ZYTIGA® (abiraterone acetate)
ZYTIGA - Mineralocorticoid Excess

SUMMARY

- ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from 17-α hydroxylase/C17,20-lyase (CYP17) inhibition and is indicated for use in combination with prednisone/prednisolone.[1] Control hypertension and correct hypokalemia before and during treatment with ZYTIGA. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.[2]
- In the combined data from 4 placebo-controlled trials using prednisone 5 mg twice daily in combination with 1,000 mg ZYTIGA daily, grades 3-4 hypokalemia were detected in 4% of patients in the ZYTIGA arm and 2% of patients in the placebo arm. Grades 3-4 hypertension were observed in 2% of patients in each arm and grades 3-4 fluid retention in 1% of patients in each arm.[3-6]
- In LATITUDE (a phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial),[7] which used prednisone 5 mg daily in combination with 1,000 mg ZYTIGA daily, at the final overall survival (OS) analysis, AEs of special interest that occurred in ≥2% of patients in any treatment group included the following in the ZYTIGA plus prednisone with androgen deprivation therapy (ADT) group vs placebos with ADT group vs crossover group, respectively: hypertension (41% vs 24% vs 6%), hypokalemia (24% vs 4% vs 13%), and fluid retention or edema (14% vs 12% vs 4%).[8]
- 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. In postmarketing experience, QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia or had underlying cardiovascular conditions while taking ZYTIGA.[9] The safety of ZYTIGA in patients with left ventricular ejection fraction <50% or New York Heart Association (NYHA) Class III or IV heart failure (in COU-AA-301) or NYHA Class II to IV heart failure (in COU-AA-302 and LATITUDE) has not been established because these patients were excluded from these randomized clinical trials.[1, 3, 4]

BACKGROUND

Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor that inhibits CYP17.[10]

Mineralocorticoid excess related adverse events (AEs), such as hypertension, hypokalemia, and fluid retention, which may result from high levels of adrenocorticotropic hormone (ACTH) and steroid precursors upstream of CYP17, provide rationale for the coadministration of ZYTIGA with a corticosteroid, such as prednisone. In a phase 1 study (N=21), treatment with single-agent ZYTIGA was associated with accumulation of steroids with mineralocorticoid properties upstream of CYP17A1. This resulted in mineralocorticoid excess related AEs, including hypertension, hypokalemia, and peripheral edema in 6, 10, and 1 patient, respectively, and all were controlled with eplerenone.[10]

In a review conducted by the European Medicines Agency, abiraterone acetate was found to be commonly associated with AEs resulting from increased mineralocorticoid activity.[11] A meta-analysis of 7 studies, including 1387 patients with metastatic castration-resistant prostate cancer (CRPC) treated with ZYTIGA plus prednisone, reported the incidence of all-grade hypertension, hypokalemia, and edema to be 13.3% (95% CI, 8.3%-20.5%), 31.4% (95% CI, 12.5%-59.5%), and 23.4% (95% CI, 15.6%-33.5%), respectively, and grade ≥3 events were reported to be low. The risk of hypertension and edema did not change with the addition of prednisone; however, the risk of hypokalemia was significantly reduced

(*P*=0.003).[12] Additional meta-analyses of special interest AEs, including hypokalemia, hypertension, and edema, in patients with metastatic CRPC treated with CYP17 inhibitors, including ZYTIGA, have been published.[13-16]

CLINICAL DATA

Data summarized within this scientific response have been limited to 3 phase 3 registration studies (COU-AA-301, COU-AA-302, and LATITUDE) included in product labeling.[3, 4, 7]

Two pivotal phase 3, randomized, double-blind, placebo-controlled, multinational studies assessed the safety and efficacy of ZYTIGA 1,000 mg daily plus prednisone 5 mg twice daily and ADT vs placebo plus prednisone and ADT in patients with metastatic CRPC. In COU-AA-301, patients were randomized 2:1 and the primary endpoint was OS.[3] In COU-AA-302, patients were randomized 1:1 and the coprimary endpoints were OS and radiographic progression-free survival (rPFS).[4]

A third phase 3, randomized, placebo-controlled, multicenter clinical trial enrolled patients who had metastatic high-risk castration-sensitive prostate cancer (CSPC). ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg once daily and ADT in the active treatment arm. Placebos plus ADT were given in the control arm. In LATITUDE, patients were randomized 1:1 and the coprimary endpoints were OS and rPFS.[7]

COU-AA-301 Study: Phase 3 Study in Post-docetaxel Metastatic CRPC

de Bono et al (2011)[3] evaluated the efficacy and safety of ZYTIGA plus prednisone compared to placebo plus prednisone in patients with metastatic CRPC whose disease had progressed after docetaxel-based chemotherapy (N=1195).

- Select exclusion criteria:[3, 17]
  - Uncontrolled hypertension (systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥95 mmHg); patients with a history of hypertension were permitted to participate if BP was controlled by antihypertensive therapy
  - Clinically significant heart disease, including myocardial infarction, arterial thrombotic events within the previous 6 months, severe or unstable angina, NYHA class III through IV heart disease, or baseline cardiac ejection fraction <50%
  - Concurrent use of spironolactone was not allowed during the study period

Mineralocorticoid-Related Safety

- AEs associated with elevated mineralocorticoid levels (fluid retention and edema, hypokalemia, and hypertension) were more common in the ZYTIGA group than in the placebo group, as shown in Table: Mineralocorticoid-Related AEs.[3]

Mineralocorticoid-Related AEs[3]

	ZYTIGA Plus Prednisone (n=791)			Placebo Plus Prednisone (n=394)		
	All Grades, %	Grade 3, %	Grade 4, %	All Grades, %	Grade 3, %	Grade 4, %
Fluid retention and edema	31[a]	2	<1	22	1	0
Hypokalemia	17[b]	3	<1	8	1	0
Hypertension	10	1	0	8	<1	0

Abbreviation: AEs, adverse events.
[a]*P*=0.04 vs placebo plus prednisone.
[b]*P*<0.001 vs placebo plus prednisone.

- The updated analysis revealed consistent results, as summarized in Table: Mineralocorticoid-Related AEs - Updated Analysis.[18]

Mineralocorticoid-Related AEs - Updated Analysis[18]

	ZYTIGA Plus Prednisone (n=791)			Placebo Plus Prednisone (n=394)		
	All Grades, %	Grade 3, %	Grade 4, %	All Grades, %	Grade 3, %	Grade 4, %
Fluid retention/edema	33	2	<1	24	1	0
Hypokalemia	18	4	<1	9	<1	0
Hypertension	11	1	0	8	<1	0
Abbreviation: AEs, adverse events.						

COU-AA-302 Study: Phase 3 Study in Chemotherapy-Naïve Metastatic CRPC

Ryan et al (2013, 2014, 2015)[4, 19, 20] evaluated the clinical benefit of ZYTIGA plus prednisone compared to placebo plus prednisone in asymptomatic or mildly symptomatic patients with chemotherapy-naïve metastatic CRPC (N=1088).

- Select exclusion criteria:[4, 21]
  - Uncontrolled hypertension (systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg); patients with a history of hypertension were permitted to participate if BP was controlled by antihypertensive therapy
  - Clinically significant heart disease, including myocardial infarction, arterial thrombotic events within the previous 6 months, severe or unstable angina, NYHA class II through IV heart disease, or baseline cardiac ejection fraction <50%
  - Atrial fibrillation or other cardiac arrhythmia requiring medical treatment
  - Concurrent use of spironolactone was not allowed during the study period

Mineralocorticoid-Related Safety

- Mineralocorticoid-related AEs and cardiac disorders at the time of a second interim analysis (IA2) are summarized in Table: Mineralocorticoid-Related AEs (IA2).[4] Additionally, data from the third interim analysis (IA3) are summarized in Table: Safety Analyses per Time on Therapy (IA3).[22]

Mineralocorticoid-Related AEs (IA2)[4]

	ZYTIGA Plus Prednisone (n=542), %		Placebo Plus Prednisone (n=540), %	
	All Grades	Grade 3/4	All Grades	Grades 3/4
Fluid retention/edema	28	<1	24	2
Hypokalemia	17	2	13	2
Hypertension	22	4	13	3
Abbreviations: AEs, adverse events; IA2, second interim analysis.				

Safety Analyses per Time on Therapy (IA3)[22a]

Exposure, Months	ZYTIGA Plus Prednisone			Placebo Plus Prednisone		
	n	Grades 1-2, %	Grades 3-4, %	n	Grades 1-2, %	Grades 3-4, %
Hypertension						
<3	542	7	1	540	6	2
12-15	302	4	<1	184	2	2

≥24	154	1	<1	76	1	0
Weight gain						
<3	542	1	0	540	2	0
12-15	302	<1	0	184	0	0
≥24	154	2	0	76	1	0

Abbreviation: IA3, third interim analysis.
[a]Median follow-up at IA3 was 27.1 months.

- At the time of the final analysis, after a median follow-up of 49.2 months, ZYTIGA plus prednisone maintained a favorable safety profile. The incidence of cardiac-related AEs of special interest is summarized in Table: Mineralocorticoid-Related AEs of Special Interest (Final Analysis).[20]

Mineralocorticoid-Related AEs of Special Interest (Final Analysis)[20]

	ZYTIGA Plus Prednisone (n=542), %				Placebo Plus Prednisone[a] (n=540), %			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Fluid retention/edema	30	1	0	0	23	1	<1	0
Hypokalemia	16	2	<1	0	11	2	0	0
Hypertension	19	5	0	0	11	3	0	0

Abbreviation: AEs, adverse events.
[a]Prior to crossover.

LATITUDE: Phase 3 Study in Metastatic High-Risk CSPC

Fizazi et al (2017)[7, 23] evaluated the efficacy and safety of ZYTIGA in combination with prednisone and ADT vs placebos and ADT for the treatment of metastatic high-risk CSPC (N=1,199).

- Select exclusion criteria:[23]
  - Uncontrolled hypertension (systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg). Patients with a history of hypertension were allowed provided blood pressure was controlled by antihypertensive treatment
  - History of adrenal dysfunction
  - Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA class II-IV heart disease or cardiac ejection fraction measurement of <50% at baseline
  - Atrial fibrillation or other cardiac arrhythmia requiring pharmacotherapy
  - Concurrent use of spironolactone was not allowed during the study period

Mineralocorticoid-Related Safety

- Grade 3 mineralocorticoid-related effects (hypertension and hypokalemia) were more common events of special interest in the ZYTIGA plus prednisone with ADT group, as shown in Table: Mineralocorticoid-Related AEs (First Interim Analysis).[7] Additionally, mineralocorticoid-related AEs that occurred in ≥2% of patients in any treatment group from the final OS analysis are summarized in Table: Mineralocorticoid-Related AEs (Final Analysis).[8]

Mineralocorticoid-Related AEs (First Interim Analysis)[7a]

	ZYTIGA Plus Prednisone Plus ADT (n=597), n (%)			Placebos Plus ADT (n=602), n (%)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hypokalemia	122 (20)	57 (10)	5 (1)	22 (4)	7 (1)	1 (<1)
Hypertension	219 (37)	121 (20)	0	133 (22)	59 (10)	1 (<1)

Abbreviations: ADT, androgen deprivation therapy; AEs, adverse events.
[a]Other events of special interest include grade 3 peripheral edema in 0.3% vs 0.5% in the ZYTIGA plus prednisone with ADT vs placebos with ADT groups, respectively; grade 3 or 4 fluid retention or congestive heart failure not reported in either group.

Mineralocorticoid-Related AEs (Final Analysis)[8]

	ZYTIGA Plus Prednisone Plus ADT (n=597), n (%)			Placebos Plus ADT (n=602), n (%)			Placebo Crossover to ZYTIGA Plus Prednisone (n=72), n (%)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hypertension	243 (41)	130 (22)	1 (<1)	144 (24)	62 (10)	1 (<1)	4 (6)	3 (4)	0
Hypokalemia	143 (24)	65 (11)	5 (1)	23 (4)	9 (1)	1 (<1)	9 (13)	2 (3)	0
Fluid retention or edema	81 (14)	5 (1)	0	71 (12)	6 (1)	0	3 (4)	0	0

Abbreviations: ADT, androgen deprivation therapy; AEs, adverse events.

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 27 April 2023. Summarized in this response are relevant data from 3 phase 3 registrational studies.

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