ZYTIGA® (abiraterone acetate)
ZYTIGA - Drug Interaction with Oral Anticoagulants

SUMMARY

- Following oral administration, abiraterone acetate is hydrolyzed to the active metabolite, abiraterone, likely through esterase activity.[1]
- Based on in vitro data, abiraterone is a substrate of CYP3A4. If a strong CYP3A4 inducer must be coadministered, increase the ZYTIGA dosing frequency as described in product labeling.[2,3]
- Abiraterone acetate is an inhibitor of CYP2D6 and CYP2C8. Avoid coadministration of ZYTIGA with substrates of CYP2D6 with a narrow therapeutic index. If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.[4] Clinicians should consider the therapeutic index of CYP2C8 substrate drugs when used concomitantly with ZYTIGA.[5]
- In vitro studies have shown that abiraterone acetate is an inhibitor of P-glycoprotein (P-gp) while abiraterone showed little inhibitory effect on P-gp.[6,7] As abiraterone acetate is quickly converted to abiraterone upon ingestion, no clinically relevant interactions with P-gp are expected.
- Clinical studies were performed to evaluate the drug-drug interaction potential only for the strongest in vitro signals. As abiraterone was a moderate inhibitor of CYP3A4/5 in vitro,[2,8-10] no clinical drug-drug interaction studies were performed to evaluate to what extent abiraterone affects CYP3A4.
- Subgroup analyses of efficacy and safety outcomes were not separately performed for patients who received an oral anticoagulant agent as a concomitant medication in the 3 phase 3, randomized, multicenter, pivotal clinical studies (COU-AA-301, COU-AA-302, and LATITUDE).
- In COU-AA-301, a phase 3 study, which evaluated ZYTIGA plus prednisone vs placebo plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) and disease progression after docetaxel-based chemotherapy,[11] 93 patients (11.8%) in the ZYTIGA group received warfarin as concomitant therapy.[12]
- In COU-AA-302, a phase 3 study, which evaluated ZYTIGA plus prednisone vs placebo plus prednisone in patients with chemotherapy-naïve mCRPC,[13] 2 patients (0.4%) in the ZYTIGA group received a direct thrombin inhibitor as concomitant therapy (dabigatran [n=1], bivalirudin [n=1]). Additionally, 19 patients (5.4%) in the ZYTIGA group received warfarin as a concomitant therapy.[14]
- In LATITUDE, a phase 3 study, which evaluated ZYTIGA plus daily prednisone with androgen deprivation therapy (ADT) compared to placebos with ADT in patients with newly diagnosed, metastatic high-risk castration-sensitive prostate cancer (CSPC),[15] 8 patients (1.3%) in the ZYTIGA group received a direct factor Xa inhibitor as concomitant therapy (apixaban [n=1], rivaroxaban [n=7]), and 2 patients (0.3%) received a direct thrombin inhibitor as concomitant therapy (dabigatran etexilate mesilate [n=1], dabigatran [n=1]). Additionally, 7 patients (1.2%) and 3 patients (0.5%) in the ZYTIGA group received warfarin and warfarin sodium as a concomitant therapy, respectively.[16]

BACKGROUND

Anticipated drug-drug interactions and management strategies for use of direct oral anticoagulants (DOACs) and warfarin with cancer therapy, including ZYTIGA plus prednisone, have been published.[6-9,17-23] Among the published literature includes a clinical framework developed for the management of patients with mCRPC receiving concomitant ZYTIGA plus prednisone and an anticoagulant,[8] reviews of actual and predicted drug-drug interactions between ZYTIGA plus prednisone and various drug classes, including DOACs

and warfarin,[9,19,23] and a safety analysis evaluating concomitant use of ZYTIGA and anticoagulants.[24]

Select pharmacokinetic characteristics of DOACs and warfarin are shown in Table: Mechanisms of Action and CYP450 and P-gp Substrate Properties of Abiraterone, Apixaban, Rivaroxaban, Edoxaban, Dabigatran, and Warfarin.

Mechanisms of Action and CYP450 and P-gp Substrate Properties of Abiraterone, Apixaban, Rivaroxaban, Edoxaban, Dabigatran, and Warfarin[2,6,22,25-27]

	Abiraterone	Apixaban	Rivaroxaban	Edoxaban	Dabigatran	Warfarin
Mechanism of Action	CYP17 Inhibitor	Factor Xa Inhibitor	Factor Xa Inhibitor	Factor Xa Inhibitor	Thrombin Inhibitor	Vitamin K Antagonist
CYP450 Substrate	Yes (CYP3A4)	Yes (CYP3A4)	Yes (CYP3A4)	Minimal	No	Yes (CYP2C9)
P-gp Substrate	No	Yes	Yes	Yes	Yes	No

Abbreviations: CYP, cytochrome P; CYP17, 17 α-hydroxylase/C17,20-lyase; P-gp, P-glycoprotein.

Drug-drug interaction clinical studies have been published for ZYTIGA plus prednisone with various medications and are summarized below.

- Results from a dedicated drug interaction trial with rifampin, a strong CYP3A4 inducer, indicated a 55% reduction in abiraterone exposure and that concomitant strong CYP3A4 inducers during treatment with ZYTIGA should be avoided. However, in a separate dedicated drug interaction trial with ketoconazole, a strong CYP3A4 inhibitor, no clinically meaningful effect on the pharmacokinetics of abiraterone were observed.[3]
- In a clinical drug interaction trial with dextromethorphan, a CYP2D6 substrate, the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of dextromethorphan were increased 2.8- and 2.9-fold, respectively, when dextromethorphan 30 mg was given with ZYTIGA 1,000 mg daily (plus prednisone 5 mg twice daily). The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold.[4,28]
- In a clinical drug interaction trial with pioglitazone, a CYP2C8 substrate, administration of ZYTIGA to healthy men resulted in mild inhibition of CYP2C8 and had only weak effects on the pharmacokinetics of pioglitazone.[5] A case report of hypoglycemia in a patient on concomitant ZYTIGA plus prednisone and repaglinide, a CYP2C8 substrate, has also been published.[29]

CLINICAL DATA

Phase 3 COU-AA-301 Study

de Bono et al (2011)[11] evaluated the efficacy and safety of ZYTIGA plus prednisone vs placebo plus prednisone in patients with mCRPC and disease progression after docetaxel-based chemotherapy (N=1195). Patients were randomized 2:1 to receive either ZYTIGA 1,000 mg orally once daily plus prednisone 5 mg orally twice daily (n=797) or placebo plus prednisone 5 mg orally twice daily (n=398). All patients received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. Patients were excluded if they had clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class III-IV heart disease or baseline cardiac ejection fraction (EF) measurement <50%.[30]

Patient baseline demographic and disease characteristics were well balanced, and there were no significant differences between groups. The median treatment duration was 8 months in the ZYTIGA group and 4 months in the placebo group.[11] Shown below is Table: Frequency of Concomitant Use of Oral Anticoagulant Agents in the COU-AA-301 Study.

Frequency of Concomitant Use of Oral Anticoagulant Agents in the COU-AA-301 Study[12,a]

	ZYTIGA Plus Prednisone Group (n=791)	Placebo Plus Prednisone Group (n=394)	Total (N=1185)
Vitamin K Antagonists, n (%) Warfarin	106 (13.4) 93 (11.8)	45 (11.4) 39 (9.9)	151 (12.7) 132 (11.1)
[a]Based on the COU-AA-301 safety population.			

Subgroup analyses of efficacy and safety outcomes were not separately performed for patients who received an oral anticoagulant agent as a concomitant medication in the COU-AA-301 study.

Phase 3 COU-AA-302 Study

Ryan et al (2013)[13] evaluated the efficacy and safety of ZYTIGA plus prednisone in patients with chemotherapy-naïve mCRPC (N=1088). Patients were randomized 1:1 to receive either ZYTIGA 1,000 mg orally once daily plus prednisone 5 mg orally twice daily (n=546) or placebo plus prednisone 5 mg orally twice daily (n=542). All patients received a concomitant GnRH analog or had a bilateral orchiectomy. Patients were excluded if they had clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, NYHA Class II-IV heart disease or baseline cardiac EF measurement of <50%, atrial fibrillation, or other cardiac arrhythmia requiring therapy.[31]

Patient baseline demographic and disease characteristics were well balanced, and there were no significant differences between groups. The median treatment duration was 13.8 months in the ZYTIGA group and 8.3 months in the placebo group.[14] Shown below is Table: Frequency of Concomitant Use of Oral Anticoagulant Agents in the COU-AA-302 Study.

Frequency of Concomitant Use of Oral Anticoagulant Agents in the COU-AA-302 Study[14,a]

	ZYTIGA Plus Prednisone Group (n=542)	Placebo Plus Prednisone Group (n=540)	Total (N=1082)
Direct Thrombin Inhibitors, n (%) Dabigatran Bivalirudin	2 (0.4) 1 (0.2) 1 (0.2)	0 0 0	2 (0.2) 1 (0.1) 1 (0.1)
Vitamin K Antagonists, n (%) Warfarin	35 (6.5) 29 (5.4)	31 (5.7) 26 (4.8)	66 (6.1) 55 (5.1)
[a]Based on the COU-AA-302 safety population			

Subgroup analyses of efficacy and safety outcomes were not separately performed for patients who received an oral anticoagulant agent as a concomitant medication in the COU-AA-302 study.

Phase 3 LATITUDE Study

Fizazi et al (2017)[15] evaluated the efficacy and safety of ZYTIGA plus prednisone with ADT in patients with newly diagnosed, metastatic high-risk CSPC (N=1199). Patients were randomized 1:1 to receive either ZYTIGA 1,000 mg plus prednisone 5 mg orally daily with ADT (n=597) or placebos with ADT (n=602). All patients received a concomitant GnRH analog or had a bilateral orchiectomy. Patients were excluded if they had clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events or history of cardiac failure in the past 6 months, severe or unstable angina, NYHA Class II-IV heart disease, existing atrial fibrillation with or without pharmacotherapy, or other cardiac arrhythmia requiring pharmacotherapy.[32]

Patient baseline demographic and disease characteristics were well balanced, and there were no significant differences between groups. The median treatment duration was 24 months in the ZYTIGA group and 14 months in the placebos group. Shown below is Table: Frequency of Concomitant Use of Oral Anticoagulant Agents in the LATITUDE Study.

Frequency of Concomitant Use of Oral Anticoagulant Agents in the LATITUDE Study[16,a]

	ZYTIGA + Prednisone + ADT (n=597)	Placebos + Prednisone + ADT (n=602)	Total (N=1199)
Direct Factor Xa Inhibitors, n (%)	8 (1.3)	1 (0.2)	9 (0.8)
Apixaban	1 (0.2)	0	1 (0.1)
Rivaroxaban	7 (1.2)	1 (0.2)	8 (0.7)
Direct Thrombin Inhibitors, n (%)	2 (0.3)	1 (0.2)	3 (0.3)
Dabigatran etexilate mesilate	1 (0.2)	0	1 (0.1)
Dabigatran	1 (0.2)	1 (0.2)	2 (0.2)
Vitamin K Antagonists, n (%)	10 (1.7)	10 (1.7)	20 (1.7)
Warfarin	7 (1.2)	2 (0.3)	9 (0.8)
Warfarin Sodium	3 (0.5)	3 (0.5)	6 (0.5)

[a]Based on the LATITUDE safety population

Subgroup analyses of efficacy and safety outcomes were not separately performed for patients who received an oral anticoagulant agent as a concomitant medication in the LATITUDE study.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) was conducted on 24 January 2024. Summarized in this response are relevant data limited to the 3 phase 3, randomized, multicenter, pivotal clinical studies (COU-AA-301, COU-AA-302, and LATITUDE).

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