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Background: Osilodrostat, a potent oral inhibitor of 11β-hydroxylase, demonstrated efficacy in normalizing urinary free cortisol (UFC) in Cushing's disease (CD) patients; however, information describing its use in clinical practice is limited. We present osilodrostat dosing and titration information from a real-world cohort of endogenous Cushing's syndrome (CS) patients, focused on CD. **Methods:** ILLUSTRATE, a retrospective chart review study analyzed confirmed endogenous CS patients who initiated osilodrostat treatment May 1, 2020 - October 29, 2021. Forty-two adult patients with endogenous CS and a prescription for osilodrostat were included in this real-world study. We describe the experience with initial osilodrostat dose, dose titration, and persistence in the CD subset (n=34, 81%). **Results:** In patients with CD (n=34) the mean total daily starting dose was 3.4 mg (SD 1; median 4 mg; range 1-6 mg/day). Twenty-one patients (62%) were initiated on 2 mg BID, 9 (27%) on 1 mg BID, and 1 each (3%) on 1 mg QD, 2 mg QD, 3 mg BID and 4 mg QD. In CD patients with multiple documented clinical encounters (n=26), 16 initiated at 4 mg/day, of which the dose was interrupted or down-titrated in 4 patients (25%) within 71 days of treatment initiation; 2/4 of these patients experienced hypocortisolism related symptoms and permanently discontinued. Five of the 16 patients (31%) were maintained on 4 mg/day throughout the observation period, with a mean (SD) treatment duration of 273 (median 278 days; SD 92) days. Seven of 16 patients (44%) had a dose up-titration; in 6/7 patients, initial dose increase was incremental (1-2 mg BID), and the mean (SD) time to up-titration was 78 (SD 25; median 83; range 40-108) days. In the 10 of 26 CD patients who initiated therapy at <2 mg BID, 6 (60%) did not require dose reduction or interruption, all of which had up-titration in small increments (1-2 mg/day) and/or first titration at ≥80 days. Treatment persistence for those enrolled ≥ 6 months prior to study end was 95.8%, mean (SD) duration of therapy was 339.2 (106.8) days. Osilodrostat was generally well tolerated. Symptoms related to decreased cortisol levels were reported in 10/26 patients (38%), including 3 patients with adrenal insufficiency and 7 patients with glucocorticoid withdrawal symptoms. **Conclusion:** ILLUSTRATE captures real-world US data describing the experience of CD patients treated with osilodrostat. Importantly, one-third (11/34) of patients were initiated on a dose lower than 4 mg/day (lower than starting dose previously used in clinical trials). Of 16 patients initiated at 4 mg/day, 4 (25%) required interruption or down-titration and 5 (31%) remained on the initial dose throughout the observation period. Overall, consistent with prior

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Dosing And Titration Of Osilodrostat In A Real-world Cohort Of US Patients With Endogenous Cushing's Disease: Analysis Of The ILLUSTRATE Study

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research data, patients with a gradual dose up-titration (i.e., prolonged titration interval) tended to have greater persistence with therapy. There were no new safety findings.

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