforms. Polymorphisms in these enzymes may result in pharmacokinetic interindividual variability.[12]
- Marked increases in liver enzymes leading to drug discontinuation or dosage modification occurred in controlled clinical studies of ZYTIGA plus prednisone.[3]
  - There have been rare postmarketing reports of acute liver failure and hepatitis fulminant, some with fatal outcome.[3]
  - Hepatotoxicity was reported for higher proportions of patients receiving ZYTIGA plus prednisone than the placebo(s) groups in the integrated safety population from 5 phase 3 randomized clinical studies (16.1% vs 13.6%, respectively).[3]
  - Liver dysfunction can decrease the excretion of 4-aminoquinolines, such as hydroxychloroquine, and can lead to greater drug retention.[13]
- This information is meant to be supportive only and does not supersede any local or government requirements or your clinical judgment to protect the health and well-being of your patient, yourself, and your staff. Prescribers should refer to product labeling information for full details and precautions regarding use of these products.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File databases (and/or other resources, including internal/external databases) was conducted on 15 May 2024.

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